CHAPTER I

Literature Overview

CHAPTER I

1. Introduction

Organic chemists are constantly developing more successful methods to prepare useful fine and bulk chemicals. Nowadays their strategies are not only influenced by economical aspects, expressed in improvement of reaction yield and purity, but the environmental aspect is gaining more importance as well. As the minimization of using hazardous reagents and solvents is one of the main reasons why this study concerning the design of reaction conditions in the absence of any solvent was performed, this chapter will start with a brief introduction describing the principles of performing more environmentally-friendly chemistry with a focus on solvent–free multicomponent reactions.

1.1. Green Chemistry

Using traditional synthetic methods, organic chemists can access almost any organic molecule, leading to widespread availability of drugs that save lives and improve quality of life for billions. While traditional synthesis has been incredibly successful, it is inherently wasteful. These wastes originate from a number of sources; and in a typical solution phase chemical synthesis they are the obvious by-products such as volatile gases or solvents, released during the reaction, by-products which must be separated from the desired product during purification; solvents, which usually are contaminated and require purification before they may be recycled which in itself is an energy consuming process and lastly; salts and solutions of salts produced in washing and separation steps. Additionally, there are other less often considered wastes such as unconverted reagents, unrecovered products, and the products of derivatising or protecting agents which are later removed from the target molecule and discarded.

The process of elimination of these wastes maybe achieved by one or more alternatives such as using alternative media like ionic liquids, supercritical carbon dioxide or water in place of volatile solvents. It may also be achieved by completely redesigning

synthetic routes to known compounds which avert the need of costly and waste producing separation techniques. In addition, newer and more effective methods of activation or methodologies maybe devised, which yield vastly purer reaction products or better conversion of starting materials, particularly with respect to atom economy.

Every step taken to avoid the formation or that result in a significant decrease of the above forms of wastes during a synthetic transformation takes us a step closer to what can be termed as a "cleaner synthesis". Thus, the research for more environment friendly materials and for mild, direct, non-polluting synthetic methods which is driven primarily by the moral imperative of avoiding an irreversible damage to the environment and by the economic motivation of avoiding the high cost of recovering polluted air and water has led to a paradigm shift in organic synthetic methodology, popularly known as Green Chemistry.[1]

The term Green Chemistry was introduced in the early 1990s and defined as "*the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances*".[1] Prof. Anastas explains that the goal of Green Chemistry was never just clean-up. In his conception, green chemistry is about redesigning chemical processes from the ground up. It's about making industrial chemistry safer, cleaner and more energy-efficient throughout the product's life cycle, from synthesis to clean-up to disposal. Green Chemistry is of global concern, with the need to develop products and processes which require less energy; generate less waste; use less organic solvents; or use no solvent; have no environmental or health problems associated with the products; allow recycling of the products or environmental degradation to harmless materials.

To address the issues in Green Chemistry, knowledge of the guiding principles and the assessment of the process sustainability constitute two important areas. Thus these two pertinent topics in Green Chemistry need to be discussed as we have focused on working on similar lines.

1.1.1. Green chemistry principles

Undoubtedly, environmental concerns have been the primary factor that has brought more awareness into the development of green chemistry. Essentially, to guide chemists towards more environmentally benign organic synthesis one needs to follow certain basic tenets, the basic principles of Green Chemistry (Anastas and Warner, 1998).

The Green Chemistry Principles

1. It is better to prevent waste than to treat or clean up waste after it has been created.
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 methods 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 minimizing their toxicity.
5. The use of auxiliary substances (*e.g.*, solvents, separation agents, *etc.*) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized.
7. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. Unnecessary derivatisation should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
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 break down into innocuous degradation products and do not persist in the environment.
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 be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

1.1.2. Green Chemistry Metrics

The synthetic methods that we use to transform our starting materials will need to be the focus of basic research in Green Chemistry, since the methods that were widely used are lacking both in terms of material and energy efficiency over and above the consequences of the reagents being used for humans and the environment. Designing systems that minimize energy consumption will be increasingly important as a Green Chemistry goal. Newer technologies with a smoother scale-up from bench scale to pilot scale and then to commercial scale needs to be developed to make large-scale synthesis more efficient. In addition, the central goal of Green Chemistry is not only to ensure that energy efficiency is ingrained from the molecular level and through our products, processes, and systems, but also to ensure that the nature of that energy is sustainable to both humans and the biosphere.

In order to achieve these goals, fundamental research is needed on several important areas and along the way, as a chemistry community, it becomes imperative to assess the sustainability of a process by focusing on green metrics. Metrics are a useful tool for analyzing the greenness of our chemistry. Early attempts to identify meaningful environmental metrics focused mainly on quantifying process waste while current green metrics are beginning to incorporate more first principles of greener design, such as Anastas and Warner's twelve principles of green chemistry. Several reviews presenting an overview of the metrics that have been used to test and compare the 'greenness' of processes and products, are available and new concepts added every now and then.[2] While a variety of metrics can be used to assess the sustainability of a system, only the most widely used measure of green chemistry efficiency, Atom Economy, will be introduced in this chapter.

Amongst synthetic organic chemists, atom economy is the most widely used measure of green chemistry efficiency as it is conceptually simple.[3] Whether considering a single step or an entire sequence of steps, Trost's concept of atom economy (AE) is one of the simplest ways to evaluate relative efficiency before running a reaction. The AE of

a reaction is a ratio comparing the mass of product relative to the mass of reaction byproducts.

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

The quantitative treatment of reaction efficiency pinpoints wasteful steps, inspiring improvements in synthetic design. Thus exposure to metrics in academia will ultimately be very valuable to industry; hence it would be quite meaningful if Green Chemistry metrics and methods are incorporated in academia.

