Vinod K. Tiwari · Abhijeet Kumar · Sanchayita Rajkhowa · Garima Tripathi · Anil Kumar Singh

Green Chemistry

Introduction, Application and Scope

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Foreword

The design of chemical reaction that reduces or eliminates the generation of hazardous substances demands the adoption of innovative and revolutionary green chemistry approach. The practice of green chemistry methodology in organic synthesis has certainly led to significant environmental benefits and has strengthened economic innovations. This book on *Green Chemistry—Introduction, Application, and Scope* provides a very interesting overview of the fundamental principles of green chemistry with their notable perspectives. This book would be useful to UG/PG students, academicians, researchers as well as chemists working in chemical industries because of the absence of any worthwhile book on this subject.

This book by Vinod K. Tiwari and coworkers begins with the introduction of green chemistry and its twelve principles coined by Paul Anastas and John Warner and moves forward with the exhaustive discussion on the important metrics of the green chemistry such as *E-factor, atom economy* to evaluate the greenness of a chemical process. Other important discussions in this chapter include principles of *inherently safer design* (ISD) and barriers in the direction of implementation of different green chemistry principles.

Various environmentally benign alternatives such as microwave, ultrasound, visible light, ball milling, *mechanocatalysis*, and electro-organic approaches to conventional C–C and C–X (X = heteroatom) bond-forming organic transformations have been elaborated in Chap. 2. Following this, the chapter deals with the introduction of greener solvents, i.e., water, ionic liquid, supercritical CO_2, switchable solvent, fluorous biphasic system, polyethylene glycol as well as using solvents derived from biobased feedstock such as vegetable oil. The *growing impact of ionic liquids in synthesis* mainly in heterocyclic synthesis and application in carbohydrate chemistry is elaborated in Chaps. 4 and 5, respectively.

A book on green chemistry today would not have been justified if this does not include catalytic reaction. The author has rightly included the application of various catalytic transformations such as oxidation, reduction, carbon–carbon, and carbon–heteroatom bond-forming reactions in this book. Emerging concept of organocatalysis, types of catalysts, and application in asymmetric synthesis is appropriately highlighted in Chap. 7.

Furthermore, the significant importance of enzyme-mediated transformation and notable applications of green chemistry in some real-world cases, e.g., the synthesis of pharmaceuticals, API, polymers, etc., have been discussed in the last two chapters. Also, the impact of employing green method and its comparison with the conventional approaches are highlighted in this book.

All the chapters provide relevant references to original papers, reviews, and some specialized books on the topic. The present book on green chemistry presents all essential and important concepts with clarity and provides up-to-date information on almost all aspects of green chemistry for UG/PG and doctoral students of chemistry. It becomes apparent that this book has basic objective of bringing the subject clarity, without compromising on most essential concepts, but avoiding less-frequently encountered components. This book should be successful in developing "fondness" for green chemistry among scientific community. This book should be useful to the chemistry academic faculty and industrial chemists equally. It is a much-welcome addition to repertoire of practicing researchers and academics. Academic and research background of the authors justify their book on the green chemistry.

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Preface

In the present scenario, the development of a greener and environment-friendly approach to minimize and/or avoid the generation of waste material during the synthesis of a vast range of compounds with diverse applications has been considered to be an important area of investigation. Especially after realizing the short- and long-term adverse effect of conventional synthetic approaches on *safety, health, and environment (SHE)*, the attention of research community took a paradigm shift in achieving the synthesis from conventional to efficient synthetic methods with utmost care of lives and environment, the essentials of sustainable development. Therefore, we are presenting this book with the title *Green Chemistry—Introduction, Application, and Scope* for a better understanding of green chemistry fundamentals with notable perspectives, particularly about the various emerging synthetic approaches under environmentally benign conditions that would prove to be an important and useful piece of study material to the readers.

This book has been divided into nine chapters that cover the topics mentioned in the *green chemistry* course of most of the academic institutions across the world. Thus, it would offer the students of UG/PG as well as researchers from both academic institutions and industry a complete understanding of the different emerging topics using the latest notable examples. Chapter 1 titled "*Green Chemistry: Introduction to the Basic Principles*" provides the fundamental information about the green chemistry and its twelve principles jointly coined by Paul Anastas and John Warner. These principles act as a guiding tool for the development of an environmentally benign process. This chapter covers the exhaustive discussion about some of the important metrics like *E-factor, atom economy*, etc., to evaluate the greenness of a chemical process. Further, different ways to prevent and minimize the generation of waste material in a chemical process have also been discussed with the help of suitable examples. Other important topics such as the principle of *inherently safer design* (ISD) and barriers in the direction of implementation of different green chemistry principles have also been covered. In Chap. 2 titled "*Energy-Efficient Process in Organic Synthesis*," various environmentally benign alternatives to the conventional heating methods adopted to achieve different types of organic transformations, for example, C–C bond-forming reactions, heterocyclic synthesis, etc., have

