CHAPTER - 1

Introduction

The science of organic synthesis is constantly enriched by new inventions and discoveries pursued deliberately for their own sake or as goals within a program directed towards the synthesis of a target molecule. The ultimate goal of organic synthesis is to assemble a target compound from readily available starting materials and reagents in the most efficient way. This process usually begins with the design of a strategy, which involves various synthetic reactions to address individual synthetic objectives in a certain sequence. The creation of molecular diversity and complexity from simple and readily available substrates is one of the major current challenges of organic syntheses.

Organic chemicals remain as the important starting materials for a great number of major chemical industries. The production of organic chemicals as raw materials or reagents for other applications is a major sector of manufacturing polymers, pharmaceuticals, pesticides, paints, artificial fibers, food additives, etc., Organic synthesis on a large scale, compared to the laboratory scale, involves the use of enormous amount of energy, basic chemical ingredients from the petrochemical sector, catalysts and solvents.

Organic synthesis relies on the transformation of functional groups, or structural features exhibiting relatively high chemical reactivity. The formation of carbon-carbon single bonds is of fundamental importance in organic synthesis. As a result, there are an ever-growing number of methods developed for carbon-carbon bond formation. Generally, formation of a new bond requires the presence of either
a heteroatom, such as oxygen or a halogen, or unsaturation in the carbon backbone.\textsuperscript{2} The construction of several carbon-carbon bonds in a single chemical step represents a particularly efficient approach to the synthesis of complex molecular structures.\textsuperscript{3} Many of the most useful procedures of C-C bond formation involve the addition of organometallic species or enolates to electrophiles, as in the cases of Grignard reaction, aldol reaction, Michael reaction, alkylation reactions and coupling reactions.\textsuperscript{1} Synthesis of organic chemicals will be followed by the separation, purification, storage, packaging and distribution processes after the completion of reaction. During these processes, there are many problems of health and safety for workers in addition to the environmental problems caused by their use and disposition as waste.

1.1. Green chemistry

The chemical industry is a major player in human development and, unsurprisingly, an increased pressure has been put on chemists to develop sustainable processes.

The unavoidable responsibilities of the chemists reside in resolving the issues like,

A The adverse effect of some chemicals on the environment, health and safety
A The diminishing non-renewable resources,
A The need for sustainable development.

For this, the following ideas may be considered while planning a synthetic reaction,
< Designing reactions which are atom economical,
< Improving the reaction mass efficiency,
< Reducing the mass intensity through reduction of solvents; acids or bases for neutralization; or other substances required for reaction.

< Avoiding protection/deprotection steps that require additional reagents and generate waste.

< Planning selective chemical reactions.

Most of the reactions are found to be hazardous for the environment and also to human beings. In order to overcome these issues, a new science for the research and commitment is required and the term ‘Green Chemistry’ has been coined by Paul T. Anastas in the year 1991. It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry known as Green Chemistry. The concept of Green Chemistry has been defined as the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances and was developed in principles to guide the chemists in their search towards greenness. Green Chemistry with its 12 principles would like to see changes in the conventional ways that were used for decades to make synthetic organic chemical substances and the use of less toxic starting materials.

Thus, Green chemistry is the practice of chemical science and manufacturing in a manner that is sustainable, safe, and non-polluting and that consumes minimum amounts of materials and energy while producing little or no waste material. The practice of green chemistry begins with recognition that the production, processing, use, and eventual disposal of chemical products may cause harm when performed incorrectly. In accomplishing its objectives, green chemistry and green chemical engineering may modify or totally redesign chemical products and processes with the objective of minimizing wastes and the use or generation of particularly
dangerous materials. And it does so in a manner that is economically feasible and cost effective. In one sense, green chemistry is the most efficient possible practice of chemistry and the least costly when all of the costs of the practice of chemistry, including hazards and potential environmental damage are taken into account.

1.1.1. Aspects of Green Chemistry

The areas proposed for special focus under the green chemistry principles were the following. They were selected with emphasis on economic considerations and for their future contribution to sustainable development.

Green Chemistry talks about the

A Waste minimization,
A Improved atom efficiency,
A Process intensification,
A Energy efficiency,
A Separation process,
A Developing alternative reaction conditions,
A Safer reactions and reagents,
A Catalysis,
A Solvent replacement,
A Use of alternative renewable feedstocks,
A Using non-toxic Reagents,
A Use of solvent free or recyclable environmentally benign solvent systems,
A Use of natural processes, like biocatalytic techniques,
A Environmental impact, and
A Cost effective.
1.1.2. Green chemistry - A sustainable chemistry

There are several important aspects in which green chemistry is sustainable:

A Economic: At a high level of sophistication, green chemistry normally costs less in strictly economic terms than chemistry as it is normally practiced.