In the present day developments in the area of Green Chemistry, excellent technologies are emerging to make syntheses more efficient. The biggest innovation is the use of catalysts for organic reactions. Catalytic reactions that replace stoichiometric reagents increase atomic efficiency and decrease the amount of waste produced. The field is getting even more green dimensions with the use of organocatalysts. Multiple reactions run in one reactor also significantly reduce the solvent demand during synthesis and workup. Multiple component condensation (MCC) reactions such as the Passerini or Ugi reaction couple three or four small molecule organic components into a single product. The results are highly efficient reactions with minimum waste generation.

During the last past decade, significant advances have been made in developing benign synthetic protocols for a large range of technologically important compounds via the green synthetic pathway. But, perhaps the largest barrier is that proven green chemistry technologies are not as readily available as are more traditional alternatives. Fundamental changes in technology are adopted by the chemical industry only when they provide real advantage. Moreover, academic research also has a considerable lead time. Only a few genuine green chemistry projects have been running long enough to make the transition from research laboratory to commercialization. The most striking example is the work on catalytic asymmetric synthesis by Knowles, Noyori, and Sharpless.[4] Although predating the birth of green chemistry, this work reflects several of its ideals[5]

namely, high selectivity, atom economy, elimination of many steps from conventional synthesis, and avoidance of waste. The scientific value of this work was recognized by the award of the 2001 Nobel Prize for chemistry. Sharpless, Noyori and Knowles have been awarded the prize for developing techniques that tailor reactions so that only one of the two chiral molecules is produced. The techniques are now widely used in industry, particularly to manufacture pure pharmaceuticals.

The challenge to green chemists is to develop such technologies on a short time scale. Some of the issues raised by the development of "green chemistry" techniques needs to be explored and potential barriers to their implementation by industry identified.

To discuss all the important methodologies/technologies with current advances in Green Chemistry and their various advantages in present day organic synthesis is beyond the scope of this work. Thus, in the following only two of the most important methodologies / technologies deeply associated with Green Chemistry – *Solventless reactions and Multi-component reactions* – will be introduced, as chemistry involving them is directly relevant to the work presented in this thesis.

1.2. Benign Methods in Organic Synthesis

1.2.1. Solventless Reactions

A general assumption with regard to organic reactions is that they are performed in a solvent medium. The rationale behind this concept is simple. That is, the reactants can interact effectively if they are in a homogeneous solution, which facilitates the stirring, shaking or other ways of agitation, whereby the reactant molecules come together rapidly and continuously. Moreover, uniform heating or cooling of the mixture, if needed, can be carried out in a solution relatively easily. However, the role of a solvent in the context of an organic reaction is much more complex than merely providing a homogeneous setting for a large number of collisions of the reactants to take place. A solvent could be deeply and inseparably associated with the process of an organic reaction through the solvation of the reactants, products, transition-state or other

intervening species. In spite of such a strong involvement, the solvent does not normally become part of the product, except in the case of solvolysis reactions, and is recovered unchanged after the reaction is over. Hence, one may not envisage or plan to perform a reaction in the absence of a solvent.

In principle, any liquid can be used as a solvent. However, the number of commonly used solvents is severely restricted. They include a few hydrocarbons, chlorinated hydrocarbons, a few ethers, esters, alcohols, amide derivatives, sulphoxides, etc. Liquid ammonia, CS_2, and of course water, are also frequently used as medium to carry out synthesis. The suitability of a solvent for a reaction depends on many factors. An experienced investigator selects a solvent for a new reaction based on its physical and chemical properties. At times the liquid reactant itself would serve as solvent. In any case, a solvent is usually considered to be an inevitable component of a reaction. GlaxoSmithKline (GSK) reported that solvents typically constitute 80–90% of the mass intensity of a pharmaceutical process manufactured in a batch operation,[6] and this was validated by a pharmaceutical industry benchmarking exercise in 2007 involving seven inventor pharmaceutical companies. Through careful assessment of many pharmaceutical batch reactions conducted over many years, GSK found that solvents are the biggest mass contributor to its processes. Thus, organic solvents are high on the list of damaging chemicals because they are employed in huge amounts and are usually volatile liquids that are difficult to store.

The solvents that currently remain the basis of our chemical operations are still largely organic, contain various health and environmental concerns, and are derived from petroleum. In Industry they are of course recycled wherever possible. However, in practice this is only rarely accomplished with complete efficiency, which means that some organic solvents from chemical production will inevitably escape and severely pollute the environment. Hence, one of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents. The development of the solvent-free alternative processes has, of course, remained the best solution.[7] This has led, in recent times, to

vigorous research activity and reinvestigation of known reactions to achieve organic synthesis under solvent-free condition.

Nevertheless, it is remarkable that chemists still carry out their reactions in solution, even when a special reason for the use of solvent cannot be found. This might be because a reaction under solvent free condition or in solid state was generally thought to be not quite feasible, or at least not quite efficient, though several solid state organic reactions have been known for a long time. But of late, organic reactions without use of conventional organic solvents have started to attract the attention of synthetic organic chemists. Development of solvent-free organic reactions is thus gaining prominence. 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.