been discussed. We have briefly covered the applications of microwave, ultrasound, visible light, and electro-organic method in achieving different types of organic transformations. Also, the application of ball milling method which is also emerging as an energy-efficient way in organic synthesis, in particular, for the *direct and indirect mechanocatalysis*, has been highlighted with the latest examples. In Chap. 3 titled "*Green Solvents: Application in Organic Synthesis*," discussion is about the application of different types of greener alternatives to conventional organic solvents in organic synthesis have been included. Organic reactions explored using water, ionic liquid, supercritical CO_2, switchable solvent, fluorous biphasic system, polyethylene glycol as well as using solvents derived from biobased feedstock such as vegetable oil have been discussed elaborately. In Chap. 4 titled "*Growing Impact of Ionic Liquids in Heterocyclic Chemistry*," the importance of ionic liquids as another greener alternative to conventional solvents and their application as a solvent in organic synthesis particularly for the synthesis of heterocyclic rings have been covered thoroughly. Chapter 5 titled "*Growing Impact of Ionic Liquids in Carbohydrate Chemistry*," highlights the applications of ionic liquids in carbohydrate chemistry in great detail. Chapter 6 titled "*Catalysis: Application and Scope in Organic Synthesis*" covers the vast discussion on different types of catalysis and their applications in various types of organic transformations including oxidation, reduction, carbon–carbon, and carbon–heteroatom bond formations. *Organocatalysis* is now emerged as a valuable area of research and beyond doubt a truly greener alternative to the transition metal-based catalysis. Considering its immense importance in asymmetric organic synthesis, this year's Nobel Prize in Chemistry has been awarded to Prof. Benjamin List and Prof. David W. C. MacMillan, and thus, a separate Chap. 7 titled "*Organocatalysis: A Versatile Tool for Asymmetric Green Organic Syntheses*" has been presented. This chapter is dedicated to organocatalysis with brief discussions related to different types of organocatalysis and their applications in various asymmetric transformations. Furthermore, the significant importance of enzyme-mediated transformation is considered and included in Chap. 8 titled "*Enzymes in Organic Synthesis*." At the last, Chap. 9 titled "*Application of Green Chemistry: Examples of Real-World Cases*" focuses on the notable application of environmentally benign approaches in some real-world cases such as for the synthesis of pharmaceuticals, APIs, polymers, etc. In addition, the impact of employing green method and their comparison with the conventional approaches have also been highlighted in this book. Overall, this book presented a detailed scope of green chemistry to a wide range of readers and investigators.

We would like to express our heartfelt thanks and deep sense of appreciation to Prof. Ganesh Pandey, Distinguished Professor at the Department of Chemistry, Institute of Science, Banaras Hindu University, for his consistent support and moreover for writing the venerated foreword to the Springer book. The authors thank Prof. Richard R. Schmidt (Universitat Konstanz), Prof. Xi Chen (University of California-Davis), Prof. R. P. Tripathi (CSIR-Central Drug Research Institute, Lucknow), Prof. Pradeep K. Tripathi (CSIR-National Chemical Laboratory, Pune), and Prof. D. Basavaiah (University of Hyderabad) for their useful suggestions during the writing of this book. We also thank both Dr. Anand K. Agrahari (UC-Davis and Mr. Mangal Singh

Yadav (BHU, Varanasi) for their great care to the reference section. The authors are highly thankful to the "*Springer Nature*" who implicit the importance of the present book and considered the publishing with great interest. Last but not least, we express our special thanks to the entire editorial team associated with Springer Nature, in particular Ms. Priya Vyas, Associate Editor—Applied Sciences and Engineering, Ms. Sharmila Mary Panner Selvam, Project Coordinator, and Mr. Madanagopal Deenadayalan, Project Manager, who extended their support in publishing this theme with the high standard of publication maintained in bringing out this book on *Green Chemistry—Introduction, Application, and Scope* with Springer Nature.

Varanasi, India — Vinod K. Tiwari
Motihari, India — Abhijeet Kumar
Guwahati, India — Sanchayita Rajkhowa
Bhagalpur, India — Garima Tripathi
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Prof. Vinod K. Tiwari is currently as Professor of Organic Chemistry at the Department of Chemistry, Banaras Hindu University, India. He earned his M.Sc. degree from BHU (in 1998) and doctoral degree from CSIR-Central Drug Research Institute, Lucknow (Mentor: Dr. R. P. Tripathi), in 2004. He has postdoctoral experience at University of Florida, USA (Mentor: Prof. Alan R. Katritzky), University of California-Davis, USA (Mentor: Prof. Xi Chen), and Universitat Konstanz, Germany (Mentor: Prof. Richard R. Schmidt). He was offered the post of Lecturer at Bundelkhand University (2004–2005) before being appointed in BHU. With more than 21 years of research and 18 years of teaching experience, he has supervised 13 Ph.D. theses, 21 M.S. dissertations and contributed significantly to 156 peer-reviewed publications (Citations: 6400, h-index: 39, i_{10} : 101) in addition to several patents and invited book chapters of high repute. He completed 7 major research projects and delivered 201 invited lectures in India and abroad. His teaching interest covers almost all branch of organic chemistry, however current research focus on Synthetic Carbohydrate Chemistry and novel synthetic methodology. He holds Hony. Secretary, ACCT(I) and has wide editorial experience. His research has received many prestigious awards, notably Young Scientist Award (Dr. D. S. Bhakuni Award in 2004, ICRABTS-2005, UP-CST in 2010, 1st H. C. Srivastava Award-2012 and CRSI-2012); Most Cited Paper Award (2006, 2013); Dr. Arvind Kumar Memorial Award, ICC (2010); Prof. R. C. Shah Memorial Award, ISCA (2011); Dr. Ghanshyam Srivastava Memorial award, ICS (2012), Prof. A. S. R. Anjaneyulu 60th Birthday Commemoration Award, ICS (2013); 1st Prof. N. Roy Award for Excellence on Synthetic Carbohydrate Chemistry-2015; Dr. S. S. Despande National Award for High Impact Contribution in Chemistry-2016; ACCT(I)-Excellence in Carbohydrate Research Award-2019; BHU Most Productive Researcher Award-2019, listed in top 2% scientist, and CRSI Bronze Medal for the year 2021.