A Materials: By efficiently using materials, maximum recycling, and minimum use of virgin raw materials, green chemistry is sustainable with respect to materials.

A Waste: By reducing in so far as possible, or even totally eliminating their production, green chemistry is sustainable with respect to wastes.

1.1.3. Environmentally benign alternatives

The rapid development of new chemical technologies and the vast number of new chemical products in the last decades turned the attention of environmentalists to remedial actions for the negative impacts (monitoring environmental pollution, reduction of pollutants, recycling, etc.,).

Consequently, many efforts have been devoted to the finding of sustainable reactions from the feedstocks to solvents, to synthesis and processing and green chemistry actively seeks ways to produce materials in a way that is more benign to human health and the environment. Green chemistry encompasses a series of considerations in the design of environmentally benign protocols. A major point in the design of greener and more sustainable processes relates to the efficiency of the process, which has to take into account several parameters including energy, material consumption (preferably use of bio-renewable resources), man-power
1.1.4. Catalysis

Catalyst is a reagent which enhances the rate of a chemical transformation but is not consumed during the reaction. Since the rate is enhanced, lower reaction temperature can be used and thus can save energy. Some catalysts can improve the selectivity of a reaction, thus giving higher yield of the desired product. A catalytic reaction is in general superior to a reaction requiring stoichiometric reagents in terms of reducing waste.

Processes catalyzed by acids and bases play a key role in the oil refining and petrochemical industries and in the manufacture of a wide variety of specialty chemicals such as pharmaceuticals, agrochemicals, flavors and fragrances. Examples include catalytic cracking and hydrocracking, alkylation, isomerization, oligomerization, hydration/dehydration, esterification and hydrolysis and a variety of condensation reactions, etc. Many of these processes involve the use of traditional Bronsted or Lewis acids in liquid-phase homogeneous systems. Similarly, typical bases include NaOH, KOH, NaOMe and KO-t-Bu. Their subsequent neutralization leads to the generation of inorganic salts which ultimately end up in aqueous waste streams.

The above conventional catalysts may be replaced by the solid acids and bases. The use of solid acids and bases (recyclable catalysts) such as zeolite,
mesoporous materials, metal oxides, etc., as catalysts provides additional benefits as follows,

A Separation and recycling is facilitated, leading to lower production costs.

A Solid acids are safer and easier to handle than their liquid counterparts, e.g. 
\[ \text{H}_2\text{SO}_4, \text{HF} \], that are highly corrosive and require expensive construction materials.

A Contamination of the product by trace amounts of (neutralized) catalyst is 
generally avoided when the catalyst is a solid.

1.1.5. Safer solvents and auxiliaries

The use of solvents is a constant source of worry since it gives rise to 
toxicity, hazard, pollution and waste treatment issues. Moreover, solvents generally 
account for the major source of the wasted mass of a given process or a synthetic 
pathway.\(^6\) The ideal green solvent should be safe for both the human beings and the 
environment and its use and manufacture should be sustainable.\(^7\)

A Solvents are used as reaction media, in separation/purification and in cleaning 
technologies;

A Many common organic solvents (e.g. hexane, chloroform, ether,) are volatile and 
contribute to environmental pollution as volatile organic compounds (VOC);

A Some common organic solvents are toxic: benzene is known to cause leukemia; 
excessive exposure to \(n\)-hexane causes neurotoxicity;

A The use of auxiliary substances (e.g. solvents, separation agents, drying agents) 
should be reduced or made unnecessary where possible, and innocuous when 
used.
In order to remove organic solvents from the chemical process, an important aspect of green chemistry pertains to the elimination of volatile organic solvents or their replacement by non-flammable, non-volatile, non-toxic and inexpensive “green solvents”. In this regard, development of solvent-free alternative processes is the best solution, especially when either one of the substrates or the products is a liquid and can be used as the solvent of the reaction. However, if solvents are crucial to a process, we should select solvents that will have no or limited impact on health and the environment. Indeed, the use of unconventional green solvents in organic reactions has improved not only the aspect of the reactions from the viewpoint of green and sustainable properties, but also the synthetic efficiency by stabilizing the catalyst, changing the reaction selectivity or facilitating product isolation.

Together with solvents, the design of more environmentally sound and low impact protocols by using a range of alternative synthetic methods has become an important practice in organic synthesis. The use of magnetically separable nanomaterials, ionic liquids, solid-state reactions, microwave-assisted synthesis, and reactions in aqueous media highlights the key developments in designing greener protocols with improved efficiency.

