Efficient Methodologies for Sustainable Advancements in Chemical Synthesis

Neelima Gupta

Centre for Advance Study, Department of Chemistry,
University of Rajasthan, Jaipur-302004
Email: guptaniilima@gmail.com

Address of correspondence Prof. Neelima Gupta Centre for Advance Study, Department of Chemistry, University of Rajasthan, Jaipur-302004 Email: guptaniilima@gmail.com	**How to site this article** Gupta Neelima, Efficient Methodologies for Sustainable Advancements in Chemical Synthesis, Chemical Synthesis Letters 2023; 01 (01): 1-4 Available from: https://csl.thecmrs.in/index.php/j/article/view/21

Significance of need of advancements in chemical synthesis lies in the ever-increasing demand of commercially important chemicals and materials that are required for manifold progress of civilization. Wide variety of new or known compounds and materials with specific physico-chemical properties are required to be produced in bulk quantities for utilization in the areas of agriculture, medicinal, polymers, electronics, dyes, textile industries, etc. Chemical synthesis may be defined as a single or multistep process involving reaction of two or more compounds in presence of certain reagents and reaction conditions to produce another chemical compound with specific properties required for explicit purposes. Success of a chemical synthesis would depend on thorough knowledge of possible reactants, reagents, catalysts and application of efficient methodologies to produce quality desired product in economic yields.

The chemical synthesis of a target molecule is a complex multistep process, often leading to unwanted bye-products and waste materials posing environmental threat. During recent years, the emphasis has been on the improvement of efficiency and sustainability of synthetic methods using novel techniques, reagents and clean processes to minimize environmental impacts. In order to attain these objectives, practise of Green chemistry principles have proliferated extensively [1]. Another important concern during the organic and inorganic synthesis is achievement of required selectivities and high yields and this has been addressed by use of catalysis [2]. Various types of catalysis - heterogeneous, homogeneous, enzymatic or photo catalysis provide strategies to overcome specific shortcomings of selective synthetic reactions in fast and energy efficient manner. During recent decades, the research in the area of sustainable chemical synthesis has witnessed enormous progress due to the development of advanced technologies that has permitted the design of new materials with desired properties and automation of many processes keeping the focus to address the environmental issues. Need of the hour demands practice of the eco-friendly and sustainable synthetic processes to minimize the damage being caused to out earth on account of human development. In this article, few such important advanced technologies and methodologies, that would impact the future evolution of chemical research and industry production of fine and bulk chemicals have been listed and an attempt has been made to direct the readers to most important literature.

Green Chemistry Principles: With the invent of the term “Green Chemistry” during early nineties to reduce the production and use of hazardous chemicals, steps were taken to reduce impact of chemicals on human health and environment. C.-J. Li and B.M. Trost in their review article entitled “Green chemistry for chemical synthesis” published in 2008 have highlighted very concisely the significant of this subject as follows – “Green chemistry for chemical synthesis addresses our future challenges in working with chemical processes and products by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes and apparat i that can simplify operations in chemical productions, and seeking greener solvents that are inherently environmentally and ecologically benign” [3]. Prior to this, B.M. Trost may be credited for identifying the significance of the phenomenon of “Atom Economy” and presenting comprehensible guidelines to evaluate the efficacy of a chemical synthesis [4]. Recognizing the necessity of eco-friendly, ecologically benign and sustainable processes, Paul Anastas and John Warner introduced the prevalent ‘Twelve Principles of Green Chemistry’ in 1998 [5]. For the beginners, who wish to practice green chemistry and the established synthetic researchers, who seek information about greener alternatives to the conventional methodologies, an introductory article on ACS Green Chemistry Institute’s Nexus Blog is much informative [6]. First and the most important principle of Green Chemistry reminds us to prevent creation of waste (useless bye-products and solvent systems), rather than finding ways to clean up or dispose-off after it has been created. Next eleven principles guide us about how to achieve this prevention. Concerns about prevention of waste was taken up by R.A. Sheldon due to the then prevalent inefficient classical organic synthesis protocols in pharmaceutical industry, that produced much more waste products than the target API's during the manufacturing at large scale, many times waste produced was more than 100 times by weight per unit amount of the API produced [7]. Consequently, the term E-factor originated, which relates the amount of waste generated to the amount of actual desired product. An excellent description of the subsequent developments in the fine chemical and pharmaceutical industry during next fifteen years to circumvent the enormous waste material production was later accounted by Sheldon in perspective published in 2007 in the journal Green Chemistry [8]. The article describes many real-world examples of practising atom economy, role of catalysis, solvents and non-conventional reaction media. Solvent was attributed to almost 85% of the total mass of chemicals involved in synthesis of pharmaceuticals [9]. Improvement of the commercial synthesis of sildenafil by reducing use of solvent from 1700 l kg-1 to 7 l kg-1 and bringing down the E-factor to 6 is one such early example of waste reduction [10]. Another recent review article [11] describes implications of Green Chemistry practises in the synthesis of pharmaceuticals. Green synthesis using alternative reaction medium, choice of green solvents including water, use of one pot synthesis or multicomponent reactions has paved way for achieving atom economy and waste reduction during commercial production of pharmaceutical compounds.