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Abbreviation

[admIm]Br	1-Allyl-2,3-dimethylimidazolium bromide
[amIm]Cl	1-Allyl-3-methylimidazolium chloride
[bdmIm]Cl	1-Butyl-2,3-dimethylimidazolium chloride
[bmIm][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
[bmim]$MeSO_4$	1-Butyl-3-methylimidazolium methanesulfate
[bmim]PO_4	1-Butyl-3-methylimidazolium phosphate
[bmpy]Cl	3-Methyl-*N*-butylpyridinium chloride
[C1mIm][Cl]	1,3-Dimethylimidazolium chloride
[C1OCH_2mIm] $N(CN)_2$]	1-Methoxymethyl-3-methylimidazolium dicyanamide
[C4-2,3-m2Im][Cl]	1-(1-Butyl)-2,3-dimethylimidazolium chloride
[C4mIm][BF_4]	1-(1-Butyl)-3-methylimidazolium tetrafluoroborate
[C4Py][PF_6]	*N*-(1-Butyl)pyridinium hexafluorophosphate
[emIm][ba]	1-Ethyl-3-methylimidazolium benzoate
[emim]BF_4	1-Ethyl-3-methylimidazolium tetrafluoroborate
[emIm]Cl	1-Ethyl-3-methylimidazolium chloride
[hmIm][ba]	1-Hexyl-3-methylimidazolium benzoate
[mIm]	1-Methylimidazolium
[mmIm]	1-Methyl-3-methylimidazolium
[moemim][OMs]	1-Methoxyethyl-3-methylimidazolium methanesulfonate
$[Ms_2N]^-$	Bis(methanesulfonyl) amide
$[N(TFMS)_2]^-$	Bis(trifluoromethanesulfonyl)imide
$[NMM]^+[HSO_4]^-$	*N*-Methylmorpholinium hydrogen sulfate
$[NTf_2]^-$	Bis(trifluoromethylsulfonyl)amide
$[OTf]^-$	Trifluoromethylsulfonate
[R(Rf)taz][Y]	1,4-Alkyl(polyfluoroalkyl)-1,2,4-triazolium ionic liquids
[taz][X]	1-Alkyl-4-polyfluoroalkyl-1,2,4-triazolium halide
3-DDM	Three-dimensional dealuminated mordenite
6-APA	6-aminopenicillanic acid
Ac	Acetyl

ACE	Angiotensin-converting enzyme
ADM	Archer Daniels Midland
ADME	Absorption, Distribution, Metabolism, and Excretion
API	Active pharmaceutical ingredient
BHT	Butylated hydroxytoluene
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
BtRC	Benzotriazole ring cleavage
Bz	Benzoyl
CAL-B	*Candida antarctica* lipase-B
cEF	Complete E-factor
CFCs	Chlorofluorocarbons
COD	1,5-Cyclooctadiene
CuAAC	Cu(I)-catalyzed azide–alkyne cycloaddition
DABCO	Diazabicyclo[2.2.2]octane
DAHP	3-Deoxy-D-arabino-heptulosonic acid-7-phosphate
dba	dibenzylideneacetone
Dca/$[N(CN)_2]^-$	Dicyanamide anion
DCM	Dichloromethane
DCOI	4,5-dichloro-2-*n*-octyl-4-isothiazolin-3-one
DDT	Dichlorodiphenyltrichloroethane
de	Diastereomeric excess
DFT	Density functional theory
D-Gal	D-galactose
D-GalNAc	*N*-acetyl-D-glactosamine
D-Glu	D-Glucose
DHQ	3-Dehydroquinic acid
DHS	Dehydroshikimic acid
DIB	Diacetoxyiodobenzene
Diglyme	Diethylene glycol dimethyl ether
DIOP	2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	(2-methoxyphenyl)-[2-[(2-methoxyphenyl)-phenylphosphanyl]ethyl]-phenylphosphane
DIPEA	*N,N*-Diisopropylethylamine
DMA	*N,N*-dimethylacetamide
D-Man	D-Mannose
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
DMM	Dimethoxymethane
DMSO	Dimethylsulfoxide
DPAT	Diphenylammonium triflate
dr	Diastereomeric ratio
DuPHOS	1,2-bis(phospholano)benzene
E4P	Erythrose 4-phosphate

EBHP	Ethylbenzene hydroperoxide
ee	Enantiomeric excess
EPA	US Environmental Protection Agency
FC	Friedel–Crafts
FDA	US Food and Drug Administration
GC	Gas chromatography
GCI	Green Chemistry Institute
GC-MS	Gas chromatographic-mass spectrometry
HCFCs	Hydrochlorofluorocarbon
HCs	Hydrocarbons
HMG	Hydroxymethylfurfural
H-MOR	H-Mordenite
HOMO	Highest occupied molecular orbital
HPB	Canadian health protection board
HPLC	High-performance liquid chromatography
ILs	Ionic liquids
IR	Infrared
ISD	Inherently safer design
ISP	Inherently safer process
LDL	Low-density lipid
LMCT	Ligand to metal charge transfer
LPG	Liquified petroleum gas
LUMO	Lowest unoccupied molecular orbital
MAEC	Maximum allowable environmental concentration
MCF	Mesocellular foam
*m*CPBA	*m*-Chloroperbenzoic acid
MIC	Methyl isocyanate
MLCT	Metal to ligand charge transfer
MSDS	Material safety data sheet
MUFA	Mono-unsaturated fatty acid
NaAsc	Sodium ascorbate
NBD	Norborna-2,5-dien
NIS	*N*-Iodo succinimide
NMO	4-methylmorpholine-N-oxide
NMR	Nuclear magnetic resonance
NSAID	Nonsteroidal antiinflammatory drug
NsNIPh	[(nosylimino)iodo]benzene
P_c	Critical pressure
PCA	Protocatechuic acid
PEG	Polyethylene glycol
PET	Poly(ethyleneterephthalate)
PLA	Polylactic acid
PMB	*p*-Methoxybenzyl
PMHS	polymethylhydrosiloxane
p-TSA	*Para*-Toluenesulfonic acid