There are many advantages of reactions performed under solventless conditions. Since solvent is not required, one saves money on the solvent so it is very economical and environmentally friendly. The reaction rates are usually very high due to the higher concentration of the reactants. Lastly, since one does not require to remove a solvent after synthesis, workup becomes very simple. These would be especially important during industrial production and benefit the environment as well.[8]

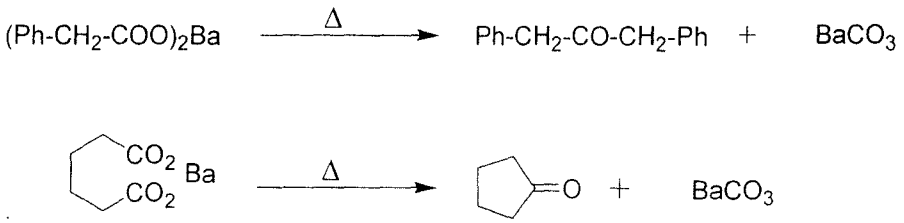
A solventless or solvent-free may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other matrices. Thermal process or irradiation with UV, microwave or ultrasound can be employed to bring about the reaction. While the advantages are many, one should be careful to mix the reactants to a homogeneous system, which becomes problematic because of the high viscosity of the system. Furthermore, the methodology becomes unsuitable for solvent assisted chemical reactions.

1.2.1.1. Developments in Solventless Synthesis

There are of course a great many reactions that can be carried out in the absence of a solvent. Solid state reactions are not really a new concept. Many of them can be found in undergraduate text books. In fact, the historically significant first organic synthesis of urea by Wohler achieved in 1828 belongs to this class (Scheme 1).[9]

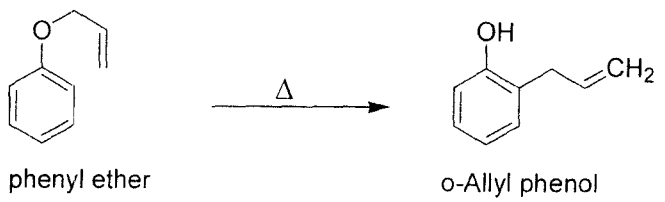
Scheme 1 Wohler's synthesis of urea

Pyrolytic distillation of barium or calcium salts of carboxylic acids to prepare ketones is even now a commonly used procedure (Scheme 2).[10]



Scheme 2 Pyrolytic distillation of Barium dicarboxylates

Another early record of an organic reaction in dry state is the Claisen rearrangement of allyl phenyl ether to o-allylphenol (Scheme 3).[11]



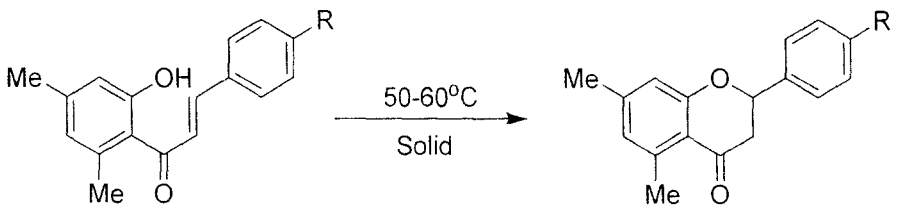
Scheme 3 Claisen Rearrangement

However, the following examples focus on the reactions studied in recent times with the specific purpose of conducting them under solvent-free condition. It should be noted that all these reactions were conventionally being performed in organic solvent media. Solvent-free reaction protocols used in the synthesis of condensation reactions such as Aldol and Michael reactions are fast becoming the best synthetic approaches. New reactors designed specifically for such processes, both in the research laboratory and

in industrial process intensification, have led to a realization of the synthetic potential of solvent-free protocols that afford near quantitative yields with little or no waste. Such reactors also deal with heat transfer for highly exothermic reactions.

Michael Addition

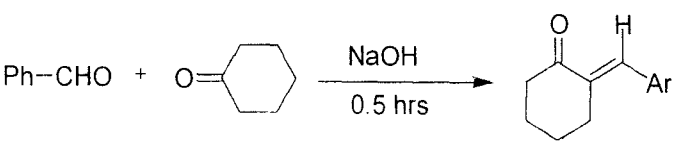
The addition of a nucleophile to a carbon-carbon double bond with a strong electron-withdrawing group at the vinylic position is known as Michael addition. A number of 2'-hydroxy-4', 6'-dimethyl chalcones undergo a solid state intramolecular Michael type addition to yield the corresponding flavonones (Scheme 4).[12]



Scheme 4 Solventless Michael Addition

Aldol Reaction

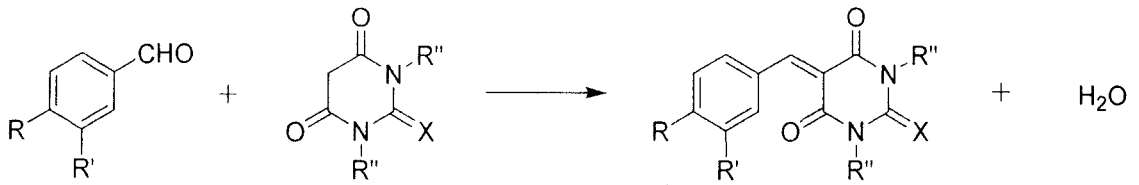
The addition of an enol or enolate ion of an aldehyde or a ketone to the carbonyl group of an aldehyde or a ketone is aldol addition, or aldol condensation, if water is eliminated in a subsequent step to produce *a, b*-unsaturated aldehyde or ketone. Some aldol condensations have been found to proceed more efficiently and stereoselectively in the absence of solvents than in solution.[13] Aldol reactions may be carried out simply by grinding together solid reagents in the presence of NaOH. No organic solvent (unless product recrystallisation is required) is utilized in the reaction and the only waste produced is a small amount of acidic aqueous waste (Scheme 5). Single crossed aldol condensation products are produced in high yields even in reactions where a mixture of products is possible. These reactions are highly atom and energy efficient and are highly chemoselective.[14]



