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Green Chemistry: Need of the Hour

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ABSTRACT

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Several reactions taught in Pharmaceutical and medicinal chemistry laboratory today are hazardous to environment and hence needs to be modified. With an impetus from Pollution control act, Green Chemistry; a relatively newer branch has originated. The article discusses basic concepts and the implementation of various green chemical reactions. Basic concepts of ionic liquids, supercritical fluids, microwave assisted organic synthesis, biocatalysts and their applications for chemical reactions are discussed. It is the need of the hour to implement this Green Chemistry in Pharmacy. This will acquaint the students with the environmental issues caused by chemical procedures. Suggested green versions of some chemical reactions should be taught in laboratory syllabus either as full experiment or as demonstration.

KEYWORDS: Green Chemistry, Ionic liquids, Microwaves, Catalyst, Undergraduate Pharmacy course

INTRODUCTION

Green Chemistry or environmentally benign chemistry is the design of chemical products and processes that eliminates the use or generation of substances hazardous to human health [1]. Green Chemistry encompasses all aspects and types of chemical processes which are associated with minimizing the negative impacts of chemicals to human health and the environment. Alternatively Green Chemistry can be defined as the design, manufacture and use of efficient, effective, safe and environment friendly chemical products and processes.

The origin of Green Chemistry [2] can be traced back to the Pollution Prevention Act, 1990 of the United States. This was followed by the establishment of Office of Pollution Prevention and Toxics (OPPT) in 1991 by the Environmental Protective Agency (EPA) of the US. The OPPT launched a research programme entitled “Alternative Synthetic Pathways for Pollution Prevention”, recognizing the fact that the processes have to be altered to reduce waste material polluting water and air. The programme received a great support from industry, academia and government in the initial stages, leading to the establishment of the Presidential Green Chemistry Challenge Awards in 1996. The first Green Chemistry and Engineering Conference was held in 1997.The constitution of Green Chemistry Institute (GCI) in 1997 helped propagate this idea and development immensely. This was followed by the Journal Green Chemistry making its debut in 1999.

The term Green Chemistry describing the arrival of environment friendly chemistry was coined by Paul Anastas [3]. It represents the assumption that chemical processes hazardous to environment can be replaced by more eco friendly processes. This goal can be achieved by use of twelve principles which are as follows.

It is better to prevent waste than to treat or clean up waste after it is formed. Synthetic methods should be designed to maximize the incorporation of all materials used in the process to the final product and whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment. Chemical methods should be designed to preserve efficacy of function while reducing toxicity. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible and, innocuous when used. 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. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable. Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical processes) should be avoided whenever

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possible. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents. 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. Analytical methods need to be further developed to allow for real time, in process monitoring and control prior to the formation of hazardous substances. 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.

Basic Concepts of Green Chemistry

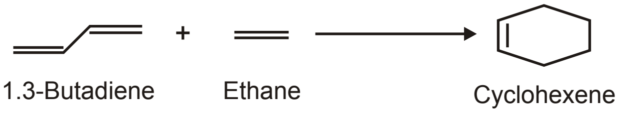
Atom Economy: The efficiency of any chemical reaction can be suitably traced by the number of atoms from the raw materials which are retained in the finished products. In simple words, if more atoms are discarded the cost of the raw materials and thus final product increases; and subsequently the waste generated also is enhanced. The synthesis of cyclohexene by Diels Alder reaction[4] is a typical example showing 100% atom economy. Increasing the atom economy is not only economically beneficial due to reduction in the waste generation; it will also assist in development of a greener[5] and thus more sustainable route.

An excellent example of application of atom economy on an industrial scale is the modified process for the synthesis of Ibuprofen[6]. Scheme 2 shows the comparison of both processes. The atom economy of the original process was 40% which by process modification increased to as much as 77% and the process also won Presidential Green Chemistry Award of 1997. Atom economy is an excellent measure of the extent of utilization of the reactants to make the product and also indicates the greenness of the process. But amount and the type of the waste produced including the solvent losses is also as important as the atom economy of the process. The waste is represented by the term Environmental factor or E-factor. It is defined as the amount of the waste produced per kg of the product. Pharmaceutical and the fine chemical industries have relatively higher E-factors reflecting the higher use of stoichiometric reagents and multistep reactions. This further highlights the need for green Chemistry for the pharmaceutical and the fine chemical industry.