PUFA	Polyunsaturated fatty acid
RERCs	Perchloroethylenes
RTILs	Room-temperature ionic liquids
RuAAC	Ruthenium-catalyzed azide–alkyne cycloaddition
SEC	Size exclusion chromatography
sEF	Simple E-factor
SFA	Saturated fatty acid
SHE	Safety, health, and environment
sn	Stereospecific numbering
SOMO	Singly occupied molecular orbital
SPS	Switchable polarity solvents
TAG	Triacylglycerol
TBAHS	Tetrabutylammonium hydrogensulfate
TBDMSCl	*Tert*-butyldimethylsilyl chloride
TBHP	*Tert*-butylhydroperoxide
TBTO	Tributyltin oxide
T_c	Critical temperature
TCA	Trichloroacetimidate
tda	Thiodiacetate
Tf	Trifluoroacetate
TFA	Trifluoro acetic acid
TFMS	Trifluoromethane sulfonate
TFMSA	Trifluoromethane sulfonate acid anhydride
TFSI	*Bis*(trifluoromethanesulfonyl)imide
Tg	Phase transition temperature
THF	Tetrahydrofuran
TNT	Trinitro toluene
TRIP	3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphates
Ts	Tosyl
TS	Transition state
TSAC	2,2,2-Trifluoro-*N*(trifluoromethylsulfonyl) acetamide
US	Ultrasound
VOCs	Volatile organic compounds
ZSM-5	Zeolite Socony Mobil–5

Chapter 1
Green Chemistry: Introduction to the Basic Principles

1 Introduction

The chemists have always been passionate about the synthesis of chemicals of diverse varieties of structurally simple to the complex compounds. These scientific efforts led to the development of vast varieties of compounds having immense importance in the areas of medicinal and material sciences. Several drugs, natural products, polymers, and materials were discovered that made our life very comfortable. In last few decades, the synthetic approaches toward the development of different varieties of compounds of medicinal and material interest have taken a paradigm shift. In contrast to the conventional approaches in chemical synthesis were achieving the best product yield and construction of diverse range of a target compound was the prime focus without paying much attention toward the impact of the synthetic methodology adopted for it, on the safety, health, and environment (SHE), the development of environmentally benign and green synthetic reaction protocols and technology is the principal goal in the present scenario. In that direction, the development of the concept of green chemistry and its twelve basic principles (Fig. 1) formulated by Prof. Paul T. Anatsas and John C. Warner works as a guiding tool for the synthetic chemist [1]. These basic twelve principles have been discussed in details in the following sections.

2 Principles of Green Chemistry

Principle 1: "*It is better to prevent waste than to treat or clean up waste after it has been created*." [2]

It is well known proverb that "*prevention is better than cure.*" Similar to that, it is advisable to prevent the generation of different varieties of waste materials that could be non-hazardous to highly hazardous in nature and gets generated in

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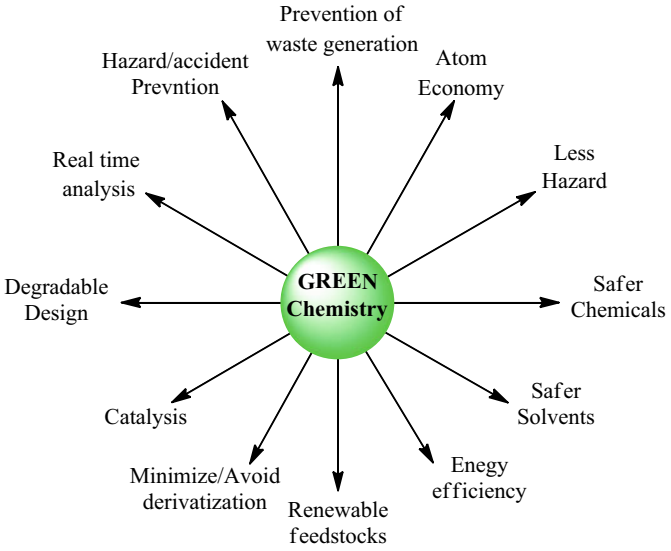


Fig. 1 Different principles of green chemistry

chemical reactions and process either in the form of by-product, reagents, and auxiliary components like solvents, etc. It may include waste material which could be flammable such as paint, coating, organic solvents, and compressed gases like LPG, acetylene, hydrogen, etc. along with solid chemicals like lithium aluminum hydride, sodium, etc. or explosive like TNT or corrosive like acids, bases, etc. Some of them are highly toxic such as pesticides, insecticides, and various heavy metals As, Cr, Pb, Hg, Cd, etc. containing chemicals. In general, it is advisable to go through the information available in the material safety data sheet (MSDS) to get idea about the different properties including physical, chemical, toxicity, etc. of a chemical and waste material also if it is fully characterized.

Sometime different chemicals which are available in the form useful drugs or chemicals when gets expired are also considered as waste material. But every type of waste material imparts economic, social, and environmental impact of varied degree and these require proper disposal as per the strict guidelines formulated by various agencies. Importantly, these waste materials would have huge impact on safety and health of the chemists and workers involved in the complete process. Apart from that, waste generated would also have impact on environment, ecosystem and it will ultimately affect the life on the earth.

Cost of the target compound will greatly be affected by the cost involved in treatment of the waste material generated during its formation. Therefore, this principle emphasizes on the complete prevention of the waste material generation or if it is not possible then minimize the waste formation by developing and adopting an environmentally benign process. In order to compare the greenness of a method or process in terms of the generation of waste material, different metrics have been devised. For

example, Roger. A. Sheldon in 1980 introduced the concept of "*E-factor* or *Environmental factor"* which is the ratio of mass of waste (Kgs) to mass of product (Kg) in order to assess the impact of various different manufacturing processes on environment [3]. Ideally, the E-factor value should be zero which is practically difficult to achieve in most of the cases. The value of E-factor varies in different types of industry of industry (Table 1). As shown in Table 1, fine chemicals and pharmaceutical industry occupies the top slots in the production of waste material primarily due to the use of organic solvents as well as use of stoichiometric amount of reagents. Although for the calculation of E-factor, it is important to identify the waste material which will not necessarily be the by-product, regent only. In fact, the waste could be defined as *everything but the desired product* [4]. But generally, solvents in particular water and some other solvents which are a part of reaction mixture either in the form of solvent or by-product in a chemical reaction get ignored while calculating E-factor. Therefore, two boundaries have been suggested to quantify the E-factor. Simple E-factor (sEF) simply takes the mass of raw material, reagents and products into account and do not consider any solvent as waste material to calculate E-factor. On the other hand, in case of complete E-factor (cEF), all the solvents including water, assuming these have not been recycled gets considered as waste material. Therefore, the true value of environmental factor lies somewhere between these two values of sEF and cEF.