Scheme 5 Solventless Aldol Condensation

Sequential Knoevenagel condensations and Michael additions

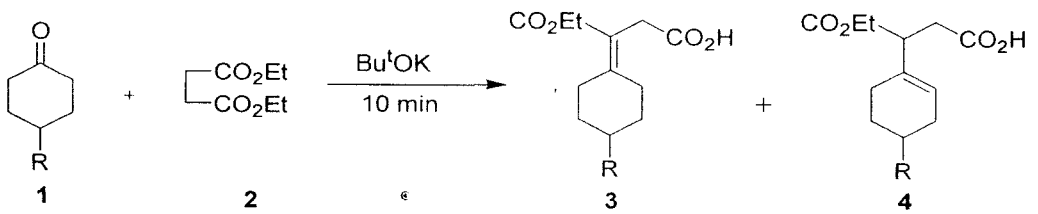
Quantitative yields in various Knoevenagel condensations from stoichiometric mixtures of pure reactants without the necessity for use of solvents, for removal of catalysts, or solvent-consuming purifying workup (Scheme 6).[15] This endeavour succeeded in numerous cases if the reactions could be run as solid-state reactions or as melt reactions with direct crystallization at the reaction temperature. The same benefits are observed if Michael additions are similarly performed with the now easily available building blocks.



Scheme 6 Quantitative un-catalyzed Knoevenagel condensation of aromatic aldehydes with Barbituric acids

Stobbe condensation

Solvent-free Stobbe condensation reactions of cyclohexanone (**1**) and diethyl succinate (**2**) in the presence of Bu^tOK at room temperature and at 80 °C gave cyclohexlidenesuccinic acid (**3**) and cyclohexenylsuccinic acid (**4**), respectively (Scheme 7). The reactions were also found to proceed more efficiently and more selectively than those in solution.[16]

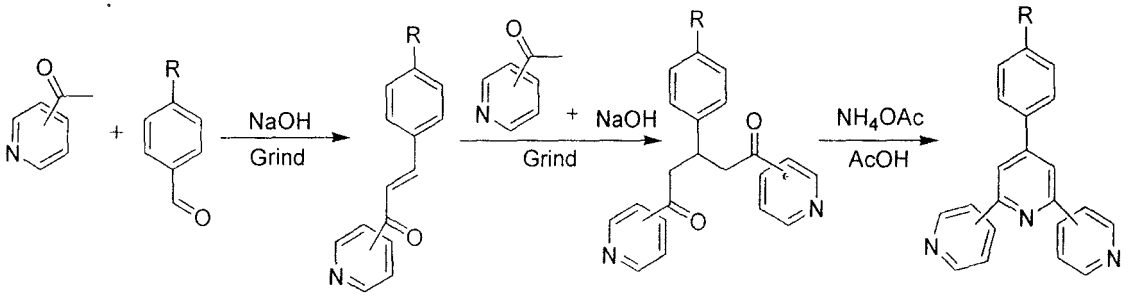


Scheme 7 Solvent-free Stobbe Condensation

Sequential Aldol and Michael addition reactions

Krohnke type pyridines are readily accessible *via* a sequential solventless aldol condensation and Michael addition involving solid NaOH, followed by treatment with ammonium acetate in acetic acid, as a one pot reaction, which enables both symmetrical

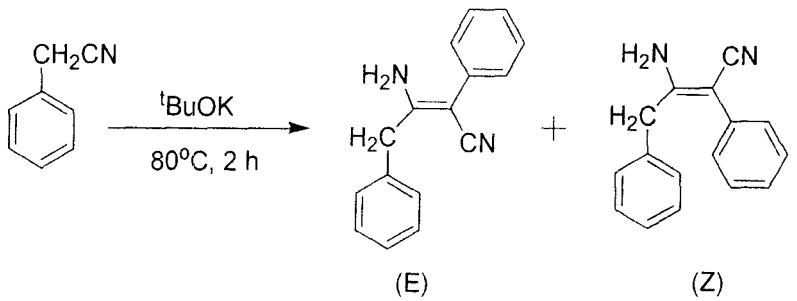
and unsymmetrical 2,6-bisaryl substituted pyridines to be isolated in high yield (Scheme 8).[17]



Scheme 8 Solventless sequential Aldol and Michael addition reaction

Thorpe Reaction

The intermolecular dimerization of nitriles and intramolecular cyclization of dinitriles, which are known as Thorpe reactions, have been found to proceed very efficiently under solvent-free conditions.[18] When the reaction product is a solid, it can be isolated just by washing the reaction mixture with water. The solvent-free procedure in Thorpe reactions is valuable not only for ecological and economical reasons but also for simplicity in procedure and for the high yields of the products. The solvent-free Thorpe reaction of benzyl cyanide at 80 °C gives a 4:1 mixture of (*E*) - and (*Z*)-enamines in 73% yield within 3 hours (Scheme 9).