Catalysis: Catalysts are recoverable and reusable means to move fast a chemical reaction in forward direction by lowering its activation barrier, hence reducing the energy requirement along with reduction of undesired by-products and waste substances in concordance with green chemistry principles. Heterogeneous catalysis has found an important place in production of variety of chemicals from biomass-derived starting materials in an efficient and eco-friendly manner. Heterogeneous catalysts are easily recoverable and reusable in cyclic process and as a result of the reaction mechanism involving specific reaction sites, have advantage of resulting in desired products with high level of selectivity. Review on "the role of catalysis in green synthesis of chemicals for sustainable future" presents an account of various roles of heterogeneous catalysis in synthesis of chemicals from biomass-derived molecules [12]. Of late, other forms of catalysis such as, electrocatalysis, biocatalysis, photocatalysis, organocatalysis with more recent addition of nanostructured catalysts have become popular among synthetic chemists due to their versatile applications.

Biocatalysts (enzymes) provide highest level of chemo-, stereo- and regio- selectivities along with the advantage of working in milder reaction conditions in aqueous media. Biocatalysis can be practised either by using isolated enzymes to avoid contamination of other enzymes or whole cell based biotransformations making the process less expensive. Enzymatic catalysis has advantage of avoiding cumbersome steps, such as functional group activation and protection-deprotection steps required in conventional organic synthesis. Importance of another form of catalysis, i.e. 'Asymmetric Organocatalysis' was recognized in 2021 when Benjamin List and David MacMillan were awarded "the Nobel Prize in Chemistry 2021 for their development of a precise new tool for molecular construction: asymmetric organocatalysis." Organic catalysts, recognized as 'new tools for finer chemistry' have a stable framework of carbon atoms, to which more active chemical groups can attach. Press release declaring the Nobel Prize underlines 'the importance of organocatalysts by identifying these catalysts as both environmentally friendly and cheap to produce having great impact on pharmaceutical research, and having made chemistry greener'.

Photocatalysis: The phenomenon inspired from photosynthesis, the natural process of synthesis of organic compounds from much simpler, low-energy substrates like carbon dioxide and water making use of the light as the energy source, is considered as a green and sustainable alternative for synthesis of fine chemicals. Photocatalytic reactions are based on the electronic excitation, through photocatalysts or photosensitizers using UV-vis light, which influences the chemical reactivity of reagents in organic synthesis. Various approaches prevalent for 'Photocatalytic Synthesis of Chemicals' that may be classified in - 'reactions of organic substrates with photocatalytically activated small molecules; direct photocatalytic activation of one organic substrate; and reactions involving a direct activation of two organic molecules' have been described in detail by Kobielisz et al. [13]. Although, chemical transformations using photocatalysis have been investigated comprehensively by large number of researchers for academic research purposes, its potential for large scale production of materials of commercial interest has not been explored extensively due to limitations in knowledge and applications of suitable photocatalytic materials. In addition to conventional semiconductors, more novel photocatalytic materials, such as quantum dots, nanoscale plasmonic matel particles have become available. An account of the fundamental principles, efficiency, scalability, stability aspects of various categories photocatalytic materials has been compiled for making the utilization of these materials feasible in large scale applications [14]. More recently, a special issue of The Journal of Organic Chemistry has been dedicated to the theme "Progress in Photocatalysis for Organic Chemistry", to highlight recent literature reports in the area of visible-light photocatalysis [15].