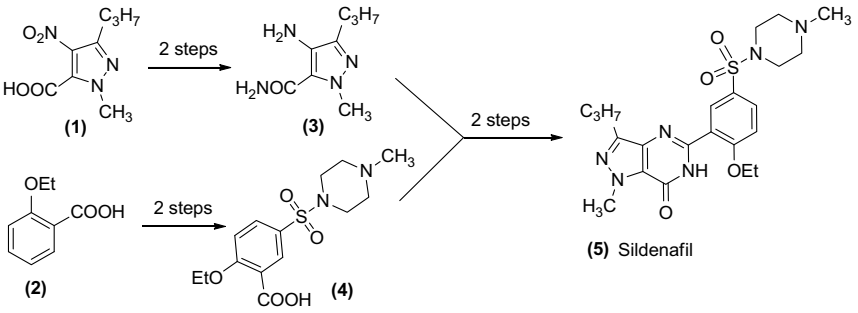
$$\text{Simple E factor (sEF)} = \Sigma\ \text{m (raw materials)} + \Sigma\ \text{m (reagents)} - \text{m(product)/m(product)}$$

$$\text{Complete E factor (cEF)} = \Sigma\ \text{m (raw materials)} + \Sigma\ \text{m (reagents)} + \Sigma\ \text{m(solvents)} + \text{m(water)} - \text{m(product)/m(product)}$$

Therefore, the value of E-factor varies and depends on various other factors such as the consideration of initial point in the synthetic pathway. In general, E-factor is calculated taking only those processes into account which are being carried out at the manufacturing site. But it is important to keep in mind that the synthesis of the target compound could be started by procuring an intermediate which itself requires multistep synthesis. So the value of E-factor would vary according to our consideration of initial starting point which could be a commodity type and commercially available raw materials or it could be an intermediate which require synthesis involving various

Table 1 E-factors in the chemical industry [3]

S. No	Industry segment	Tons per annum	E-factor (kg waste per kg product)
1	Oil refining	10^6–10^8	<0.1
2	Bulk chemicals	10^4–10^6	<1–5
3	Fine chemicals	10^2–10^4	5–50
4	Pharmaceuticals	10–10^3	25– >100

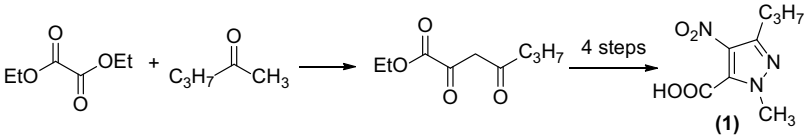


Scheme 1 Commercial method for the preparation of Sildenafil by Pfizer

steps. For example, the synthesis of sildenafil citrate which is popularly known with brand name Viagra is manufactured by Pfizer starting using pyrazole derivative (**1**) and 2-ethoxybenzoic acid (**2**) as starting materials to prepare another pyrazole (**3**) and piperazine derivatives (**4**) separately. These two combine together to produce the target compound sildenafil (**5**) (Scheme 1) [5].

In this case, the E-factor value reported by Pfizer was 6 kg/kg which was very low compared to the earlier reported processes. This improved process for the synthesis of sildenafil citrate developed by Pfizer also received the UK Award for Green Chemical Technology in 2003. But the synthesis of the starting material pyrazole derivative 1-methyl-4-nitro-3-propyl-1*H*-pyrazole-5-carboxylic acid (**1**) used in Scheme 1, itself requires five steps starting with commodity like starting material diethyl oxalate and 2-pentanone (Scheme 2). Therefore on taking this fact into consideration, the value of overall E-factor increases to 13.8 kg/kg. But the value itself does not reflect about the overall greenness and its environmental impact as the nature of waste material is also an important parameter to consider while comparing the greenness of different processes.

For example, environmental impact of 1 kg of NaCl would entirely be different from the same amount of organic solvent such as DCM, benzene, or heavy metal (Cr, Hg)-based waste material. Therefore to compare the greenness, another term "*Environmental quotient (EQ)*" was introduced by Sheldon. It is the product of E-factor and an unfriendliness quotient, Q which is an arbitrarily assigned number [4]. For example, the value of Q could be assigned 1 for NaCl, whereas it could be 100–1000 for salts of toxic heavy metals. Although Q is an arbitrary number and so its magnitude is debatable. But it does reflect about the environmental impact of a



Scheme 2 Synthesis of pyrazole derivative **1**

chemical method. Various factors such as whether the chemical under consideration is being disposed or recycled also affect the value of EQ. Waste generation could be avoided or minimized by employing various innovative approaches, some of which have been discussed below:

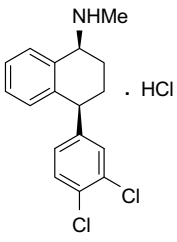
(a) **Step or Pot-economic synthesis**

This approach involves the synthesis of a compound by clubbing various synthetic steps in the same pot in case of a multistep synthesis as long as it is possible. It avoids the use of auxiliaries substances such as solvents, reagents required for performing the reaction, purification and isolation of intermediates in each individual steps. Apart from that, one-pot synthesis also saves time and energy which are also very important factors that contribute to the cost of the compound. Most importantly, this approach allows the minimization of waste generation which otherwise would have been generated in each individual steps. For example, the syntheses of *sertraline hydrochloride* (6) (Fig. 2) which is an antidepressant and is being marketed under the brand name "*Zoloft*" by Pfizer was performed employing green approach which not only minimized the waste generation but also at the same time reduced the cost, energy consumption, etc.