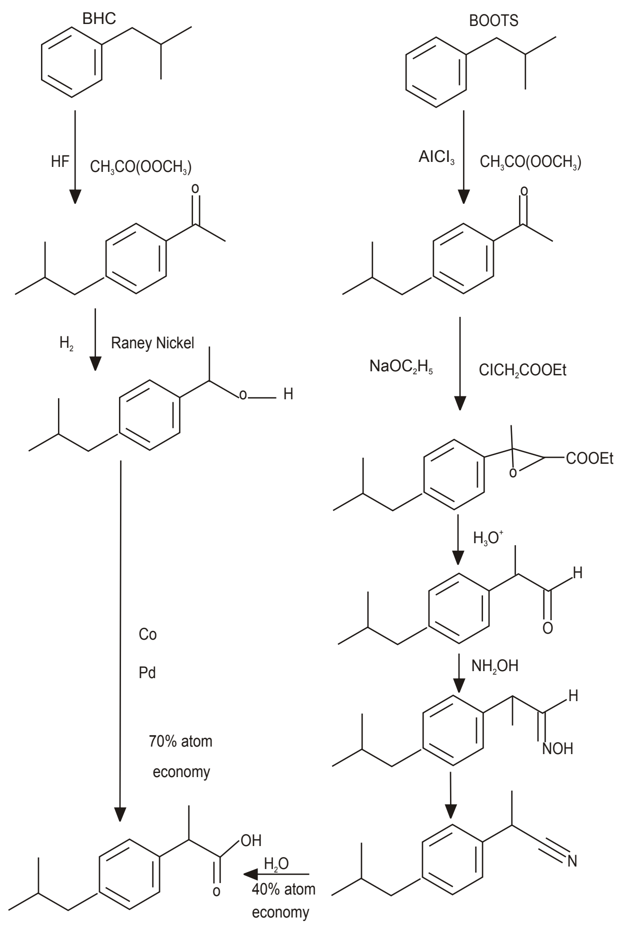
Implementation of Green Chemistry

The implementation of Green Chemistry should involve reconsideration of the economic viability of the process by taking into account the environmental hazards associated with the process. This may require a review of the reagents including the catalysts, solvents and byproducts which are the three important components of any chemical reaction apart from the desired product.

Scheme 1: Diels Alder reaction



Scheme 2: Green Method for Ibuprofen



Catalysis

The heterogenization of catalysts (and reagents) so that they can easily be separated (and reused) at the end of a process, is a logical and versatile approach to simplifying the process, removing the need for an aqueous quench (or other destructive separation steps) and reducing the demand for raw materials[7]. It is possible to prepare heterogeneous analogs of most, if not all, commonly used soluble and homogeneous catalysts. Heterogenization through chemical surface modification is most conveniently carried out using a silica (or silica-rich) backbone[8].

Many transition metals are widely used in the industrial processes. However most of these processes are homogenous and recovery of the metal catalyst at the end of the process is a major hurdle. This can be overcome by the use of catalyst supports including natural materials such as silica, alumina and synthetic materials such as polystyrene and polyacrylates. Palladium, a highly versatile metal for organic synthesis, can be effectively immobilized on chemically modified mesoporous materials that provide the right ligand geometry. Such materials can be very useful in reactions including the important carbon–carbon bond forming Heck and Suzuki reactions [9].

Solid acid catalysts of different kinds have gained considerable importance in the synthesis of fine chemicals due to factors including the use of milder reaction conditions, shorter workup times, favorable selectivity of the desired product, cheap materials of construction, reuse of catalysts, their ecofriendliness, and elimination of hazardous conditions or processes. Besides, the corrosion problem associated with homogeneous catalysis is also avoided due to the binding of acidity within the porous matrix of the solid catalysts. The examples of these types of catalysts include clays and pillared clays, zeolites and zeotypes, ion exchange resins, supported heteropolyacids (HPA), and other modified metal oxides such as sulfated zirconia.

Natural and Modified Clays

Clays were the first solid acid catalysts used in organic synthesis. However, due to their wide variety they lack perfect reproducibility in yields with different samples. Otherwise, they have considerable potential as environmental friendly solid acid catalysts. Some of the types of clays frequently used are Bentonite, Montmorillonite K10 and Montmorillonite-KSF[10]. Their anhydrous forms have a general structure as shown in Fig. 1a, where M = Si or Al. On hydration, some divalent oxide linkages are replaced by M-OH bonds in the matrix. The protons released on ionization of these O-H bonds are the source of Bronsted acidity (Fig. 1b).

