Introduction

1. Biologically active heterocycles

Synthesis of heterocycles by far form the largest of the classical divisions of organic chemistry. Heterocycles are of immense importance not only biologically and industrially but also to the functioning of any developed human society. Their participation in a wide range of areas cannot be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following natural models.\(^1\) Heterocycles play a major part in biochemical processes and are also side groups of the most typical and essential constituents of living cells. Other important practical applications of these compounds can also be cited, for instance, their use as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A vast number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most diverse physical, chemical, and biological properties.\(^1,2\) Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately one-half are heteroaromatic.\(^2\) It is, therefore, easy to understand why both the development of new methods and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. Organic chemists have been engaged in extensive efforts to produce various heterocyclic compounds by developing new and efficient synthetic transformations. Among them, cyclocondensation reactions are of the most attractive methodologies for synthesizing heterocyclic compounds,\(^1\) and the need for improved cyclocondensation reactions is evident. Cyclocondensation reactions generally involve the elimination of water, alcohol, or amine and have been performed with great success under solvent-free conditions using multicomponent strategies or using environmentally benign solvents or environmentally safe, readily available and less expensive catalysts.
2. Functional group transformations

The next class of reaction that are important in organic chemistry are functional group transformations. Selective functional group transformation of complex molecules to target compounds is the most important requirement of modern organic synthesis. Interconversion of functional groups has always played an important role in organic synthesis. There have been many developments in the last decade regarding this area and two excellent editions “Comprehensive Organic Functional Group Transformations I” and recently “Comprehensive Organic Functional Group Transformations II” have presented the vast subject of organic synthesis in terms of the introduction and interconversion of all known functional groups, providing thus a unique information source documenting all methods of efficiently performing a particular transformation.\(^3,4,5\) Functional group conversions, however constitute an extremely important element of every target-oriented organic synthesis as a tool to make the necessary modifications of intermediate products and to establish the required functionality in the target molecule. Conversions of this type can be encountered at almost any stage of a multistep synthesis or total synthesis.\(^6\)

Many authors have described and have been working on development of green protocols for functional group transformations, and there is a rapidly growing demand of reports describing quick, selective, and efficient transformations, that allow a high degree of conversion of reactants to products.\(^7-9\) Such protocols merit further investigation as they may offer distinct advantages such as improved atom utilization\(^10\) or atom economy\(^11\) by avoidance of common derivation procedures;\(^12\) decreased byproduct formation and, hence, decreased waste\(^13\) resulting from purification procedures required to separate the desired product from impurities; and, in many cases, reduced energy utilization both in the reaction and purification stages as well as opportunities for process intensification. The magnitude of these advantages is clear when considering the 12 Green Chemistry Principles and the international tendency to develop green and sustainable chemical processes, with lesser generation of toxic and nontoxic waste.\(^14\)
Introduction

*The 12 Green Chemistry Principles:*

Anastas and Warner have developed the Twelve Principles of Green Chemistry to aid one in assessing how green a chemical reaction or a process is\(^{15}\)

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible and, innocuous when used.
6. 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.
7. A raw material feedstock should be renewable rather than depleting whenever technically and economically practical.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. 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.
11. 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. Substances and the form of a substance used in a chemical process should chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

One of the most important and used strategy to achieve green synthesis is *via* multicomponent reactions.
3. **Multicomponent strategy**

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions.\(^{16}\) Multi-component reactions (MCRs)\(^{7}\) are also a subject of recent interest in organic synthesis, and MCRs are emerging as useful tools for carbon–carbon and carbon–heteroatom bond-forming reactions and for the synthesis of organic molecules with several degrees of structural diversity. MCRs are also increasingly employed in the total synthesis of natural products. Applications of MCRs in all areas of applied chemistry are very popular because they offer a wealth of products, while requiring only a minimum effort. As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one pot.

