Green Chemistry: A practical elegance in chemical synthesis

Nitya Sharma, Extension Lecturer, Govt. College, Kaithal

ABSTRACT

Green chemistry expresses an area of research developing from scientific discoveries about pollution awareness and it utilizes a set of principles that reduces or eliminates the use or generation of hazardous substances in all steps of particular synthesis or process. Chemists and medicinal scientists can greatly reduce the risk to human health and the environment by following all the valuable principles of green chemistry. The most simple and direct way to apply green chemistry in pharmaceuticals is to utilize eco-friendly, non-hazardous, reproducible and efficient solvents and catalysts in synthesis of drug molecules, drug intermediates and in researches involving synthetic chemistry. Microwave synthesis is also an important tool of green chemistry by being an energy efficient process.

ISSN 2454-308X
9 770024 543081

Keywords: Green chemistry, green solvents, green catalyst, microwave synthesis

INTRODUCTION

During the twentieth century, chemistry changed the way people lived. And the greatest perceived benefits came from pharmaceutical industries with development of organic medicinal molecules. Pharmaceutical chemistry encompasses major chemicals, reagents, solvents, catalysts and almost all type of organic reactions for synthesis of active pharmaceutical molecules. Herein, many chemicals and chemical processes are very hazardous, toxic and may have adverse effects on the environment and on human health. Industries associated with pharmaceuticals and fine chemicals are employing much more complex chemistry and produce relatively much more waste, which is not at all suitable for environment and nature[1].

During the early 1990s the US Environmental Protection Agency (EPA) coined the phrase Green Chemistry to promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products. Green chemistry is designed to reduce or eliminate negative environmental impacts such that the use and production of chemicals may involve reduced waste products, non-toxic components, and improved efficiency. Green chemistry is not a particular set of technologies, but rather an emphasis on the design of chemical products and processes. This approach offers environmentally beneficial alternatives to more hazardous chemicals and processes, and thus promotes pollution prevention[2-4].

PRINCIPLES OF GREEN CHEMISTRY

Green chemistry is a highly effective approach to pollution prevention as it applies innovative scientific solutions to real-world environmental situations. The following 12 principles of Green Chemistry provide a way for chemists to implement green chemistry[5].

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

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

3. Less Hazardous Chemical Syntheses Synthetic methods should be designed, wherever practicable, to use and generate substances that possess little or no toxicity to human health and the environment.

4. Designing Safer Chemicals Chemical products should be designed to achieve their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries Unnecessary use of auxiliary substances (e.g., solvents, separation agents, etc.) should be avoided wherever possible and made innocuous when used.

6. Design for Energy Efficiency 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.

7. Use of Renewable Feedstocks Whenever technically and economically practicable, raw material or feedstock should be renewable rather than depleting it.

8. Reduce Derivatives Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

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

10. Design for Degradation 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.

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.

12. Inherently Safer Chemistry for Accident Prevention Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential of chemical accidents, including releases, explosions, and fires.

The greenness of a chemical transformation can only be assessed on the context of its application and practice[6]. To complement Anastas and Warner's 12 principles and to address Glaze's concerns, 12 more green principles have now been suggested[7]. These are process orientated but still omit mentioning key green concepts relating to minimizing number of unit operations in work up and maximizing space, time and yield.

For implementation of green chemistry all these principles must be well considered and practiced. In this review article we have focused on solvents and catalysts which can be used as ―Green Solvents and Green catalysts.‖, which comprise an important part of almost all type of organic reactions.

SOLVENTS

Solvents define a major portion of the environmental performance of a process and also influence safety and health issues. In the industry, selection of solvents for chemical processes and subsequently the waste-solvent management are based on economic, safety and logistical considerations[8]. The industry has made significant efforts towards identifying organic solvents with a reduced ecological footprint as compared to traditional reactions. Green solvents such as water, liquid polymers, ionic liquids, bio-ethanol, supercritical fluids and ethyl lactate hold considerable additional promise[9]. Results of comprehensive framework demonstrated by Capello et al on 26 organic solvents have shown that simple alcohols (methanol, ethanol) or alkanes (heptane, hexane) are environmentally preferable solvents, whereas the use of dioxane, acetonitrile, acids, formaldehyde and tetrahydrofuran are not recommendable from an environmental perspective. Additionally, results of another case study indicate that methanol–water or ethanol–water mixtures are environmentally favorable compared to pure alcohol or propanol–water mixtures[10].