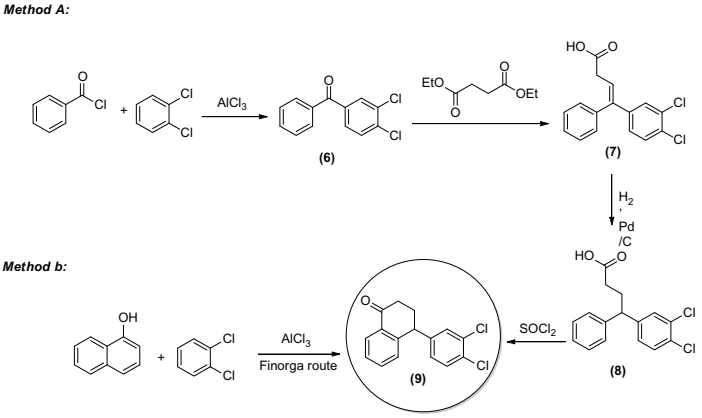
The aryl-substituted tetralone (9) is an important intermediate in the preparation of sertraline. Earlier synthetic route involves the four steps which begins with the formation of benzophenone derivative (6) using benzoyl chloride, o-dichlorobenzene as starting materials (Scheme 3).

It further reacts with diethyl succinate to provide another an acid intermediate (7), which after hydrogenation led to the formation of another intermediate (8). Finally, this intermediate cyclized in presence of thionyl chloride and furnish the desired aryl-substituted tetralone (9) (Method A, Scheme 3). Later, Finorga developed a new process; the synthesis of this tetralone derivative was achieved in one step involving Friedel–Crafts reaction between α-naphthol and o-dichlorobenzene (Method b, Scheme 3). This slight modification drastically minimized the waste generation. The tetralone derivative (9) was further used for the synthesis of sertraline (12) involving three different steps (Method A, Scheme 4) that involved the formation of different intermediates (10–11) which was isolated after completion of the reaction and further subjected to another step. Overall, it requires isolation at each step, use of different solvents such as toluene, hexane, THF, and ethanol. In

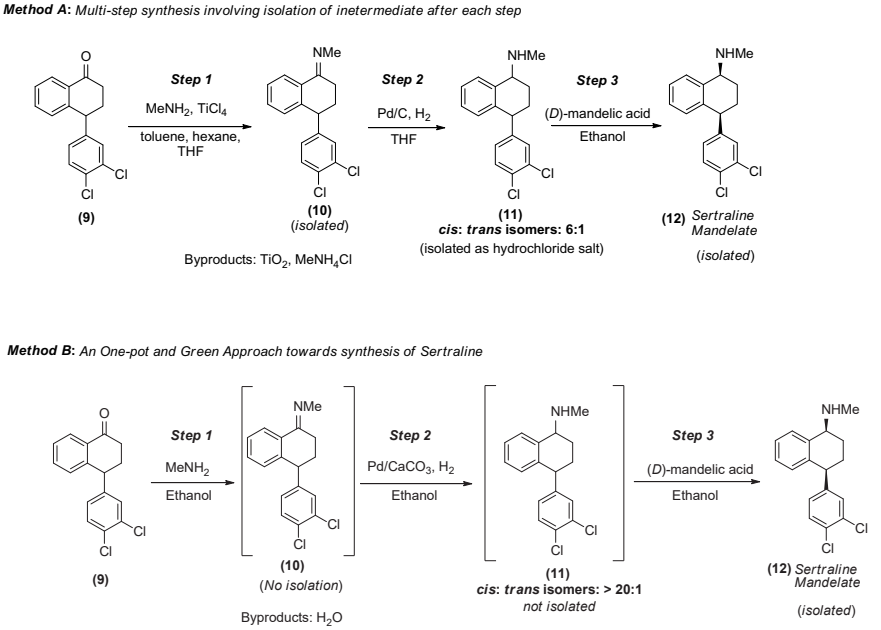
Fig. 2 structure of *Sertraline Hydrochloride* (***6***)



(6)



Scheme 3 Synthesis of tetralone derivative (9) using two different methods



Scheme 4 Comparison between two different synthetic routes to sertraline

addition to that, generation of TiO2 as waste material is another drawback associated with this method. Therefore, Pfizer modified the synthetic route and developed a greener synthetic route for the formation of sertraline where the synthesis of sertraline (12) was achieved in one-pot operation using ethanol as single solvent (Method

B, Scheme 4). Importantly, no intermediate was isolated along with that there was no generation of waste material like TiO2.

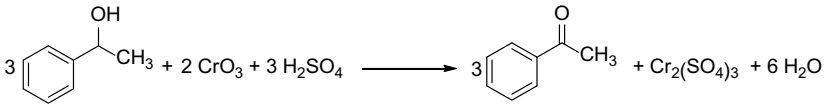
Overall, this improved route established by Pfizer increased the product yield, energy efficiency, and time. Apart from that, this optimized synthetic routes decreased waste toxic waste generation either in the form of solvents or by-products. More importantly one-pot synthesis saved the time and energy and solvents in the isolation and purification of intermediates. Considering the immense importance of this method, it was awarded US EPA Presidential Green Chemistry Challenge award in year 2002.

(b) **Development of catalytic methods**

In order to prevent or minimize the generation of the chemical waste, the reaction protocol developed using a catalyst has been found to be superior compared to the conventional approach using stoichiometric amount of reagents. For example, the oxidation of secondary alcohol 1-phenylethanol could be achieved employing two different methods (Scheme 5). In conventional approach, the CrO_3 is used as an oxidizing agent in presence of H2SO4 as an acid source. The reaction produces $Cr_2(SO_4)_3$ as a by-product along with water (Method 1, Scheme 5). While in another approach, oxidation was achieved under catalytic condition using molecular oxygen (Method 2, Scheme 5). In this case, the only by-product is water and the E-factor value drastically reduced to 0.1. Importantly, it also avoided the use of Cr-based reagent which was used in stoichiometric amount and also resulted into large amount of waste material.