![Figure 1: A convergent 4- and 6-component reactions](image)

The MCRs satisfy many of the principles of Green Chemistry as these reactions can be carried out in solvent-free conditions, or in water as a solvent with high atomic economy.\(^{17}\)

The multicomponent reaction story began as far back as 1850 with the publication of the Strecker reaction,\(^{18}\) arriving nowadays at its apogee. During this one and a half century period, some notable achievements include the discovery of the Biginelli,\(^{19}\) the Mannich,\(^{20}\) and the Passerini\(^{21}\) reactions culminating in 1959 when Ugi published\(^{22}\) probably the most versatile MCR based on the reactivity of isocyanides.\(^{23}\)
4. MCRs: Synthetic Applications

Below are listed recent reports of organic molecules synthesized using multicomponent strategy

4a. Synthesis of β-amino ketones

At room temperature, zirconium oxychloride efficiently catalyzes the direct Mannich-type three-component reaction of aldehydes and anilines with ketones under solvent-free conditions to afford the β-amino ketones with good stereoselectivities (Scheme 1). The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.

\[
\text{R} : \text{Ph, Me}
\]

Scheme 1

4b. Synthesis of 2-(sulfonylimino)-4-(alkylimino)azetidines

Functionalized 2-(sulfonylimino)-4-(alkylimino)azetidine derivatives were prepared in good to via a copper-catalyzed multicomponent reaction of readily available terminal alkynes, sulfonyl azides, and carbodiimides without the assistance of a base under very mild conditions (Scheme 2).

\[
\text{R'}= \text{alkyl}
\]
4c. Synthesis of substituted 5,6,7,8-tetrahydro-4H-chromenes

The electrochemically induced catalytic multicomponent reaction of cyclic 1,3-diketones, aldehydes and malononitrile in alcoholic solvents in an undived cell results in the formation of substituted 5,6,7,8-tetrahydro-4H-chromenes (Scheme 3).26

4d. Synthesis of 2,3-disubstituted indoles

A practical one-pot, regiospecific three-component process for the synthesis of 2,3-disubstituted indoles based on Cacchi's protocol was developed. This mild Pd-catalyzed domino indolization procedure allows rapid access to various indoles via consecutive Sonogashira coupling, amidopalladation, and reductive elimination (Scheme 4).27

4e. Synthesis of highly functionalized pyrroles

A new and efficient three-component reaction between dialkyl acetylenedicarboxylates, aromatic amines, triphenylphosphine, and aryglyoxals to get polysubstituted pyrrole derivatives has been developed by Anary-Abbasinejad et al as shown in Scheme 5. The reactions were performed in dichloromethane at room temperature and under neutral conditions.28
4f. Synthesis of N-substituted 2,4-diarylimidazoles

A one-pot, four-component synthesis of 1,2,4-trisubstituted 1H-imidazoles was achieved in very good yields by heating a mixture of a 2-bromoacetophenone, an aldehyde, a primary amine, and ammonium acetate under solvent-free conditions as shown in Scheme 6.\textsuperscript{29}

\[
\begin{align*}
\text{ArCO}_2\text{H} + \text{Ar}’-\text{NH}_2 + \text{CO}_2\text{R} \rightarrow & \quad \text{1 eq. PPh}_3 \\
\text{CH}_2\text{Cl}_2, \text{r.t.}, 24 \text{ h} \rightarrow & \quad \text{Ar}_2\text{NCO}_2\text{R}
\end{align*}
\]

Scheme 5

4g. Synthesis of 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles

Adib \textit{et al} reported that N-Isocyaniminotriphenylphosphorane, aldehydes, and benzoic acids undergo a one-pot, three-component reaction to afford 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles (Scheme 7).\textsuperscript{30}

\[
\begin{align*}
\text{ArCO}_2\text{H} + \text{Ph}_3\text{P} & \equiv \text{N} \equiv \text{NC} + \text{RCHO} \rightarrow & \quad \text{CH}_2\text{Cl}_2, \text{r.t.}, 24 \text{ h} \\
& \rightarrow & \quad \text{Ar}_2\text{N} \equiv \text{N} \equiv \text{O} \quad \text{OH}
\end{align*}
\]