Water

Water can replace many toxic and hazardous solvents and has been found very efficient in many organic reactions, out of which some reactions are mentioned in this review. An efficient and handy method for the synthesis of chromeno-isoxazole/isoxazolines under on-water conditions has been described[11]. Hydrolysis of hydrophobic glycidyl ethers in pressurized water media can afford the corresponding glyceryl ethers in good to excellent selectivity within several minutes without a catalyst[12]. Selective and efficient aerobic oxidative iodination of ketones in aqueous media has been achieved by using molecular iodine as the source of iodine atoms, air as the terminal oxidant and sodium nitrite as the catalyst[13]. 1,3-Dipolar cyclo-additions of different hydrophobic nitrones have been studied in both homogenous organic solutions and aqueous suspensions. Here, reactions in water suspensions showed great rate accelerations over homogenous solutions[14]. The rearrangement of benzil is base catalyzed procedure under conventional conditions. In this reaction at high temperatures, water between 300–380°C (Near critical water) proceeds solely by base catalysis with more environmentally benign medium[15]. A convenient and clean on water mediated synthesis of benzothiazoles/benzothiazolines is reported. Aromatic, heteroaromatic and styryl aldehydes are converted to 2-substituted benzothiazoles in high yields in a one-pot reaction with 2-aminothiophenol in water[16]. Thioesters can be prepared by direct reaction of tertiary thioamides and alkyl halides in water and in the presence of catalytic amounts of Sodiun iodide (NaI), hexadecyltrimethylammonium bromide (HTAB) and 1,4-diazabicyclo[2.2.2]octane (DABCO)[17]. Novel SO_3H-functionalized ionic liquids bearing two alkyl sulfonic acid groups in the imidazoliumcations were designed and successfully applied as catalysts for the one-pot Fischer indole synthesis in water medium[18]. Usually organic solvents are considered to be necessary for the best efficiency in the reactions of aliphatic nitro compounds; it has been shown that these reactions are also very efficient using water as reaction medium[19]. Superheated water has organic solvent like properties and behaves as ideal low cost green solvent for chromatography and other separation methods avoiding use of hazardous solvents[20].

Glycerol

Glycerol has been recently proposed as a valuable green solvent. Glycerol may combine the advantages of water (low toxicity, low price, large availability, renewability) and ionic liquids (high boiling point, low vapour pressure) and can afford innovative solutions to the substitution of the conventionally used volatile organic solvents21. Besides solubility of the reactants and the catalysts and easy separation of the product, glycerol offers several other benefits such as catalyst recycling microwave assisting reaction and biphasic and emulsion modes[22]. A family of glycerol derivatives, consisting of over sixty 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes, both symmetrically and unsymmetrically substituted at terminal positions, have been synthesized and these glycerol derivatives can act as green solvents[23]. Glycerol has been employed as an alternative green reaction medium in various carbonyl reduction methodologies. The high polarity of glycerol allows for the simple reduction of different carbonyl compounds with sodium borohydride and the enantioselective reduction of ethyl acetoacetate. As a solvent, glycerol also allows electro-reduction and microwave assisted reactions[24].