Zeolites

Zeolites[11] are a family of minerals called tectosilicates. They consist of AlO_4^{-5} and SiO_4^{-4} molecules bound by oxygen atoms. Zeolites contain microporous channels[12] in which molecules of appropriate size can diffuse, so as to allow the reaction to take place at lower temperatures and pressures resulting in lower operational costs. As seen in the structure, the silicon site is neutral whereas the aluminium site is negatively charged thus requiring positively charged counter ion such as Na^+ to be associated with it. These Na^+ counter ions can be exchanged for protons so as to make Zeolites acidic. This indicates that the ratio of Si/Al ranges from 1 to infinity; in the Zeolites determines the acidity, polarity and the exchange capacity of the Zeolites. Since the protons are placed inside the pores, the pore size determines the size and the shape of the molecules which can enter in and undergo a reaction. Water being a small molecule, the Zeolite pores can absorb and hold a large quantity of water. Thus they form excellent drying agents. A major application of zeolites pertinent to green chemistry is their use as acid catalysts in the reactons such as alkylation[13], acylation[14], electrophilic aromatic substitution[15], and synthesis of dienes[16]. Scheme 3 shows some of the reactions catalyzed by zeolites.

Fig. 1a

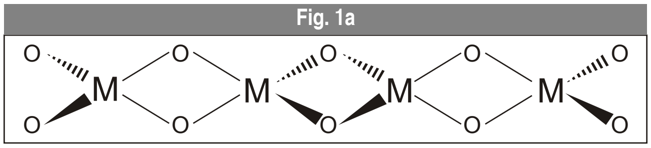
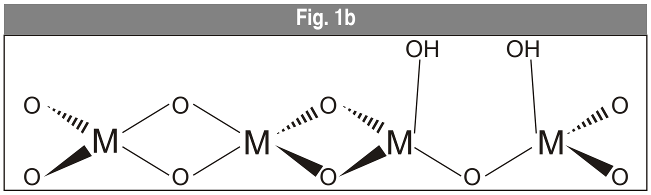


Fig. 1b



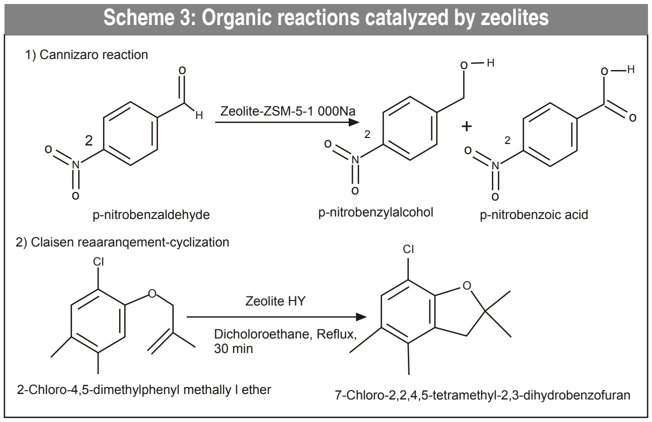
Synthetic Resins

Resins are supports made of synthetic polymers like polystyrene or co-polymers of polystyrene and divinylbenzene. They are used very often in the form of beads[17] of various sizes. The beads may be micro-porous (pore size < 20 Å), meso-porous (pore size 20–100 Å) or macro-porous (pore size > 100 Å) or non-porous. The diameters of the of the spherical beads decide the surface area. If the bead is also porous then this contributes to enhancement of surface area. The amount of cross-linking of the polymer decides the mechanical strength of the bead and other properties such as the extent of solvation possible in the bead. If the extent of cross-linking of the polymer is less, then the bead is soft. If the bead has polar groups grafted on it, then it will have a tendency to swell as polar solvent molecules will penetrate its pores. When the bead swells, more active sites are exposed and that is good for the chemical reaction. The active sites are acidic sites located either on the surface or in the pore or both. Scheme 4 shows some of the reactions carried out using synthetic resins.