1.1.6. Solvent-free organic syntheses

Solvent-free processes make use of neat or solid-state materials. Solid-state organic reaction occurs more efficiently and more selectively than does its solution
counterpart, since molecules in a crystal are arranged tightly and regularly. Furthermore, the solid-state reaction (or solvent-free reaction) has many advantages: reduce pollution by minimizing waste and volatile organic compound (VOC) emission; low costs, and simplicity in process and handling. These factors are especially important in industry. When greater selectivity is required in the solid-state reaction, host-guest chemistry techniques can be applied efficaciously.

Baeyer Villiger oxidations of ketones with m-chloroperbenzoic acid proceeded much faster in the solid state than in solution.\textsuperscript{22} When a mixture of powdered ketone and 2 mol equiv of m-chloroperbenzoic acid was kept at room temperature, the oxidation product was obtained in good yield.

![Scheme 1.1 Baeyer Villiger oxidation](image)

1.1.7. Alternative reaction media

Glycerol

In recent years, biodegradable glycerol has been used in more than 2000 established procedures as an important starting material in the drug, food, beverage, fine chemicals and synthetic raw materials industries. The major applications are in toiletries, sweeteners, softening agents, cosmetics, surface coatings, and paints, among other products, and especially in important organic transformations.\textsuperscript{23}
A highly efficient and catalyst-free green method has been described for the one-pot three-component synthesis of 4H-pyran derivatives using glycerol as an inexpensive, biodegradable, commercially available and reusable promoting medium.\(^{24}\)

![Scheme 1.2 Synthesis of pyran](image)

Deep eutectic solvents (DESs)

Deep eutectic solvents (DESs) are mixtures of solid ammonium salt and a hydrogen bond donor and have low melting points (often below room temperature), low vapor pressures, high thermal stabilities, and are commonly water-soluble.\(^ {25}\) In general, DESs are synthesized from low-cost starting raw materials, typically by mixing ethylammonium chloride or choline chloride (ChCl) with an organic hydrogen-bond donor like acetamide, urea, malonic acid, etc., DESs have the advantage of being, in general, non-toxic and biodegradable as compared to ionic liquids; they have been successfully used for the synthesis of greener raw materials.\(^ {26}\)

A one-pot three component reaction of 2-aminoaryl ketones, aldehydes and ammonium acetate has been reported in maltose/DMU/NH\(_4\)Cl deep eutectic solvent and the desired quinazoline was obtained with 92% yield.\(^ {27}\)
Ionic liquids

Ionic liquids are used extensively in recent years as alternative solvents in organic synthesis. These substances are variously called liquid electrolytes, ionic melts, ionic fluids, fused salts, liquid salts or ionic glasses. Ionic liquids have many applications, as powerful solvents and electrically conducting fluids (electrolytes). Salts that are liquid at near ambient temperature are important for electric battery applications. Ionic liquids are fused salts with melting points less than 100 °C and they are liquids containing only ions.

Cations                  Anions

NR₄⁺                     X⁻
PR₄⁺                     BF₄⁻, PF₆⁻, SbF₆⁻, AlCl₄⁻
SR₃⁺                     CF₃CO₂⁻, CF₃SO₃⁻
\[\text{N}^+\text{N}^-\text{n-Bu} \quad \text{(CF₃SO₂)}₂\text{N}⁻\]
\[\text{n-Bu} \quad \text{N}^-\text{SO₂} \]

Scheme 1.3 Synthesis of quinazoline
Intriguing properties of ionic liquids

A air stable,
A no measurable vapor pressure,
A lack of flammability,
A high conductivity,
A high thermal and chemical stability for wide temperature range,
A Recycling of ionic liquids for reuse is possible without decrease in yield and hence environmentally friendly,
A Zero volatile organic compound emissions (VOC),
A Fine tuning of the properties of ionic liquids resulting from the variation of cations or anions.

The reaction of an enolizable ketone, aryl aldehyde and acetonitrile or benzonitrile in the presence of TMSCl using a Bronsted-acidic ionic liquid 3-methyl-1-(4-sulfonic acid) butylimidazolium hydrogen sulfate [MIM-(CH$_2$)$_4$SO$_3$H][HSO$_4$] as catalyst gave a family of $\beta$-amido ketones in good yield.$^{28}$

\[
\begin{align*}
\text{Ar}^\text{CN} + \text{R}_1^\text{CN}^\text{CN} + \text{R}_2^\text{CN}^\text{CN} & \xrightarrow{\text{TMSCl}} \text{R}_1^\text{CN}^\text{CN}^\text{CN} + \text{R}_3^\text{CN}^\text{CN} \\
\text{Ar}^\text{CN} + \text{R}_1^\text{CN}^\text{CN} & \xrightarrow{\text{TMSCl}} \text{R}_2^\text{CN}^\text{CN} + \text{R}_3^\text{CN}^\text{CN} \\
\end{align*}
\]