Scheme 7
4h. Synthesis of substituted 2-aminothiophenes

An efficient one-pot procedure allows the synthesis of various functionalized 2-aminothiophene scaffolds catalyzed by L-proline (Scheme 8). Low catalyst loading, simple procedure, and high yields are the important attributes of this methodology.\textsuperscript{31}

\[
\begin{align*}
\text{Y : CH}_2, \text{CHMe, NMe, NBoc, O, C} & \longrightarrow \text{O(\text{CH}_2)_2O-} \\
\text{EWG : CO}_2\text{Et, CN}
\end{align*}
\]

Scheme 8

4i. Synthesis of 4,5-disubstituted pyrimidines

A ZnCl\textsubscript{2}-catalyzed three-component coupling reaction allows the synthesis of various 4,5-disubstituted pyrimidine derivatives in a single step from functionalized enamines, triethyl orthoformate, and ammonium acetate (Scheme 9). The procedure can be successfully applied to the synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines.\textsuperscript{32}

\[
\begin{align*}
\text{R} & \text{ : Ar, EWG} \\
\text{R'} & \text{ : alkyl,H}
\end{align*}
\]

Scheme 9

4j. Synthesis of polyhydroquinoline derivatives

Yb(OTf)\textsubscript{3} Hantzsch four-component coupling reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate at ambient temperature to yield polyhydroquinolines is presented in Scheme 10.\textsuperscript{33}
5. Pasha et al exploration

Pasha et al have been exploring a number of organic reactions using multicomponent methodology under different reaction conditions, for the preparation of biologically or pharmacologically important compounds using readily available and inexpensive catalysts. Some of them are discussed below.

5a. Synthesis of 3,4-dihydropyrimidine-2(1H)-ones/-thiones

The novel protocol of synthesis of 3,4-dihydropyrimidine-2(1H)-ones/-thiones via a three-component coupling of substituted arylaldehyde, \(\beta\)-keto ester and urea or thiourea under solvent free microwave irradiation using catalytic amounts of metal chloride or acetate has been reported. The yields are high and the reactions go to completion within 10 minutes (Scheme 11).\(^ {34}\)

\[
\begin{align*}
\text{Scheme 11}
\end{align*}
\]

R = H, F, Cl, OMe, CH\(_3\), NO\(_2\), OH

5b. Synthesis of 2-aminobenzochromene

A TBABr catalyzed three-component coupling reaction of substituted aldehyde, \(\alpha\)-naphthol or \(\beta\)-naphthol and malononitrile to afford the corresponding 2-aminobenzochromene has been developed by Pasha and Jayashankara, the new protocol under microwave irradiation works in the absence of organic solvent, the yields are high and the reactions go to completion within 2-3 min (Scheme 12).\(^ {35}\)
Highly versatile and efficient synthesis of aryl-14H-dibenzo[a,j]xanthenes (Scheme 13) from araldehydes and β-naphthol was achieved by catalytic amount of iodine. In a typical reaction, a mixture of 1:2 equivalents of araldehydes and β-naphthol respectively and iodine (cat.) was heated for 15–20 min on a pre-heated hotplate at 90–95 ºC under solvent-free condition to get aryl-14H-dibenzo[a,j]xanthenes in good-to-excellent yield. 36

A four component tandem reaction of an araldehyde, arylmethyl ketone, acetyl chloride and acetonitrile in the presence of a catalytic amount of iodine was developed for the synthesis of β-acetamido-β-aryl-propiophenones. 37 In this experiment, the reaction mixture is heated for 10–15 min on a hotplate at 80–85 ºC under solvent-free condition to get the desired β-acetamido-β-aryl-propiophenones in good-to-excellent yield as shown in Scheme 14.
5e. Synthesis of 3,4-dihydropyrano[c]chromenes

A highly efficient, three-component condensation reaction of aromatic aldehyde, malononitrile and 4-hydroxycoumarin catalyzed by α-Fe₂O₃ nanoparticles at room temperature is also available. The method offers an excellent alternative to the synthesis of 3,4-dihydropyrano[c]chromenes (Scheme 15). The reactions are rapid, clean, and give the products in good yield and high purity.³⁸

![Scheme 15](image)

5f. Synthesis of pyranopyrazoles

A facile and convenient protocol is developed by Pasha et al for the fast and high yielding synthesis of fused pyranopyrazoles from ethyl acetoacetate, hydrazine hydrate, an aldehyde and malononitrile in the presence of non-toxic, simple and readily available organocatalyst glycine in aqueous medium at 25°C as shown in Scheme 16.³⁹