Biocatalysis

Biocatalysis involves the use of different enzymes as

Scheme 3: Organic reactions catalyzed by zeolites



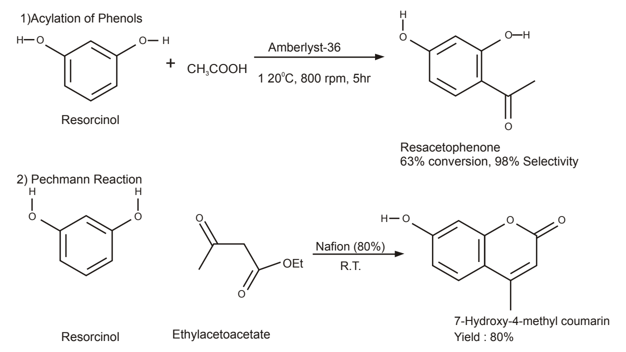
catalysts. These include L-lysine –aminotransferase, porcine lipases, formate dehydrogenase etc. The use of the biocatalytic procedures can also minimize the problems of isomerization, epimerization, recemization etc, thereby improving the atom economy of the reactions. These reactions can also be carried out at ambient temperatures and at atmospheric pressure[18] thereby avoiding the use of extreme conditions which results in problems such as degradation. Avoiding heating and the use of nonpolar solvents makes these reactions more eco-friendly. Over expression of the enzymes[19] can make the biocatalytic processes economically viable. The economic efficiency can also be increased by use of immobilized systems which can be used for many cycles. The random and site-directed mutagenesis has enabled[20] the production of thermostable and pH-stable enzymes. The reduction in the synthetic steps, improved usage of raw materials minimizing energy-driven and unfriendly operations as well as the regioselectivity and stereoselectivity offered by the biocatalysts[21] are some of the major advantages of use of Biocatalysts. Biocatalysis has been effectively used in the synthesis of some of the drug substances such as Simvastatin[22].

Solvents

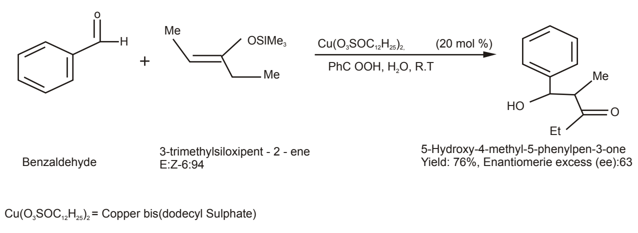
The use of Green Chemistry has succeeded to the extent of synthesis of compounds without utilizing any solvent or even water. The primary benefits include high yields, faster reaction, eco friendliness and lower cost. However the drawbacks include increased temperature or energy consumption, requirement of different equipment and scaling up difficulties on a larger scale. The reactor too has to be designed with care. This has led to change in the process by adopting softer options such as change of solvent from water immiscible to water miscible and more preferably use of water as a solvent. This is illustrated in the following example as shown in Scheme 5.

Newer and safer solvents are being discovered which can replace the water immiscible solvents used previously. Ionic liquids present one such newer solvent option.

Scheme 4: Organic reactions using resins



Scheme 5: Asymmetric Aldol reaction using water as solvent



Ionic Liquids

An ionic liquid[23] is a salt consisting of atleast one organic ion and is liquid at room temperature. The delocalization of charge on atleast one ion along with a low symmetry of atleast one ion prevents the formation of a stable crystal lattice. The cation part includes cations such as imidazolium, pyridinium, quaternary ammonium and quaternary phosphonium whereas the anions are chloride, tetrafluoroborate, hexafluorophosphate etc[24]. Most of the ionic liquids have negligible vapour pressure and minimum flammability. This makes the ionic liquids safe as compared to the conventional solvents for organic synthesis. They also exhibit high thermal stability and a wide temperature range. Additionally, the physical and the chemical properties of the ionic liquids can be adjusted by changing the combination of the cation and the anion. Thus acidic, basic, hydrophilic or even hydrophobic ionic liquids can be synthesized.

A variety of chemical reactions are reported using ionic liquids as solvents. These include Friedel-Craft's acylation[25], Aldol condensation[26], Heck reaction[27].

Supercritical Fluid Extraction

Supercritical fluids are produced by heating a gas above its critical temperature or compressing a liquid below its critical pressure. Such fluids possess the gaseous property of penetration as well as the liquid property of dissolving materials. Additionally they can change density to a great extent in a continuous manner. Due to these properties, the supercritical fluids become efficient extraction solvents with high mass transfer characteristics[28]. The volatile substance easily partitions into supercritical phase during extraction. The extracted component can then be separated from the supercritical fluid by means of change of temperature and/or pressure and supercritical fluid can be recycled. Use of supercritical CO_2 as a greener solvent is being explored. The primary benefits include good solvent properties, useful in oxidation reactions and no residue generation. The drawbacks are high pressure requirements and low reaction rates.