Scheme 1.4 Synthesis of $\beta$-amido ketones

Supercritical carbon dioxide and water

Supercritical fluid is any liquid substance at a temperature and pressure above its critical point, where distinct liquids and gas phases do not exist. It can effuse through the solids like a gas and dissolve materials like a liquid. In addition,
close to the critical point, small changes in the pressure or temperature results in large changes in density, allowing many properties of a supercritical fluid to be “fine-tuned”. Supercritical fluids are suitable for organic reactions in a range of industrial and laboratory processes. Carbon dioxide and water are the most commonly used supercritical fluids. The supercritical properties can be explained as “green chemistry” credentials in chemistry with high yields and minimum waste.

The Baylis-Hillman reaction has been efficiently carried out in scCO₂. Enhanced reaction rates were observed relative to comparable solution phase reactions.²⁹

![Scheme 1.5 Baylis-Hillman reaction](image)

Water

In view of greenness approach and economic concerns, research endeavors are directed towards aqueous-mediated reactions in recent years.³⁰ The related investigations have highlighted certain limitations and drawbacks such as insolubility of reactants, longer reaction times, lower yields, limited selectivity, etc., The limitations can be circumvented by means of ingenious “chemical tricks” such as mixing reactants in water or mixtures of solvents like water : ethanol,³¹ the use of surfactant in aqueous media, etc.,³²
Inspite of the solubility problems, it is now well established that the unique structure and physicochemical properties of water lead to particular interactions like polarity, hydrogen bonding, hydrophobic effect and trans-phase interactions that might greatly influence the reaction course.\textsuperscript{33} In this way, organic synthesis in water will be a part of the effort for sustainable development.

For clear solutions of soluble organic reactants in water, the effects operating are (i) the hydrophobic effect, which speeds reactions, (ii) hydrogen bonding effects on reactants and transition states, which may add to or oppose the hydrophobic effect, and (iii) water polarity effects, which may again increase or decrease the reaction rates.\textsuperscript{33} For highly insoluble reactants involving two-phase systems, the on-water effect involves trans-phase interactions of water with transition states and reactants. As the reactant solubilities decrease, the organic reactions performed in the water medium pass through wide boundary regions where in-water and on-water phenomena are occurring simultaneously and many reactions between small organic molecules take place in these realms. The extent of the insolubility of the reactants in water has rarely been quoted to date in accounts of reactions which are described as being on-water because of the visible appearance of two phases.\textsuperscript{33}

The early work of Breslow demonstrated how water enhanced the Diels Alder reactions, one of the first cases of which was originally reported using water as a reaction medium.\textsuperscript{34} The subsequent exploration of the hydrophobic effect in organic reactions by the Breslow group greatly increased the interest in water by organic chemists.\textsuperscript{35} The use of water as a medium for organic synthesis has further enhanced since the masterful use of concept and language by Narayan et al. who
described successful reactions as being “on-water” for cases where the reactants are insoluble in water.\textsuperscript{36}

The use of water as the reaction medium offers several advantages as:

A Cheap, non-inflammable, non-toxic and safe for use;

A Eliminates the additional efforts required to make the substrates/reagents dry before use and thus reduces/eliminates the consumption of drying agents, energy and time;

A The unique physical and chemical properties of water often increase the reactivity or selectivity unattainable in organic solvents;\textsuperscript{37} and

A The product may be easily isolated by filtration.\textsuperscript{38}

1.1.8. Biocatalysis

Through millions of years of evolution and “sustainability,” nature developed highly efficient and selective means to achieve the desired transformations. The potential usefulness of various catalysts of nature, such as enzymes\textsuperscript{39} for organic synthesis, has become more and more recognized. Frequently, biocatalysis leads to extremely high reaction rates and enantio selectivities that go beyond the reach of chemical catalysts. These developments have provided powerful and parallel tools in the synthetic chemist’s toolbox. However, the high substrate specificity of enzymes presents a dilemma for synthetic chemistry in which wide substrate applicability is desired.

1.1.9. Alternative energy sources

Environmentally challenged protocols have to be changed from their traditional methods. Unconventional alternative energy sources including microwave and ultra-sound irradiation as well as more recently introduced flow.
chemistry have been explored as useful tools to improve the green credentials of organic synthetic protocols.

**Sonochemistry**

It is well reported recently that, the use of ultrasound can start and enhance the chemical reaction. Sonochemical reactions by ultrasound are very advanced “green” techniques with exceptional high yields. There are three classes of sonochemical reactions: homogeneous sonochemistry of liquids, heterogeneous sonochemistry of liquid-liquid or solid-liquid systems, and overlapping with the previous techniques, sonocatalysis. The chemical enhancement of reactions by ultrasound has been explored and has beneficial applications in mixed phase synthesis, materials chemistry, and biomedical uses. All these techniques have been advanced with green chemistry principles in mind, since industrial production of chemical substances is the fundamental technology producing environmental problems, waste and toxic by-products.