Ionic liquids In the search for less hazardous manufacturing solvents, Dame et al reported a new process to separate problematic chemicals from ionic liquids[25]. Ionic liquids come in two main categories, namely simple salts (made of a single anion and cation) and binary ionic liquids (salts where equilibrium is involved). For example, $[EtNH_3][NO_3]$ is a simple salt whereas mixtures of aluminum(III) chloride and 1,3-dialkylimidazolium chlorides (a binary ionic liquid system) contain several different ionic species and their melting point and properties depend upon the mole fractions of the aluminum(III) chloride and 1,3 dialkylimidazolium chloride present. Room-temperature ionic liquids, such as $BMIM\text{-}PF_6$ **[**1-Butyl-3-methylimidazolium hexafluorophosphate] have been used as direct replacements for conventional organic solvents in multiphase bioprocess reactions, including liquid-liquid extraction of the antibiotic erythromycin and two-phase biotransformation processes. The addition of organometallic reagents to carbonyl compounds is an important reaction. Formation of homoallylic alcohols, from the addition of allylstannanes to aldehydes in the ionic liquids $[BMIM\text{-}PF_4]$ and $BMIM\text{-}PF_6$ have been reported. It has been found that the ionic liquid can be recycled and reused over several reaction cycles. Synthesis of (S)-Naproxen in the ionic liquid $BMIM\text{-}PF_4$ has been reported, which is example of asymmetric hydrogenation reactions in ionic medium. The very common organic reaction, Friedel-Crafts alkylation proceeds smoothly and efficiently in chloroaluminate(III) ionic liquids. Numbers of commercially important molecules have been synthesized by Friedel-Crafts acylation reactions in these ionic liquids. Ionic liquids with a pyridinium cation bearing an ester side chain moiety can be prepared from either pyridine or nicotinic acids which are biodegradable.

Supercritical carbon dioxide Supercritical carbon dioxide (scCO2) works similarly with other problematic chemicals without hazardous effects with advantages of water. Hydrogenation, epoxidation, radical reactions, Palladium-mediated C-C bond formation, ring closing metathesis, biotransformation, polymerization and many others reactions can be performed with scCO2 as a reaction medium. It has been demonstrated that Ibuprofen can be loaded into mesoporous silica using liquid (near-critical) carbon dioxide as the solvent and the resulting material obtained high Ibuprofen content.

CATALYST

A Green catalyst can play a very important role in chemical processes by replacing reagents, by enabling more efficient processes, by reducing the environmental impact of processes and by reducing the costs of the processes. This can be achieved by designing the appropriate catalyst which would be cheap, readily preparable, and reproducible and fully environment friendly. Some of these green catalysts are included in this article.

Catalytic systems based on immobilized metal complexes have been reported which are capable of catalyzing reactions of pharmaceutical value, such as the selective oxidation of steroidal compounds. In one study, chloroauric acid ($HAuCl_4$) is used as a catalyst in water for the stereoselective cycloisomerization of various functionalized allenes to five or six membered oxygen or nitrogen containing heterocycles. Compared to traditional gold catalysts in organic solvents, this catalytic system is more environmentally friendly and can be reused after complete conversion of the substrate. An economical and sustainable transfer hydrogenation for aldehydes and ketones has been reported with mild, chemo-selective procedure which uses neither precious/non-precious metals nor ligands. Wacker oxidation of higher alkenes and aryl alkenes has been developed using molecular oxygen as the oxidant, in which colloidal palladium nanoparticles stabilized in ethylene carbonate are considered to facilitate its reoxidation under co-catalyst free conditions. A simplified one-step procedure for making some mesoporous solid sulfonic acids has been reported and can achieve environmentally friendly replacements for traditional acids such as sulfuric acid and its organic derivatives. Invention of clay-supported zinc chloride (clayzic) is the basis of a commercial ―Envirocat‖, catalyst, which has proven to be useful for Lewis acid catalyzed reactions, including benzylations, olefinations, and some cyclizations. A new solid Lewis acid, HMS-supported zinc triflate has shown reasonable selectivity in the rearrangement of α-pinene oxide to campholenic aldehyde with excellent reusability compared to conventional homogeneous processes. Zeolites, popular green catalysts, are crystalline alumino-silicates with exchangeable cations. A major application of the zeolites in catalysis is in acid catalyzed reactions such as alkylation, acylation, electrophilic aromatic substitution, cyclization, isomerization and condensation. A convenient and rapid method for Knoevenagel condensation has been developed by using 1,4-Diazabicyclo[2.2.2]octane-base ionic liquid catalysts. These catalysts can be recycled seven times without activity loss. Biocatalysis is an emerging tool for the green technologies. Enzymes are highly efficient with excellent regioselectivity and stereoselectivity. By conducting reactions in water under ambient reaction conditions, both the use of organic solvents and energy input can be minimized. Biocatalysts can catalyze many organic reactions such as epoxidation of terpenes and fatty acids, generation of polymers, polylactides and polyesters, production of 1,3-propanediol from corn etc. One of these biocatalysts is Candida Antarctica Lipase, which catalyses alcoholysis, ammoniolysis, and perhydrolysis reactions. These reaction rates are comparable with or better than those observed in organic media. One of the key principles of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents.