Chemical reactions in supercritical CO_2 have become an area of growing interest[29] due to the associated advantages. Enantioselective hydrogenation of prochiral enamines is efficiently catalysed by iridium complex in supercritical CO_2 as solvent[30]. Asymmetric catalytic hydrogenations have also been reported using supercritical CO_2 as solvent[31]. The reactions are as shown in the Scheme 6.

Efforts are also going on to develop reactions using supercritical water[32]. Supercritical water is water above its critical point i.e. 374 ^{0}C and 218 atm. Properties of water change above critical point with lower dielectric constant and diminished Hydrogen bonds. As a result, this water behaves like organic solvents and many substances have higher solubilities in either supercritical or near critical water. This gives an advantage of single phase reaction and increased reaction rates.

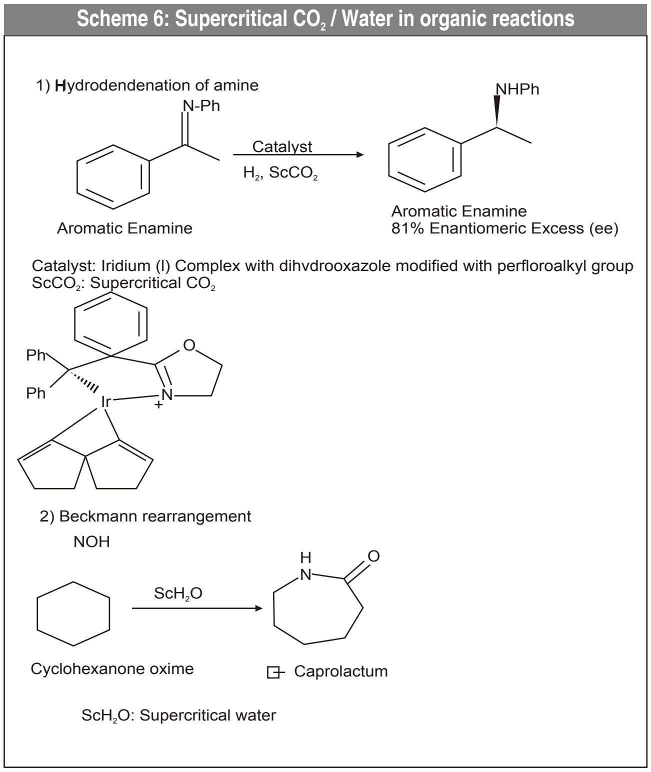
Microwave Assisted Organic Synthesis

In the electromagnetic spectrum, microwaves are associated with a large wavelength. Microwaves are a form of non-ionising radiation and are manifested as heat when they interact with the medium. The polar molecules can selectively absorb microwave energy whereas the nonpolar molecules are inert. Microwave assisted organic reactions are of great interest because of its advantages.

Current pharmacy undergraduate syllabus:

Pharmaceutical and medicinal chemistry laboratory syllabus taught in Indian pharmacy colleges at undergraduate level aims at synthesizing various reaction intermediates or the drug intermediates. Generally, experiments related to acetylation, nitration, bromination, sulphonation, aldol condensation etc. are the part of the syllabus. The procedures used are however same as the ones taught fifty years ago and involve use of eco-unfriendly reagents and chemicals. Acylation, nitration and sulphonation in particular generate a lot of spent acid which causes damage to the sinks and the drain pipes in the chemistry laboratory. The authors therefore feel a need to replace some of these experiments with greener alternatives so as to acquaint the pharmacy students with the basic concepts of green chemistry. The monograph[33] on Green Chemistry Laboratory Experiments, edited and published by Green Chemistry Task Force Committee, DST has listed some syntheses which are either modified or altered from the original procedures so as to introduce green component. Synthesis of acetanilide by green procedure involves use of acetic acid and zinc dust as catalyst instead of acetic anhydride and pyridine. Cost comparison of both methods revealed that both are equivalent methods and can be easily implemented at the undergraduate level in pharmacy. Bromination of the aromatic nucleus is another reaction in the chemistry laboratory syllabus. Synthesis of p-bromoacetanilide is traditionally achieved very easily using bromine in acetic acid. The green modifications reported in the literature use various alternatives such as $HBr\text{-}H_2O_2$ or NBS[34], Dioxane dibromide[35] and KBr with Cerric ammonium nitrate. All these methods are costlier than the traditional method. Instead addition of bromine across the double bond using NBS, which is a greener method, can be included in the syllabus without the cost burden.