The synthesis of 1,8-dioxo-octahydroxanthene derivatives has been described by Jin and co-workers. Reactions between aromatic aldehydes and 2 equiv of 1,3-cyclohexanedione were carried out in water using ultrasound resulted in products in excellent yields and high purity. p-Dodecyl benzene sulfonic acid (DBSA) was employed as a catalyst and aromatic aldehydes possessing either electron-donating or electron-withdrawing substituents all reacted very well.

![Scheme 1.6 Synthesis of 1,8-dioxo-octahydroxanthene](image)

Scheme 1.6 Synthesis of 1,8-dioxo-octahydroxanthene
Microwave

Microwave radiation is generated by a magnetron; the microwaves are guided into the cavity by a waveguide and reflected by the walls of the cavity. When a molecule is irradiated with microwaves, it rotates to align itself with the applied field. Qualitatively, the larger the dielectric constant of a substance, the greater the coupling with microwave, and thus the greater heating, (ie..) polar compounds like water, methanol, dimethyl formamide, etc., are heated when irradiated with microwave whereas, non-polar compounds, hexane, toluene, ethers, carbon tetrachloride, etc., may not be heated with microwave irradiation.

Microwave-assisted eco-friendly organic synthesis has become a new trend with many applications in synthesizing organic chemicals. Organic reactions under the microwave irradiation have many advantages compared to the conventional reactions which need very high temperatures. Microwave assisted reactions are “cleaner”, last only very few minutes, have high yield and produce minimum waste. Microwave assisted organic synthesis has become an expanding field in synthetic research. The rapid microwave heat transfer allows reactions to be carried out very much faster compared to conventional heating methods often resulting in increased product yield. Furthermore, the products of temperature sensitive reactions from kinetic or thermodynamic pathways can be selectively tuned and isolated.

The Biginelli reaction has been successfully carried out to yield phenyl-substituted derivatives of dihydropyrimidinones on a microwave reactor.
1.2. Multi Component Reactions (MCR)

The conventional multistep preparation of a complex molecule generally involves a large number of synthetic operations, including extraction and purification processes in each individual step. This leads to not only synthetic inefficiency but also generates large amounts of waste. The development of processes that allow the creation of several bonds in a single operation has become more attractive. Multicomponent reactions (MCRs)\(^\text{45}\) can be defined as convergent chemical processes, where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials. MCRs offer the opportunity to achieve a number of fascinating and challenging transformations in organic synthesis. The eco-friendly multicomponent approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently. The synthesis of many important heterocycles could be acquired by MCRs. MCRs have gained significant importance as a tool for the synthesis of a wide variety of useful compounds, including pharmaceuticals.\(^\text{46}\) MCRs offer advantages like convergence, operational simplicity, facile automation, reduction in the number of workup, extraction and purification processes, and hence minimize waste generation, rendering the transformations green. One-pot MCRs often shorten reaction periods, giving higher overall chemical yields than multiple-
step syntheses, and therefore can reduce the use of energy and man-power. MCRs are useful for the expedient creation of chemical libraries of drug-like compounds with high atom economy and high levels of molecular complexity and diversity, thereby facilitating identification/optimization in drug discovery programmes. They exhibit a very high bond-forming-index (BFI), for example, several non-hydrogen atom bonds are formed in one synthetic transformation. Therefore MCRs are often a useful alternative to sequential multistep synthesis. For all these reasons, the development of new multicomponent reactions is rapidly becoming one of the frontiers of organic synthesis. Many basic MCRs are name reactions, such as, Ugi, Passerini, van Leusen, Strecker, Hantzsch, Biginelli, or one of their many variations.

Many new one-pot MCRs have been successfully developed by means of using an innovative solvent instead of conventional organic solvents. Moreover, taking advantage of utilizing unconventional solvents as reaction media, various known MCRs have also been improved in terms of reaction yield, substrate generality, isolation of products and catalyst recycling.