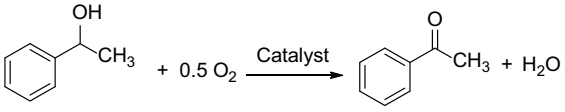
Similarly, small modification in the process could drastically reduce the waste production. For example, different synthetic routes could be adopted for the preparation of propylene oxide (Scheme 6). For example, in case of chlorohydrine route, the

Method 1: *Oxidation using Cr(VII)*



[Atom Efficiency: 360/860 = 42%; Byproduct: $Cr_2(SO_4)_3$ and H_2O ; E-factor (theoretical): 1.5]

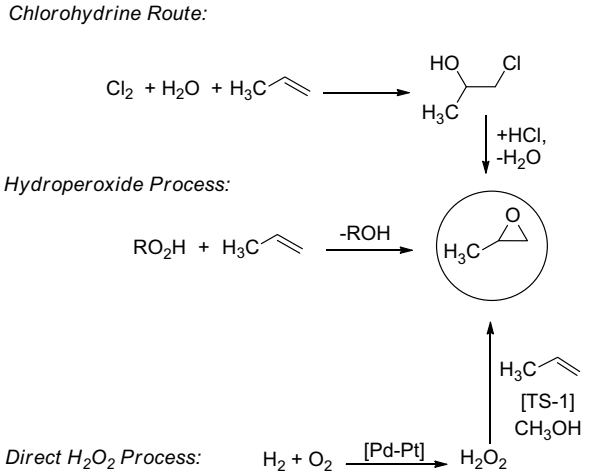
Method 2*: Oxidation using O_2 in presence of catalyst:*



[Atom Efficiency: 120/138 = 87%; Byproduct: H_2O; E-factor (theoretical): 0.1]

Scheme 5 Oxidation of acetophenone to benzophenone

Scheme 6 Preparation of propylene oxide using different methods

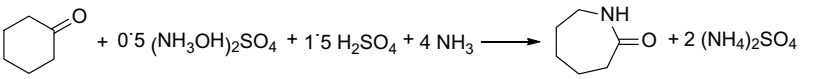


chlorohydrine produced through the reaction between alkene, chlorine, and water undergoes epoxide formation in presence of acid. In addition to that in another method, peroxy acid was used as source of oxygen for the expoxidation of alkene. Instead of these two steps process and using peroxy acid, epoxidation of alkene was achieved through the in situ generation of hydrogen peroxide using metal-catalyzed reaction condition (Scheme 6).

Synthesis of *caprolactum* which is a precursor for the synthesis of nylon-6 using Sumitomo process is another striking example where modification in the conventional process led to the generation of water as the only by-product compared to the conventional approach where ammonium sulfate was being produced in large amount. In conventional method, the transformation of cyclohexanone to its oxime derivative is achieved using hydroxylamine sulfate. The oxime further undergoes Beckmann rearrangement in presence of H_2SO_4 or oleum which is used in stoichiometric amount (Method 1, Scheme 7). In this process, for the production of each kg of caprolactum, 4.5 kg of $(NH_4)_2SO_4$ gets generated as a by-product. Compared to this conventional method, only water gets produced as the only by-product using Sumitomo method with E-factor value significantly reduces to 0.32 (Method 2, Scheme 7).

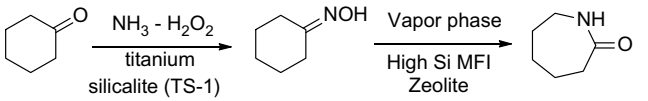
Similarly, the chemical transformation achieved using biocatalyst is also an attractive way for the reduction of chemical waste generation. For example, the synthesis of 6-aminopenicillanic acid (6-APA) (**15**) using conventional approach requires two different steps through the formation of an intermediate (**14**) using chlorinated reagents, solvents (Scheme 8). At the same time, it also needs to maintain reaction temperature at −40 °C. Compared to this approach, the improved synthetic route using *penicillin acylase* (Pen-acylase) as a biocatalyst, the enzymatic cleavage of penicillin G (**13**) to 6-APA (**15**) could be achieved in a single step at 37 °C [6, 7]. So for the production of 1 kg of 6-APA under conventional method, Me_3SiCl (0.6 kg), PCl_5 (1.2 kg), $PhNMe_2$ (1.6 kg), NH_3 (0.2 kg), *n*-BuOH (8.4 l Kg), and CH_2Cl_2 (8.4 l kg) were required, whereas for enzymatic cleavage, NH_3 (0.09 kg)

Method 1: *Conventional approach for the preparation of caprolactum*



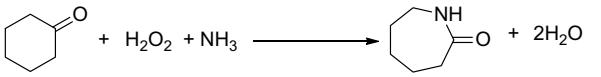
[E = 4.5; Atom efficiency: 29%]

Method 2*: Sumitomo Process for caprolactum*



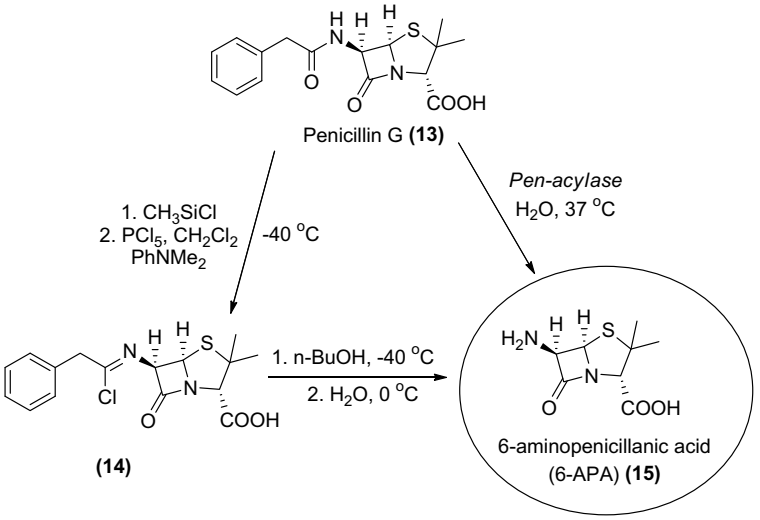
[Ammoximation] *[Beckmann Rearrangement]*