![Scheme 16](image)

5g. Synthesis of azalactones

Azalactones have been synthesized in high yields under solvent-free condition by heating a mixture of an araldehyde, hippuric acid and acetic anhydride in the presence of molecular iodine as a catalyst in a microwave oven (Scheme 17). The short reaction time, cleaner reaction, and easy workup makes this protocol practical and economically attractive.⁴⁰
5h. Synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs)

Nanocrystalline-ZrO₂ has been employed as a catalyst for the solvent-free synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) by a microwave (MW) assisted one-pot, multicomponent Biginelli condensation reaction of araldehydes, ethyl acetoacetate and urea or thiourea. DHPMs are obtained in good to excellent yield (Scheme 18) within short interval of time (10-20 min).⁴¹

5i. Synthesis of 4,6-diarylpyrimidin-2(1H)-ones (DAHPs)

An efficient, solvent-free, one-pot three-component cyclocondensation reaction between aldehyde, methylketone and urea to give 4,6-diarylpyrimidin-2(1H)-ones (DAPMs) using iodine as catalyst is described (Scheme 19). This new protocol provides a simple and environmentally benign route along with the associated advantages of good to excellent yield of the products (90-96%) and short reaction times (5-15 min) at 80 °C.⁴²
5j. Synthesis of α-Aminonitriles

Pasha et al report a highly efficient one-pot three-component condensation of carbonyl compounds, amines and TMSCN in MeCN; the reaction is significantly promoted by the catalytic amount of Cerium (III) chloride at ambient temperature in excellent yields without any adverse effect on the other substituents (Scheme 20). The method afforded an elegant alternative to the synthesis of α-aminonitriles. The reactions are fast, clean and the products obtained are of high purity.43

\[
\text{R-CHO} + \text{R'NH}_2 \xrightarrow{\text{TMSCN, Anhydrous CeCl}_3 (\text{10 mol \%)}} \text{MeCN, r.t.} \xrightarrow{1.25-2.5 \text{ h}} \text{R-CN} \]

\text{Scheme 20}

6. Organic reactions under solvent-free conditions

Due to the growing concern on the influence of the organic solvent on the environment as well as on human body, organic reactions without use of conventional organic solvents have attracted the attention of synthetic organic chemists.14 Although a number of modern solvents, such as fluorous media, ionic liquids and water have been extensively studied recently, not using a solvent at all is definitely the best option. Development of solvent-free organic reactions is thus gaining prominence. It is believed that solvent free organic synthesis and transformations are industrially useful and largely green.

In addition to this solvent-free organic synthesis is associated with many other advantages and synthetic applications are discussed in detail in chapter I.

7. Microwave Chemistry

Microwave chemistry is the science of applying microwave irradiation to chemical reactions.44-47 Microwaves act as high frequency electric fields and will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid. Polar solvents are heated as their component molecules are forced to rotate with the field and lose
energy in collisions. Semiconducting and conducting samples heat when ions or electrons within them form an electric current and energy is lost due to the electrical resistance of the material. Microwave heating in the laboratory began to gain wide acceptance following papers in 1986, although the use of microwave heating in chemical modification can be traced back to the 1950s. Although occasionally known by such acronyms as MEC (Microwave-Enhanced Chemistry) or MORE (Microwave-organic Reaction Enhancement) synthesis, these acronyms have had little acceptance outside a small number of groups.

Conventional heating usually involves the use of a furnace or oil bath, which heats the walls of the reactor by convection or conduction. The core of the sample takes much longer to achieve the target temperature. Microwave heating is able to heat the target compounds without heating the entire furnace or oil bath, which saves time and energy. It is also able to heat sufficiently thin objects throughout their volume, in theory producing more uniform heating.

Microwave heating can have certain benefits over conventional heating:

- reaction rate acceleration
- milder reaction conditions
- higher chemical yield
- lower energy usage
- different reaction selectivities

The concepts of microwave chemistry, its importance and the use of this methodology by various researchers and scientist is dealt in elaborate in Chapter II.