1.2.1. Literature review for Multi Component Reactions

Mannich reaction

Mannich reaction catalysed by L-proline, using different ketones, such as acetone and α-hydroxy-acetone as a source of the nucleophile, aniline derivatives and aldehydes as the source of the electrophile has been reported by List et al.
Tietze reaction

The Tietze multicomponent reaction (Knoevenagel/Diels-Alder process) between Meldrum’s acid, aldehydes and \( \alpha,\beta \)-unsaturated methyl ketones catalyzed by the thiazoline derivative gave spirolactones.\(^{56}\)

Michael reaction

Michael-type multicomponent reaction was performed by an aldol reaction of benzaldehyde with acetone to give the corresponding benzylidenacetone, which suffered the 1,4-addition of diethyl malonate in the presence of substoichiometric amounts of proline amine derivative.\(^{57}\)
Ugi reaction

The Ugi four-component reaction, first described in 1959, involves the condensation of carbonyl derivatives, amines, carboxylic acids and isocyanides to afford α-amino acid derivatives. The Ugi reaction is the most studied and widely used MCR reaction, resulting from the high degree of diversity imposed by this process. An interesting example was described by Dyker and co-workers towards the synthesis of chiral isoindoles and dihydroisoquinolines.

![Scheme 1.11]

Passerini reaction

The Passerini three-component reaction involves the condensation of carbonyl compounds, carboxylic acids and isocyanides to afford α-acyloxy carboxamides. Andreana et al applied chiral tridentate indan (pybox) Cu(II) Lewis acid complex to activate the carbonyl species and control the stereochemical outcome.

![Scheme 1.12]
Synthesis of pyrano[2,3-c]pyrazoles

Vasuki et al reported an interesting four component reaction for the synthesis of pyrano[2,3-c]pyrazoles using water as a solvent. The reaction of hydrazine hydrate, ethyl acetoacetate, p-anisaldehyde, and malononitrile was carried out in the presence of catalytic piperidine (5-10 mol %), the product was obtained in a yield of 94% within 5 min.

\[
\begin{align*}
&
\begin{array}{c}
\text{H}_2\text{N–NH}_2 \\
\text{O} \\
\text{O}
\end{array} \\
&
\begin{array}{c}
\text{C} \\
\text{C} \\
\text{O}
\end{array}
\end{align*}
\]

Water, RT

![Scheme 1.13](image)

Synthesis of pyrano pyrazoloamines

Eco-friendly multicomponent protocols have been reported for the synthesis of pyrano pyrazoloamines in excellent yields by employing water as the reaction medium and L-proline as the catalyst.

\[
\begin{align*}
&
\begin{array}{c}
\text{R}^1
\end{array} \\
&
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
&
\begin{array}{c}
\text{R} \\
\text{O}
\end{array}
\end{align*}
\]

\[
\begin{align*}
&
\begin{array}{c}
\text{NC–R}^3 \\
\text{C} \\
\text{C} \\
\text{O}
\end{array} \\
&
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{align*}
\]

L-Proline

Water, reflux

![Scheme 1.14](image)
Four-component catalyst-free reaction in water

A catalyst-free combinatorial library of novel 2-amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives has been developed through a four component reaction between hydrazine hydrate, ethyl acetoacetate, 2-hydroxybenzaldehydes and malononitrile in water at ambient temperature. The four-component catalyst-free reaction protocol developed in water resulted in a potential medicinal scaffold.

![Reaction Scheme](image)

Scheme 1.15

Synthesis of 2-amino-chromene

Solhy et al. described an efficient catalytic system by using nanostructured diphosphate Na$_2$CaP$_2$O$_7$, with which an environmentally benign synthesis of 2-amino-chromene through a three-component reaction of 1-naphthol, malononitrile and aldehyde has been successfully performed in water.

![Reaction Scheme](image)

Scheme 1.16
1.3. Spiro compounds

Natural compounds present sometimes very complex scaffolds with a well-defined three-dimensional structure. This complexity is generally correlated with stereospecificity in their biological properties. One of the most common goals for organic chemists is the development of new methodologies to build very complex structures in a stereocontrolled fashion.

Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their interesting conformational features and their structural implications on biological systems. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of their biological activities. Compounds with spiro skeletons not only constitute subunits in numerous alkaloids, but are also templates for drug discovery and have been used as scaffolds for combinatorial libraries. Synthesis of new substituted spiro derivatives has attracted the attention of synthetic organic chemists due to their remarkable biological activities.

Spirocyclic structures are abundant in many natural products and their enantioselective syntheses have always been a challenge for synthetic organic chemists. These natural products have a fascinating architecture, and possess various biological activities such as anticancer properties, contraceptive action, and antimigraine activity. Several natural products have this motif in their structure: gelsemine, spirotryprostatin A and B, marcfortine B, phalarine, coerulescine, horsfiline, pseurotin, agarospirol, pteropodine, isopteropodine, etc., are few
examples. For this reason, the quest for new synthetic methodologies that allow the construction of spiro compounds is a common goal for many chemists.