MICROWAVE SYNTHESIS

In the development of solvent-free alternative processes, microwave assisted organic synthesis is the best solution for achieving this. Thermal reactions proceed optimally when they are rapidly heated to the highest tolerable temperatures, held there for the shortest possible time and then quenched. Microwave heated reactions proceed faster and more cleanly than their conventionally heated counterparts and thus are more energy efficient. A solid acid-catalyzed microwave-assisted synthesis of substituted quinolines is reported. The quinolines can be synthesized by a multicomponent reactions of anilines, aldehydes and terminal aryl alkynes and involve long reaction path. The use of microwave activation reduces the reaction time significantly. Fast and eco-friendly microwave-irradiated reactions permitting the green synthesis of 2-substituted quinazoline derivatives in aqueous medium via S-alkylation from 2-chloromethyl-3-methylquinazolin-4(3H)-one derivatives with different benzene sulfinic acids and nitronate anions has also been reported. Microwave-assisted synthesis of benzimidazole and thiazolidinone derivatives as HIV-1 Reverse Transcriptase inhibitors has achieved reductions in reaction times, higher yields and cleaner reactions. In some cases eco-friendly solvent less methodology has been used. Over-the-counter analgesics such as aspirin, acetanilide, phenacetin, and acetaminophen are conveniently prepared in a microwave at 30% power for five minutes.

Green Chemistry in some Pharmaceuticals

Pharmaceutical companies can influence and improve the environmental performance with utilizing green chemistry. Green chemistry is being employed to develop revolutionary drug delivery methods that are more effective and less toxic and could benefit millions of patients, some of them are described here. Phosphoramidite-based, solid-phase synthesis of antisense oligonucleotides has been modified to accommodate principles of green chemistry by eliminating the use and generation of toxic materials and allowing reuse of valuable materials such as amidites, solid-support and protecting groups, thus improving the atom economy and cost-efficiency.

Anastas et al has described synthesis of Naproxen with chiral metal catalyst containing BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) ligand with good yields. This chiral ligand is widely used in asymmetric synthesis. The green synthesis for a key intermediate of atorvastatin has been developed in two steps. First step involves the biocatalytic reduction of ethyl-4-chloroacetoacetate using a ketoreductase in combination with glucose and a NADP-dependent glucose dehydrogenase (GDH) for cofactor regeneration. The (S)ethyl-4-chloro-3-hydroxybutyrate product is obtained in very good yield. In the second step, a halohydrindehalogenase (HHDH) is employed to catalyze the replacement of the chloro substituent with cyano, by reaction with HCN at neutral pH and ambient temperatures. These natural enzymes were highly selective for the reactions. Some workers have discovered an inexpensive, clean and quick way to prepare amines, bearing a wide portion of drug molecules. Currently, industries produce amines in a costly two-step process that results in massive amounts of byproducts as waste. Green chemistry method produces no waste, reaction is a quick one-step reaction and a very little amount of catalyst is utilized. Methods for synthesis of Aspirin with microwave irradiation using catalysts such as $AlCl_3$, H_2SO_4, H_3PO_4, $MgBr_2.OEt_2$, $CaCO_3$, NaOAc, Et_3N and solvent-free approach have been designed. This study shows new alternative and greener methodology for traditional synthetic procedure.

CONCLUSION

Green chemistry has grown from a small idea into a new approach to the scientifically based environmental protection. By using green chemistry procedures, we can minimize the waste of materials, maintain the atom economy and prevent the use of hazardous chemicals. Researchers and pharmaceutical companies need to be encouraged to consider the principles of green chemistry while designing the processes and choosing reagents.