Non-conventional forms of energy activation: Use of alternative sources of energy was an innovative idea in achieving quality and quantitative products from the reactions where catalysts could not help in dealing severe conditions of a reaction. Photochemical synthesis involving free radicle intermediates and electro-chemical synthesis could be such alternatives. Microwave radiations and ultrasonic waves have become widespread alternative energy sources in synthetic methodologies during last two decades. MW energy is non-ionizing radiation, which does not influence on the molecular structure of compounds. MW radiation is instantaneous, non-ionizing form of energy used to heat the sample in uniform manner assisting in increased collision among molecules of reactants. Another advantage of MW energy is selective heating of the active points of sample and ability to be turned off the supply instantaneously. Other advantages of microwaves as alternative energy source are less reaction time, purity of products, energy efficiency, fewer side products, economic viability at large scale production. Solvent-free reaction conditions using inorganic support such as clays, zeolites, ceramics, alumina, silica, etc. which themselves are microwave inactive and good adsorbent properties for reagents and catalysts, provide solution to solvent related concerns in eco-friendly manner. An elaborate and illustrious description of fundamental aspects of modern microwave methods and their application for manufacturing in solid-state inorganic Materials Chemistry has been presented by Kitchen et al. in their chemical review article [16]. Success of the microwave assisted synthesis has led to the development of a variety of specialized microwave reactors for laboratory level as well as bulk manufacturing.

Organic electro-synthesis has emerged very rapidly as another promising alternate synthetic approach in pharmaceutical chemistry, due to cost effective methodologies, incredible selectivities, ease of operation, accurate control and environmental sustainability. Electro-organic synthetic methodologies are being perceived as methodologies of choice in forthcoming decades. A number of examples showing effective utilization of electro-organic synthesis in organic and pharma industry verify the potential of this methodology [17-18]. applications are available.

Solvents with low environment impact: As mentioned above, the solvents are the main reason for high E-factor in production of pharmaceuticals. Also, excessive use of organic solvents in conventional synthesis present hazard due to their flammable, carcinogenic, toxic and high vapour pressure properties. Two types of steps have been undertaken to combat these issues, first one by reducing the volume of solvent using higher concentration or using same solvent throughout the process and second by choosing greener solvents varying from water, ionic liquids, supercritical fluids and liquid polymers. Ionic liquids, often quoted as the ‘designer solvents’ have emerged as solvent of choice for both the academic and industrial level synthesis, due to their fluid state at room temperature, ionic nature and almost nil vapour pressure. Although the first ionic liquid was identified as early as 1914, their application as binary solvent system could be practised quite late. Several review articles appeared during late nineties, which highlighted their versatile applications and potential as green solvent for future [19-21]. Supercritical green solvents are another class of good alternative for the synthesis of polymers due to non-flammable, non-toxic and environmentally friendly properties. Supercritical carbon dioxide and supercritical water are advantageous in synthetic processes for obtaining variety of nanomaterials including semiconductors [1].

With the invasion of artificial intelligence and digital technologies in every aspect of our life, application of automation has been introduced in form of the digitally controlled synthesis technology. Automated laboratory reactors employing sophisticated hardware, software combined with machine learning and AI tools can ensure better understanding of reaction kinetics, thermodynamics, identification of optimal conditions, monitoring of reaction variables for management of complexities of chemical synthesis [22]. Machine learning tools are now a days handy for design of new and viable synthesis of organic molecules. Future progress of commercial synthetic chemistry depends on application of interdisciplinary approaches and automation of processes.

Multi-component reactions, metathesis, bio-inspired methodologies are some other domains which have attracted attention of synthetic chemists as methods of choice due to selectivities and sustainability. The advances in modern chemical synthetic processes and methodologies presented above have enough potential for further evolution of more novel and efficient technologies. It is the need of the hour that the synthetic chemists should update themselves with emerging techniques and innovative methods and practice them with novel applications for the benefit of the society and protection of the environment.

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