Heterocyclic compounds particularly spirooxindoles with nitrogen-containing five membered ring have played an important role in the field of medicinal chemistry. Spirocyclic oxindoles in particular have emerged as attractive synthetic targets because of their prevalence in numerous natural products and important biological activities. Furthermore, the three-dimensional shape of spirooxindoles is an attractive target to complement the flat heterocyclic compounds encountered in many drug discovery programs. The synthetic challenge of the spiro motif continues to encourage the development of creative methods to access these important structures. Recent synthetic methods to access spirocyclic oxindoles include formal cycloaddition, \(^\text{72}\) organocascade, \(^\text{73}\) Prins cyclization, \(^\text{74}\) and other cyclization reactions. \(^\text{75}\) Each of the aforementioned methods results in a different class of spirocycle that may show promise as biologically active compounds.

1.3.1. Biologically active spirooxindole moieties

The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids. \(^\text{76}\) The spirooxindole structural system represents an important structural motif present in a number of bioactive natural products such as coerulescine, horsfiline, welwitindolinone A, spirotetryprostatin A and B, elacomine, alstonisine, nonpeptidyl growth-hormone secretagogues (MK-0677) (Fig. 1.1). \(^\text{77}\) For example, the alkaloids spirotetryprostatin A and B, isolated from the fermentation broth of Aspergillus fumigatus, have been identified as novel inhibitors of microtubule assembly, \(^\text{78}\) and pteropodine and isopteropodine have been shown to
modulate the function of muscarinic serotonin receptors and coerulescine displays a natural local anesthetic effect.\textsuperscript{79} The spirooxindole system is also the core structure of many synthetic pharmaceuticals of very wide ranging pharmacological and biological activities such as antimicrobial, antitumor, antibiotic, and inhibitors of human NK-1 receptor.\textsuperscript{80}

Fig. 1.1 Naturally occuring products with spirooxindole core

1.3.2. Literature review on the synthesis of spiro compounds using catalysts

Synthesis of spirochromene

A clean and simple one-pot three-component reaction of the synthesis of spirochromene derivatives catalyzed by ammonium chloride in water\textsuperscript{81} has been reported by Dabiri et al., The utility of the described methodology in MCRs is highly promising as it allows the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the procedure.
Synthesis of spiroindoline-pyranopyrazoles

A facile, one-pot and four-component procedure has been developed for the preparation of 10H-spiro[indoline-3,4’-pyrano[2,3-c]pyrazole]-5’-carbonitiles\(^{82}\) of potential synthetic and biological interest. The method is simple, starts from readily accessible commercial reagents, and provides biologically interesting spirooxindole derivatives in good yields.

Synthesis of spirooxindoleoxazolines

A regio- and stereoselective cyclization between isatins and 5-methoxyoxazoles has been developed using catalytic titanium(IV) chloride (10 or 20 mol %) to afford spiro[3,3’-oxindoleoxazolines] in excellent yield and diastereoselectivity.\(^{83}\) Substitution at the 4-position of the oxazole controls
nucleophilic attack to provide either the 2-oxazoline or 3-oxazoline spirocycle with excellent regiocontrol.

Scheme 1.19

Synthesis of spirooxindoles

The synthesis of spirooxindoles via Michael-Michael gold catalyst has almost diastereo- and enantiopure forms. Moreover, the reaction worked well with several heterocycles such as oxindoles, benzofuranones, pyrazolones or azlactones rendering the final spiro compounds in good yields and excellent stereoselectivities.

Scheme 1.20

Synthesis of spiro chromanone

A direct and facile access to various enantio enriched spirocyclic [4-chromanone-3,3’-pyrrolidine] derivatives has been achieved via Cu(I)/TF-Bipham Phos-catalyzed asymmetric 1,3-dipolar cycloaddition reaction. 

28
Scheme 1.21

Synthesis of dioxolanes

The reaction of isatin with ethylene glycol has been reported to form the spiro-dioxolane-oxindoles under homogeneous\textsuperscript{86} condition, using p-TSA as a catalyst.

Scheme 1.22

Synthesis of xanthenes derivatives

A 2:1 molar reaction of 2-hydroxynaphthalene-1,4-dione and isatin in the presence of a catalytic amount of p-TsOH proceeded smoothly in water under refluxing for 24 h to furnish the spiro[dibenzo[b,i]-xanthene-1,3,3′-indoline]-2′,5,7,12,14-pentaone in 80% yield.\textsuperscript{87}

Scheme 1.23
Synthesis of spiro benzothiazoline

The spiro benzothiazoline oxindoles in this phenolic series can be prepared via a substitution at the isatin ring nitrogen and subsequent reaction with thioanisole at reflux temperature to afford the spiro benzothiazoline-oxindole as a sole product.