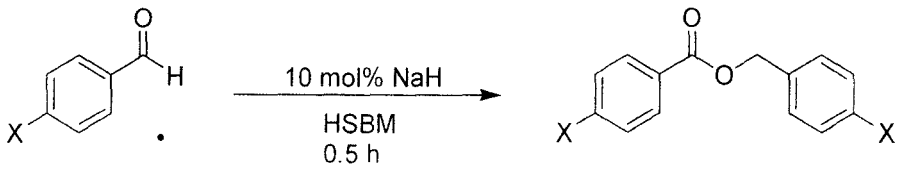


Scheme 9 Solvent-free Thorpe Reaction

Tischenko reaction

The conversion of aldehydes to their dimeric esters, better known as the Tischenko reaction has been known for more than a hundred years. This reaction is heavily used in industry and it is inherently environmentally benign since it utilizes catalytic conditions and is 100% atom economic. Over the years, chemists have looked to

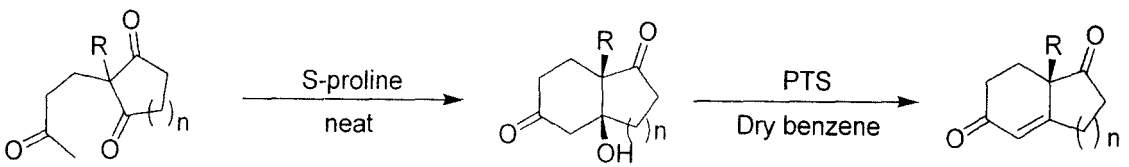
develop new reagents that are more efficient than the aluminum based catalysts traditionally used. Waddell *et al.* reported that the solvent-free ball milling Tishchenko reaction could be performed for aryl aldehydes in high yields in 0.5 hours using high speed ball milling and a sodium hydride catalyst (Scheme 10).[19]



Scheme 10 Solventless Tischenko reaction

Robinson Annulation

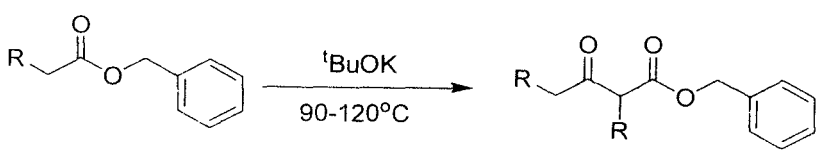
A tandem reaction comprising a Michael addition step followed by an aldol condensation to produce a cyclic compound is Robinson annulation. A number of such reactions have been successfully carried out under solvent-free condition. The incorporation of (S)-proline in the reaction produces a chiral intermediate that ultimately yields a high percentage of one enantiomer (Scheme 11).[20]



Scheme 11 Solventless Robinson annulation

Claisen and Cannizzaro reactions

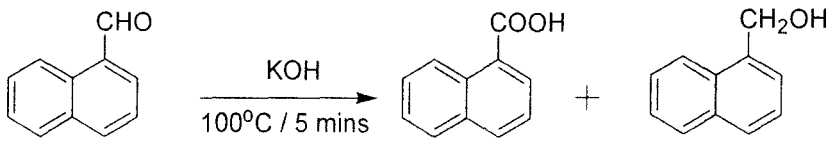
Claisen and Cannizzaro reactions were found to proceed efficiently under solvent-free conditions.[21] The solvent-free Claisen reactions were especially effective for the ester substituted with sterically bulky groups, which does not react in solution (Scheme 12).



a:R=H b:R=Me
c:R=Et d:R=Ph

Scheme 12 Claisen reaction under solvent-free condition

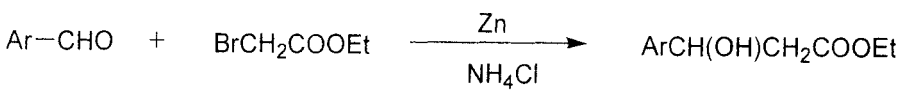
The solvent-free Cannizzaro reaction has some advantages. In addition to simplicity and cleanness of the procedure, the solvent-free reaction proceeds much faster than a solution reaction. Solvent-free Cannizzaro reactions were found to proceed efficiently under milder conditions and the products were obtained in moderate yields by a simple separation method (Scheme 13).



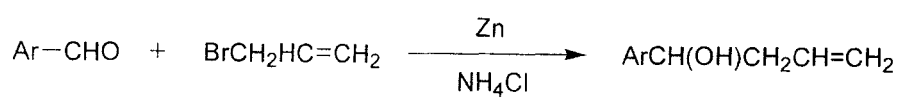
Scheme 13 Cannizzaro reaction under solvent-free condition

Reformatsky and Luche Reaction

Tanaka *et al.* reported Reformatsky (Scheme 14) and Luche reactions (Scheme 15) with Zn provide more economical C-C bond formation methods than Grignard reactions with more expensive Mg metal.[22] In addition, it was pointed out that the reactions proceed efficiently in the absence of solvent, although Grignard reactions under similar conditions are not very efficient and give more reduction product than the normal carbonyl addition product. The nonsolvent Reformatsky and Luche reactions can be carried out by a very simple procedure and give products in higher yield than with solvent.



Scheme 14 Solventless Reformatsky Reaction

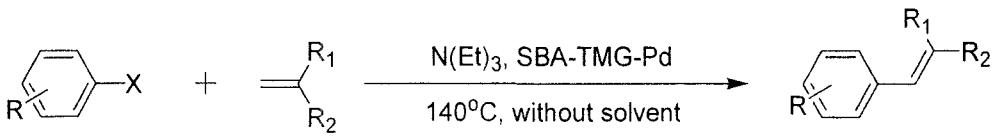


Scheme 15 Solventless Luche Reaction

Heck Reaction

The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is one of the most powerful methods to form a new carbon–carbon (Csp^2–Csp^2) bond in modern synthetic chemistry. The solvent-free Heck reaction

catalyzed by a recyclable Pd catalyst supported on SBA-15 via an ionic liquid was discovered to be highly effective for the acylation of phenols, alcohols and thiols under metal and solvent-free conditions (Scheme 16).[23]