8. Mechanochemistry (Grinding)

Mechanochemistry can be as simple as grinding two reactants using a pestle and a mortar or with the use of ball mills. Ball mills, however are an alternative to grinding for large scale preparations in industries, ball mills have the advantages of requiring no physical effort, supplying greater power, being programmable, and allow more systematic studies of the process. The kinetic energy supplied during grinding can have several effects on a crystalline solid, including heating, reduction of particle size (with concomitant increase in surface area and the generation of fresh surfaces), formation of defects and dislocations in crystal lattices, local
melting, and even phase changes to alternative polymorphs.\textsuperscript{49,50} This mechanical-induced breaking of molecular bonds (mechanochemistry), results in more efficient mixing and increases the contact of reactants with each other.\textsuperscript{52,53} Besides that, other factors such as an increased temperature and an enhanced pressure can be responsible for the reactivity changes observed. The advantages and the different organic compounds synthesized using this methodology by various scientific groups in discussed in chapter V.

9. Sonochemistry

Besides solvent-free organic synthesis, ball milling and microwave heating, ultrasound irradiation has emerged as a powerful technique for the promotion of organic reactions.\textsuperscript{54} In order to affect chemical reactivity in liquids (power ultrasound), its frequency range must lie between microwaves and diagnostic ultrasound. The activation is caused by cavitation, which involves the creation, growth, and collapse of micrometer-sized bubbles that are formed when an acoustic pressure wave propagates through a liquid. According to the so-called “hot spot theory”, extreme local conditions occur inside the cavitating bubbles and their interfaces when they collapse. These have been estimated to be in the range of 4900-5200 K\textsuperscript{55} and 1700 atm.\textsuperscript{54} The interactions of acoustic waves with chemical systems lead to an energy transfer that can result in enhanced mechanical effects in heterogeneous processes and induce new reactivities. In most cases, the application of ultrasound does not affect the chemical pathways. The reaction rates are often comparable to those of non-irradiated systems, and the only role of ultrasound is then to mix the phases of a heterogeneous system. Thus, the increased yields and reaction rates are due to mechanical effects associated with the sound waves. Chemical effects of ultrasound (true sonochemistry) can only be expected if high-energy species that are released after cavitational collapse act as reaction intermediates. In these cases, changes in product distribution, switching of reaction mechanisms, or changes in regio- or diastereoselectivity may occur.\textsuperscript{54a}

10. Use of eco-friendly catalysts and solvents

Catalytic technologies play a key role in the economic development and growth of the chemical industries and contribute to around 20\% of world GNP (Gross National Product). A major
emerging and challenging area of catalysis is that of environmental pollution control. Great scientific efforts are being performed to find reactions that can be good alternatives for reactions that aren’t environment friendly, involves use of toxic chemicals, heavy metals, low yield and undesired byproducts. Catalysts provide a promising solution for many of the problems encountered in the field of organic synthesis, it may reduce or eliminate by-products in certain reactions or increase the activity by changing the catalyst by another one. Therefore, it is of great advantage and demand to carry out organic reactions using eco-friendly, less expensive and easy to handle catalysts.

Next, the solvent is a strategic parameter for chemical transformations occurring in solution phase and plays a crucial role for the implementation of such processes on a laboratory and industrial scale. On a molecular level, the solvent helps to bring reagents in direct contact and stabilises or destabilises intermediates and transition states. In process design, the use of solvents determines the choice of work-up procedures and requires recycling or disposal strategies. The aim should be on developing innovative ideas for the substitution of volatile organic solvents in solution phase synthesis. Emphasis will be laid on the development and application of alternative reaction media based on advanced fluids such as aqueous phases, ionic liquids (IL), supercritical phases, green organic solvents, or soluble polymers in all areas of chemical synthesis. The use of an universal eco-friendly solvent water in organic synthesis, its benefits and applicability is discussed in the forthcoming chapters.
11. References


5. Antigoni, K. Special Issue Reviews and Accounts *ARKIVOC*, 2009, 1, 81.


Introduction

Introduction

48. Microwave chemistry, Wikipedia, the free encyclopedia. (http://en.wikipedia.org/wiki/Microwave)