Scheme 6: Supercritical CO_2 / Water in organic reactions



Nitration of the aromatic nucleus is another reaction which results in the generation of a lot of spent acid. The alternate methods reported in the literature for the same include use of sodium nitrate and an inorganic acidic salt in presence of SiO_2[36], $NaNO_2$ and $KHSO_4$ in presence of silica[37] etc. Like bromination, the cost of the modified procedure is much more than the traditional method. Recycling of the catalyst should however be considered as an attractive option. Sulphonation reactions using Silica-sulphuric acid are reported[38] in the literature as greener version of the original procedure involving excess of conc. sulphuric acid. A greener procedure for the synthesis of resacetophenone is reported[39] using Amberlyst-36. Thought must be given to the use of more supported catalysts in the synthetic procedures. Many of these procedures need standardization before being given in the undergraduate laboratory either as a full experiment or atleast as a demonstration experiment if the cost of the full experiment for 60 students is prohibitive.

CONCLUSION

Green chemistry is the contribution of the chemists towards sustainable development. Although it is a relatively newer branch which originated with an impetus from the pollution control act, it has come a long way with many new products, processes and technologies such as ionic liquids, microwave assisted reactions, newer catalysts and newer pathways of old reactions. The time calls for the implementation of Green Chemistry at the undergraduate level in the pharmacy course so as to make the students aware of the environmental issues and the efforts going on worldwide to address these issues. It is hoped that after some years, Green Chemistry will be the only way in which Chemistry will be taught, practiced and implemented.

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REFERENCES

1. Collins T, Towards Sustainable Chemistry. Science 2001; 291: 5501:48-49.
2. Sanghi R, Better Living Through Sustainable Green Chemistry. Current Science 2000; 79: 1662-1665.
3. Anastas PT, Warner C. Green Chemistry: Theory and Practice; Oxford University Press: New York , 1998;30.
4. Trost BM, A Search for Synthetic Efficiency. Science, 1991; 254: 1471-1477.
5. Sheldon RA, Organic Synthesis – Past, Present and Future. Chem. & Ind., 1992**;** 12: 903.
6. Cann MC, Connely ME, Real world cases in Green Chemistry. American Chemical Society: Washington, 2000.
7. Clark JH and Rhodes CN, Introduction: Catalyst and catalysis, Royal Society of Chemistry, RSC Clean Technology Monographs: Clean Synthesis Using Porous Inorganic Solid catalysts, Thomas Graham House,Cambridge, 2000, 3-4.
8. Price PM, Clark JH and Macquarrie DH, Modified silicas for clean technologies. J. Chem. Soc. Dalton Trans*,* 2000; 101-110.
9. Clark JH, Macquarrie DH and Mubofu EB, Prepration of novel silica-supported palladium catalyst and its use on the Heck reaction. Green Chem*.,* 2000; 2: 53-55.
10. Wilson K and Clark JH, Solid acids and their use as environmentally friendly catalysts in organic synthesis. Pure Appl. Chem., 2000**;** 72 : 1313-1319.
11. Marcus BK and Cormier WE, Going Green with Zeolites. Chemical Engineering Progress*,* 1999; 6: 35-38
12. Dyer A, Introduction to Zeolite molecular sieves, 1st Ed. John Wiley & Sons Ltd, Chemistry of Zeolites and Related Porous Materials: Synthesis and structures. Chichester, New York, 1988,65.
13. Tanabe K and Holderich WF, Industrial application of solid acid-base catalyst. Appl. Catal. A General, 1999; 181: 399-434.
14. Vogt A. and Pfenninger A., Ueticon AG, Process for preparation of aromatic ketones, European Patent 0701987A1, 1996 Oct 25.
15. Narender N, Krishna Mohan KVV, Vinod Reddy R, Srinivasu P., Kulkarni SJ., and Raghavan KV, Liquid phase bromination of phenols using potassium bromide and hydrogen peroxide over zeolites. J. Mol. Catal. A: Chemical, 2003, 192: 73-77.
16. Kuhn P, Pale P, Sommer J and Louis B, Probing Cu-USY zeolite reactivity: design of a green catalyst for the synthesis of diynes. J. Phys. Chem. C, 2009; 113 : 2903–2910.
17. NIIR Board of Consultants & Engineers, Acrylamide resins, NIIR Board of Consultants & Engineers, Synthetic ResinsTechnology Handbook, Delhi, Asia Pacific Business Press Inc, 2010, 50-55.
18. Zak A, Industrial biocatalysis**.** Curr. Opin. Chem. Biol., 2001; 5: 130–136.
19. Patel RN, Microbial/Enzymatic Synthesis of Chiral Intermediates for Pharmaceuticals. Enz. Microb. Tech., 2002; 31: 804-826.
20. Mahmoudian M, Biocatalytic Production of Chiral Pharmaceutical Intermediates. Biocatal. Biotrans., 2000; 18: 105-116.
21. Tao J and Xu J., Biocatalysis in the development of green pharmaceutical Processes. Curr. Opin. Chem. Biol., 2009; 13: 43-50.
22. Xinkai Xie, Yi Tang., Efficient synthesis of Simvastatin by Use of Whole-Cell Biocatalysis. App. Environ. Microbiol.*,* 2007; 73: 7: 2054-2060.
23. Wasserscheidt P and Weldon T, Ionic Liquids in Synthesis, John Wiley & Sons Ltd., Wiley-VCH, Properties of ionic liquid solvents for catalysis, New York, 2003, 174-332.
24. Earle MJ and Seddon KR, Ionic liquids: Green solvents for the future. Pure Appl. Chem*.,* 2000; 72 : 1391-1398.
25. Ross J and Xiao J, Friedel-Crafts acylation reactions using metal triflates in ionic Liquids. Green Chem, 2002; 4: 129-133.