Sumitomo Process for caprolactum



[E = 0.32; Atom efficiency: 75%]

Scheme 7 Comparison between Sumitomo and conventional methods for caprolactum synthesis



Scheme 8 Deacylation of Penicillin G under chemical and enzymatic method

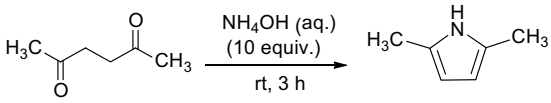
was used as the only reagent to maintain the pH, and the conversion was achieved in single step (Scheme 8). Therefore, this environmentally benign biocatalytic method allowed the drastic reduction in production of toxic chemicals waste. Several such transformations are known in the literature and will also be discussed in the separate chapter.

(c) **Development of solvent-free method**

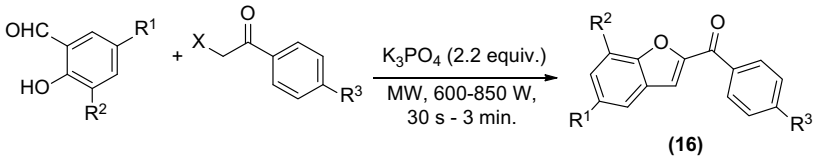
Among various types of wastes, solvents are a major contributor due to their multiple role in a chemical process. Most of the chemical reaction require organic solvents as a reaction medium due to its role in efficient mass transfer, control of localized temperature, reaction kinetics, and also for the stabilization of certain reaction intermediates. In addition to that, purification process either through column chromatography, crystallization, etc. also requires ample solvents. Therefore, in order to minimize the waste generation in the form of solvent, various synthetic methods have been explored under the solvent-free condition. For example, syntheses of diverse range of medicinally important heterocycles have been reported under solvent-free reaction condition. For example, the synthesis of functionalized pyrroles could easily be achieved under solvent-free reaction condition (Scheme 9) [8]. Similarly, the synthesis of benzofuran (**16**) could also be achieved through Rap–Stoermer reaction under solvent-free reaction condition (Scheme 10) [9].

Principle 2: *"Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product."* [2]

The minimization of the waste could also be achieved via the efficient use of the raw materials used in a process. For the synthesis of any compound especially if the synthesis requires more than one step as generally happens in case of structurally complex natural products and drugs, different synthetic routes could be designed. And every route will demand a particular set of reactants, reagents, solvents, catalyst, etc. Apart from these, every synthetic scheme would also require different set of chemical transformations. Some of which may be common. Depending on the



Scheme 9 Preparation of 2,5-disubstituted pyrrole under solvent-free condition



Scheme 10 Solvent free synthesis of benzofuran

number of synthetic steps, types of reactions and reagents involved, product yield, amount and types of waste generated would also differ. In general, the primary goal of a chemist was to achieve the synthesis and improving the desired product yield and selectivity of the product. But after realizing the environmental impact and deteriorating effect of some of the organic solvents, toxic reagents, by-products, etc. along with the fast depletion in the non-renewable resources especially petroleum, the approach is slowly moving toward the minimization of waste generation and maximum incorporation of the raw material into the product. In order to evaluate and compare the efficiency and greenness of a chemical process, various matrices have been proposed. Along with E-factor, "*atom economy*" which sometimes also referred to as "*atom efficiency"* was another important tool that was first introduced by B. M. Trost [10]. This value of % atom economy helps in evaluating the greenness of a process.

Atom economy could be represented as follows (Fig. 3)

Therefore, with the help of the E-factors value and % atom economy, the greenness of a process could be compared. Every metrics has some sort of limitation and the value does not fully reflect the greenness of a process. Unlike E-factor value that takes all the by-product, reagents, solvents, etc. into account, the value of atom economy only provides information about the conversion of starting material used into the product and do not account for the other substances which are not a part of the stoichiometric equation. With the help of atom economy value, the theoretical E-factor could be calculated. For example, an atom economy of 80% indicates the conversion of rest of the 20% of the starting material into by-product so the E-factor would be 20/80, i.e., 0.25. But practically, the E-factor value would be much higher than the theoretical one if reaction involves the use of excess amount of reagents, solvents, salt formation, etc. Therefore, in order to enhance the atom economy and reducing E-factor of an overall process, the synthetic routes could be designed in such a way that would include the synthetic steps having high atom economy. Different types of reactions which have high value of atom economy, i.e., maximum incorporation of atoms of starting material into product, have been developed under catalytic protocol that led to the higher value of atom economy (Fig. 7) which has been discussed below with few examples (Fig. 4).

(a) **Addition Reaction**: The atom economy in case of the addition reaction of alkene and alkyne is 100% as it simply involves the addition of the entire reagent. For example, in case of the addition reaction of HBr to 2-methylprop-1-ene, all the atoms of the starting materials get incorporated into the product 2-bromo-2-methylpropane without losing anything in the form of by-product (Scheme 11).

(b) **Pericyclic Reactions**: The atom economy in case of pericyclic reaction such as cyclcoaddition, electrocyclci reaction, and sigmatropic rearrangement is

$$\text{Atom Economy} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weights of all reactants}} \times 100\%$$

Fig. 3 Calculation of % atom economy