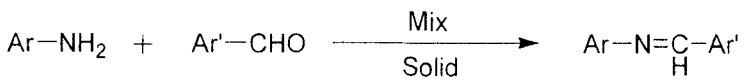


Scheme 16 Heck reaction under solvent-free condition

Other Miscellaneous Reactions

Condensation of Amines with Carbonyl Compounds; Synthesis of Azomethines

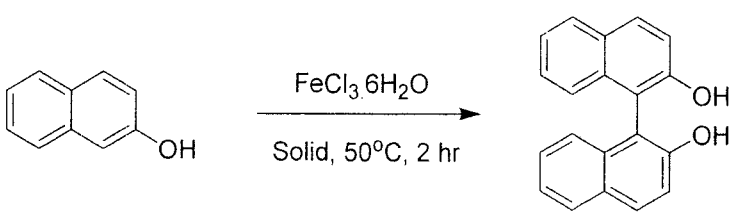
Solid state reactions of anilines and aromatic aldehyde by grinding the reactants give quantitative yield of various azomethines also known as Schiff bases (Scheme 17).[24]



Scheme 17 Synthesis of azomethines

Oxidative Coupling

Oxidative coupling of phenols in the presence of $FeCl_3.6H_2O$ proceed much faster in the solid state than in solution. The reaction is carried out by mixing the phenol and $FeCl_3.6H_2O$ in powdered state and leaving the mixture for 2 hr at 50°C (Scheme 18).[25]

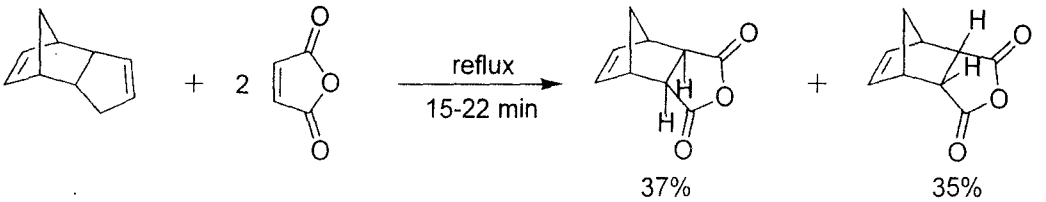


Scheme 18 Oxidative coupling of phenols in the solid state

Pericyclic Reactions: Diels-Alder Cycloaddition

Solvent-free Diels–Alder reactions of in situ generated cyclopentadiene with the dienophile by just mixing the reactive dienes and dienophiles is enough to bring about a number of these [4+2] addition (Scheme 19).[26] Advantages of this procedure are that cyclopentadiene reacts as it is generated and thus there are neither safety problems associated with use of cyclopentadiene nor problems with formation of oligomers. By

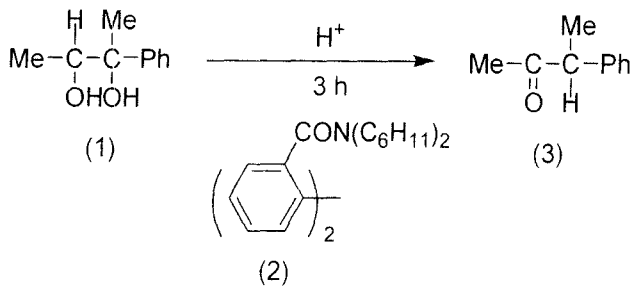
avoiding use of a reaction solvent this is a "greener" procedure compared to traditional Diels– Alder reactions. Related ene-reactions or sigmatropic rearrangements also occur under neat conditions.



Scheme 19 Diels Alder Reaction

Rearrangement Reactions: Pinacol-Pinacolone

The pinacol rearrangement is usually carried out under drastic conditions such as heating in H_2SO_4. The reaction was found to proceed faster and more selectively in the solid state. More drastic control of the pinacol rearrangement in the solid state was achieved by using a host-guest complex of pinacol. Treatment of the powdered 1 : **1** complex of **(1)** and the host compound **(2)** with HCl gas at room temperature for **3** h gave **(3)** in 44% yield as the sole isolable product (Scheme 20).[27]



Scheme 20 Solvent-free Pinacol-Pinacolone rearrangement

Apart from the few well known reactions that have been mentioned above the solventless reaction protocol has been used in numerous other cases such as the synthesis of chalcones,[28] the synthesis of Dihydropyrimidinones,[29] synthesis of 3-carboxycoumarins,[30] Bis-*N*-Boc Protection of Adenosine, Cytidine, and Guanosine derivatives,[31] manufacture of Polypropylene and Polycarbonate,[32] preparation of primary imines from (2-hydroxyaryl)ketones.[33] the synthesis of bis-imine Schiff bases,[34] and so on. The above-mentioned examples show that a variety of organic reactions, which are traditionally conducted in solvent media, can be carried out more profitably in the

absence of solvents. As an organic chemist our endeavor would certainly be to continue bringing more and more reactions into the fold of the solvent-free synthetic methodology.

The examples of various thermal and photochemical reactions under solvent-free conditions are only a glimpse of the immense possibilities of such reactions in organic synthesis. We may not be able to totally avoid organic solvents, but continuous attempts have to be made to devise and explore synthetic methods in this direction. It is the need of the hour to save the environment and cut costs of production. One way of achieving this is to keep the solvents away whenever it is possible. It is also academically rewarding to study how the solid state structure influences the outcome of a reaction. It is gratifying to note that several Indian scientists are working in this area now. At this point it becomes imperative, to get an increased understanding on a molecular level of reactions in the absence of any media and how, if at all, the reaction mechanisms differ from those in more conventional media.