26. Mehnert CP, Dispenziere NC and Cook RA, Preparation of C_{8-} aldehyde via aldol condensation reactions in ionic liquid media. Chem.Commun., 2002, 1610-1611.

27. Xu L, Chen W and Xiao J, Heck Reaction in Ionic Liquids and the in Situ Identification of *N*-Heterocyclic Carbene Complexes of Palladium. Organometallic*s*, 2000; 19: 1123-1127.

28. McHugh MA and Krukonis VL, Supercritical Fluid Extraction: Principles and Practice, Butterworth publishers, Stoneham MA, 1986, 23-76.

29. Kendall JL, Kenlasas DA, Young JL et. al., Polymerizations in supercritical Carbon dioxide. Chem. Rev, 1999**;** 99: 543-563

30. Kainz S, Brinkmann A, Leitner W, Pfaltzs A et. al., Iridium-Catalyzed Enantioselective Hydrogenation of Imines in Supercritical Carbon Dioxide. J. Am. Chem. Soc.,1999; 121 (27): 6421-6429.

31. Burk MJ, Feny S, Gross MF and Tumas W., Assymetric catalytic hydrogenation reations in Supercritical Carbon Dioxide., J. Am. Chem. Soc., 1995; 117: 8277-.8278.

32. Savage PE, Organic chemical reactions in supercritical water. Chem. Rev., 1999; 99: 603-621.

33. Monograph on Green Chemistry Laboratory Experiments, edited and published by Green Chemistry Task Force Committee, DST, 1-79.

34. Ajda P, Stojan S, Marko Z., Environmentally benign electrophilic and radical bromination 'on water': H_2O_2-HBr system versus N-bromosuccinimide. Tetrahedron, 2009; 65: 4429-4439.

35. Chaudhuri S, Roy S, Saha M and Bhar S, Regioselective Aromatic Electrophilic Bromination with Dioxane Dibromide Under Solvent-Free Conditions. Synth. Commun,, 2007; 37: 579-583

36. Zolfigol M, Ghaemi E, Madrakian E., Nitration Of Phenols Under Mild And Heterogeneous Conditions, Molecule*s*, 2001; 6: 614-620.

37. Heravi M, Hossein A, Baghernejad B, Facile, Regioselective and Green Synthesis of Ortho-nitrophenoles using $NaNO_2$, $KHSO_4$. J. Chin. Chem. Soc., 2007; 54: 767- 770

38. Hajipour A, Mirjalli BB, Zarei A et.al., A novel method for sulphonation of aromatic rings with silica sulphuric acid. Tetrahedron Lett., 2004; 45: 6607-6609

39. Yadav GD and Joshi AV, A Green Route for the Acylation of Resorcinol with Acetic Acid. Clean Techn Environ Policy, 2002; 4 : 157–164.

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