REFERENCES

1. Sheldon RA. Catalysis: The Key to Waste Minimization. J Chem Tech Biotechnol 1997;68(4):381–388
2. Noyori R. Pursuing practical elegance in chemical synthesis. Chemical Communications 2005;14:1807–1811
3. Chemistry for the Environment. Interuniversity Consortium. http://www.incaweb.org/.
4. Green & Sustainable Chemistry Network, Japan. Green & Sustainable Chemistry Network. http://www.gscn.net/aboutE/index.html
5. Anastas PT, Warner JC. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30.
6. Glaze WH. Sustainability engineering and green chemistry. Env Sci Technol 2000;34:449A
7. Winterton N. Twelve moregreen chemistry principles? Green Chem 2001;3:G73–G75
8. Seyler CC, Hellweg S, Bruder B et al. Waste-Solvent Management as an Element of Green Chemistry: A Comprehensive Study on the Swiss Chemical Industry. Ind Eng Chem Res 2006;45:7700–7709
9. Walter L. Green Solvents–Progress in science and application. Green Chem 2009;11:603
10. Christian CF and Konrad H.What is a green solvent? A comprehensive framework for the environmental assessment of solvents. Green Chem 2007;9:927–934
11. Mustafa JR, Veerababurao K, Chun-Wei K, RajuBR and Ching-Fa Y. On-water synthesis of chromeno-isoxazoles mediated by [hydroxy(tosyloxy)iodo]benzene(HTIB) Green Chem 2010;12:1090-1096
12. Akira S, Takeshi S, Shinichiro T, Mitsuru U, NobuhiroT and Tomohito K. An efficient synthesis of glyceryl ethers: catalyst-free hydrolysis of glycidyl ethers in water media. Green Chem 2009;11:753-755
13. Gaj S, Jernej I, Marko Z and Stojan S. Aerobic oxidative iodination of ketones catalysed by sodium nitrite on water or in a micelle-based aqueoussystem. Green Chem 2009;11: 1262-1267
14. Evdoxia CA, Prodromos S and Petros G. Water as the medium of choice for the 1,3-dipolar cycloaddition reactions of hydrophobic nitrones. Green Chem 2009;11:1906-1914
15. Craig MC and Phillip ES. The benzil–benzilic acid rearrangement in high-temperature water. Green Chem 2005;7:800-806
16. Asit KC, Santosh R, Kirtikumar BJ, Gurmeet K and Sunay VC. On water organic synthesis: a highly efficient and clean synthesis of 2-aryl/heteroaryl/styrylbenzothiazoles and 2-alkyl/aryl alkyl benzothiazolines. Green Chem 2007;9:1335-1340
17. Hassan ZB and Maryam EK. Highly efficient synthesis of thioesters in water. Green Chem 2009;11:1987-1991
18. Dan QX, Jian W, Shu-Ping L, Ji-Xu Z, Jia-Yi W, Xiao-Hua D and Zhen-Yuan X. Fischer indole synthesis catalyzed by novel SO3H-functionalized ionic liquids in water. Green Chem 2009;11:1239-1246
19. Roberto B, Luciano B, Francesco F, Alessandro P, Ferdinando P and Luigi V. Recent developments on the chemistry of aliphatic nitro compounds under aqueous medium. Green Chem 2007;9:823-838
20. Roger MS. Superheated water:the ultimate green solvent for separation science. Anal Bioanalchem 2006;385:419-421
21. Yanlong G and Francois J. Glycerol as a sustainable solvent for green chemistry. Green Chem 2010;12:1127-1138
22. Adi W,Christina D, Yoram S.Glycerol as a green solvent for high product yields and selectivities. Environ Chem Lett 2007;5:67–71
23. Jose IG, HctorGarcia-M, Jose AM and Pascual P. Green solvents from glycerol. Synthesis and physico-chemical properties of alkyl glycerol ethers. Green Chem 2010;12:426-434
24. Adi W and Christina D. Glycerol as an alternative green medium for carbonylcompoundreductions. Org Commun 2009;2:34-41

25. Lynnette AB, Dan H, Eric JB and Joan FB. Green processing using ionic liquids and CO2. Nature1999;399(6731):28