1.2.2. Multicomponent Reactions

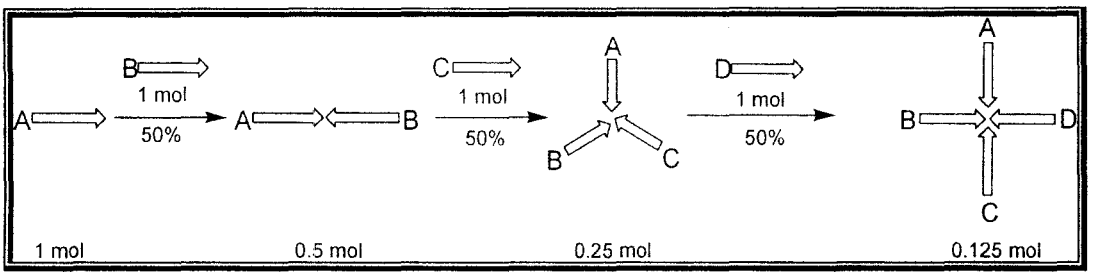
Every effort to increase the efficiency of a process serves to minimize the impact on environment from the chemical industry which encompasses everything from polymers, ceramics, paints, and textiles to drugs and pharmaceuticals, food and beverage, fossil fuels and other non-renewable resources of energy. Though in recent years, new strategies have been introduced in almost every chemical enterprise, the amount of waste resulting from even highly optimized syntheses has not reduced as much. Diverse approaches for redesigning of old methodologies are leading to a significant change and moving towards the ultimate goal of an ideal synthesis. From the chemist's point of view, this would refer to a process which is simultaneously safe, short, selective, high yielding, environmentally benign, based on readily available starting materials, and highly diverse. Additionally, the criterion of selectivity has to be matched with increasing economical significance and ecological aspects.

The advent of Green Chemistry or sustainable chemistry has put major thrust on the above aspects and is nowadays measuring the efficiency of a chemical synthesis not only by parameters like selectivity and overall yield, but also by its raw material, time, human resources and energy requirements, as well as the toxicity and hazard of the chemicals and the protocols involved. Chemical syntheses designed on the Green chemistry protocol is certainly addressing many of the issues but is far from getting outright acceptance from the industry right away. In deviating from conventional procedures, sustainable chemistry advocates the use of diverse environmental-friendly protocols ranging from energy efficient systems like microwave, microreactors, ultrasound etc., to the use of alternative media, solventless methodologies and organocatalytic systems.[35]

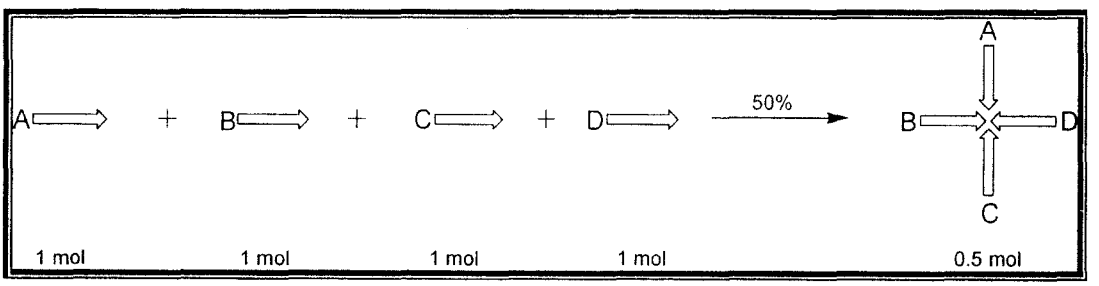
Apart from catalytic reactions, multicatalyst systems in the form of multistep, one-pot reactions, and micro reactors, one-pot multicomponent condensations have become a versatile tool for clean and efficient transformations. Multicomponent coupling reactions (MCRs) represent a highly valuable synthetic tool for the construction of novel and complex molecular structures with a minimum number of synthetic steps. It is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a final product containing significant portions of all reactants, ideally all reactants.[36] An appropriate definition of an MCR as put forward by Jieping Zhu in *Multicomponent Reactions* is "Multicomponent reactions (MCRs) are processes involving sequential reactions among three or more reactant components that co-exist in the same reaction mixture. In order to be efficient, MCRs rely on components that are compatible with each other and do no undergo alternative irreversible reactions to form other products or by-products." Because of their ability to build one product in a single operation from three or more reactant molecules with high atom-economy and multiple-bond-forming efficiency, MCRs are now well-established approaches to reach this near ideal goal.

A MCR is a domino process, a sequence of elementary steps according to a program in which subsequent transformations are determined by the functionalities

produced in the previous step. They are hence sometimes also referred to as tandem or domino reactions. These types of reactions have some advantages over conventional linear syntheses, including lower costs, shorter reaction times, high degrees of atom economy, the possibility for combinatorial surveying of structural variations, and environmental friendliness. Linear total syntheses require significant amounts of time and money to advance starting materials to complex targets.



MCRs on the other hand minimize cost in the form of time and material by generating complex targets in a single convergent step while avoiding time-consuming isolation and purification of synthetic intermediates.