\[
\begin{align*}
\text{R} & \quad \text{H}_2\text{N} & \quad \text{dryxylene} & \quad \text{ZnCl}_2 \\
\text{O} & \quad \text{HS} & \quad \text{ZnCl}_2 \\
\text{R} & \quad \text{HN} & \quad \text{S} & \quad \text{N} \\
\text{O} & \quad \text{S} & \quad \text{N} & \quad \text{S} & \quad \text{N} \\
\end{align*}
\]

Scheme 1.24

1.3.3. Literature review on the synthesis of spiro compounds without using catalysts

Synthesis of spirooxindoles

A series of novel spirooxindoles have been synthesized through 1,3-dipolar cycloaddition of an azomethine ylide generated from isatin and sarcosine or L-proline with the dipolarophile 1,4-naphthoquinone followed by spontaneous dehydrogenation.

\[
\begin{align*}
\text{O} & \quad \text{NH} & \quad \text{OH} & \quad \text{O} & \quad \text{Reflux} & \quad \text{EtOH} \\
\text{O} & \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{O} \\
\end{align*}
\]

Scheme 1.25
Synthesis of azetidinones

The reactions of diarylketenes, obtained from 2-diazo-1,2-diarylketenes with 3-alkylimino-N-methylindolin-2-ones have been reported to yield spiro fused 2-azetidinones in good yields.\textsuperscript{90}

\[
\begin{align*}
\text{Ar}_2\text{C}=\text{O}_2\text{N}_2 + \text{N}-\text{R} & \xrightarrow{\text{benzene}} \text{Ar}_2\text{C}=\text{O}
\end{align*}
\]

Scheme 1.26

Synthesis of spiroindoline derivatives

A green, operationally simple and highly efficient one-pot three-component approach for the synthesis of spiro[indoline-3,4′-thiopyrano[2,3-b]indole] derivatives has been developed by the domino reaction of indoline-2-thione, isatin and ethyl cyano acetate or malononitrile in ethanol at 80 °C for just 20 min.\textsuperscript{91}

\[
\begin{align*}
\text{R} + \text{CN} & \xrightarrow{\text{EtOH, 80 °C}} \text{R} \text{N} \text{O} \text{H} \text{S}^2
\end{align*}
\]

Scheme 1.27

Synthesis of spiroquinazoline oxindoles

The reaction of isatins with 2-aminobenzylamine in methanol at room temperature led to the formation of spiro tetrahydroquinazoline oxindoles as products.\textsuperscript{92}
1.4. Scope of the present work

The work presented in this Ph.D. thesis was undertaken with the aim of replacing hazardous reaction conditions by greener methods for the effective synthesis of spiro compounds and a few other important heterocyclic compounds.

The chapter-I presents an overview of the basic introduction and need for green chemistry. The environmentally benign alternatives such as catalysis, solvent-free organic synthesis, alternative reaction media like glycerol, deep eutectic solvents, ionic liquids, supercritical fluids and water have been concisely reported. A brief description on biocatalysis and alternative energy resources has also been given. An account on multicomponent reactions with selected examples and general introduction on spiro compounds, their biological activities and their synthetic methods using catalysts and without catalysts have been presented in this chapter.

Chapter-II presents the catalyst free synthesis of novel spiropyrrrolizidine/spirothiapyrrolizidine/spiropyrrolizidine derivatives and acenaphthenequinone spiropyrrrolizidine/acenaphthenequinone spirothiapyrrolizidine derivatives using the easily available starting materials such as isatin, secondary amino acids and chalcone at ambient conditions in methanol without any hazardous substances such as catalysts. Chapter-III presents the synthesis of a range of various
spiroquinazolinone derivatives from anthranilamide and ketones such as 1,2-
dicarbonyl compounds/simple cyclic ketones/cyclic 1,4-dicarbonyl compounds
using p-TSA as a catalyst under milder reaction conditions. Chapter- IV includes
the synthesis of novel spiro chromene/spiro chromene indene derivatives via a one-
pot water mediated multicomponent reaction of isatin, cyclic dicarbonyl compounds
and acyclic esters, under reflux conditions.

Chapter-V explains the one-pot multicomponent, ceric ammonium nitrate
catalyzed synthesis of indazolotrione from phthalic anhydride, hydrazine, dimedone
and aromatic aldehydes and a few novel indazolodione derivatives from phthalic
anhydride, hydrazine, 1,2-dicarbonyl compounds and malononitrile at room
temperature. Chapter-VI deals with the one-pot multicomponent water : ethanol
mediated synthesis of a number of novel chromeno pyrimidine derivatives
from salicylaldehyde, 1,3-cyclic/acyclic dicarbonyl compounds and barbituric/
thiobarbituric acid.

Finally, we have presented a brief summary of the thesis.
References