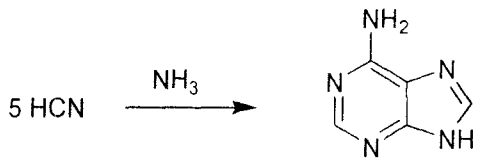


Though the most obvious applications lie in the sphere of library synthesis, the extreme convergence afforded by these reactions provides a quick, efficient, and low-cost alternative to current linear syntheses. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses and provide rapid access to large libraries of organic compounds with diverse substitution patterns. In comparison to an analogous multi-step sequence, a low-yielding MCR is not as costly. By reducing the number of reaction steps and starting from simple, inexpensive starting materials, the cost of constructing highly

diverse and complex small molecules is reduced to a minimum. In addition, both waste production and expenditure of human labor are significantly reduced. Most MCRs have a broad substrate scope capable of tolerating diverse functionality in addition to the reactive centers. This can set up MCR products for further cascade transformations.[37]

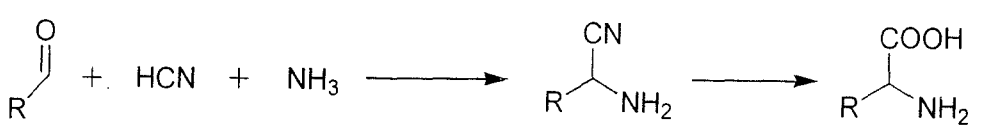
1.2.2.1. History of Multicomponent Reactions

Nature itself chose to use a versatile mechanism, in prebiotic times to synthesize adenine, one of the major constituents of DNA and RNA.[38] It seems that adenine was prebiotically formed by the condensation of five molecules of HCN, which was found in abundance, in a reaction catalyzed by NH_3 (Scheme 21). The other nucleic bases might have been generated in similar multicomponent reactions involving HCN and H_2O.



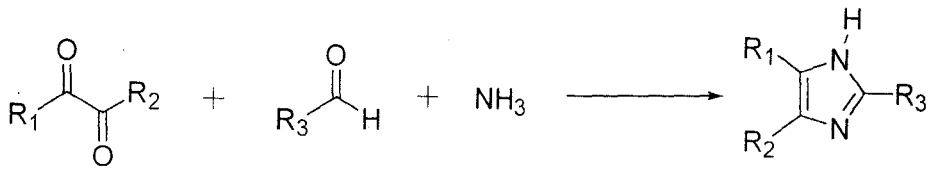
Scheme 21 Prebiotic synthesis of adenine

In present day organic synthesis, the early development of the concept of multicomponent reaction appears to be from Strecker's contributions in 1850 on the synthesis of α-amino acids. Adolf Strecker involved a one-pot multicomponent condensation of aldehydes, HCN and NH_3 for the formation of α-amino nitriles which forms the crucial step in the well-known Strecker synthesis of α-amino acids.[39] Subsequent hydrolysis of these synthetically valuable intermediates results in the amino acids (Scheme 22). Historically, the Strecker reaction was the first multicomponent reaction and represents one of the most straightforward and economically useful multicomponent methods.



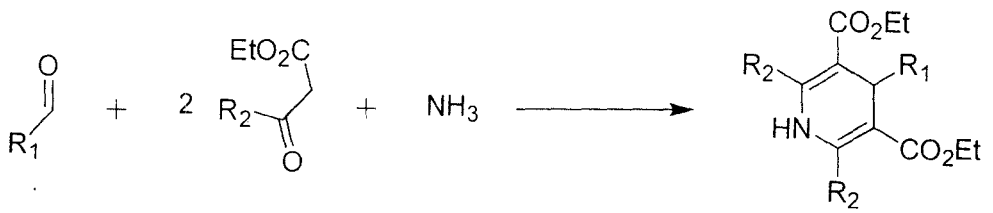
Scheme 22 Strecker synthesis of α-amino acids

The Debus-Radziszewski imidazole synthesis was another multicomponent reaction which was discovered by Heinrich Debus[40] in as early as 1858 and fully developed by Bronisław Leonard Radziszewski[41] in 1882. It describes the synthesis of an imidazole from a diketone, an aldehyde and ammonia (Scheme 23).



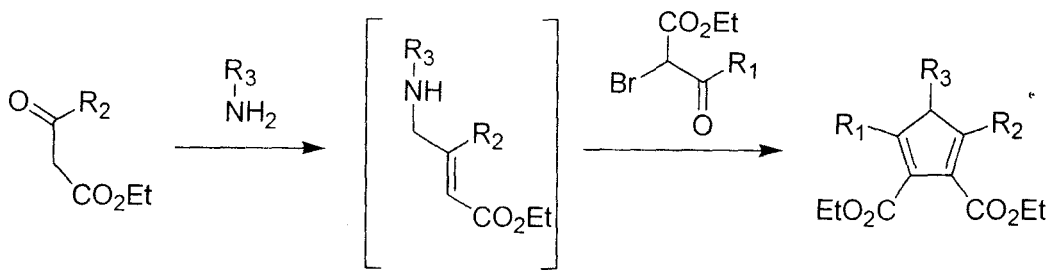
Scheme 23 The Debus-Radziszewski Imidazole synthesis

The Hantzsch synthesis (1881) of symmetrically substituted dihydropyridines brought about further progress in multicomponent chemistry. He synthesized the dihydropyridines from NH_3, aldehydes and two equivalents of β-ketoesters (Scheme 24).[42]



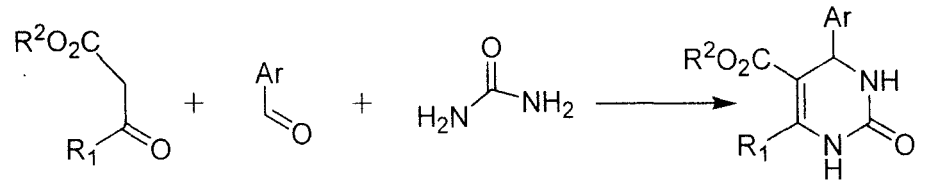
Scheme 24 Hantzsch multicomponent synthesis of dihydropyridines

The Hantzsch synthesis of pyrroles involving primary amines, β-ketoesters and α-halogenated β-ketoesters (Scheme 25) is yet another of his contributions to MCRs.[43]



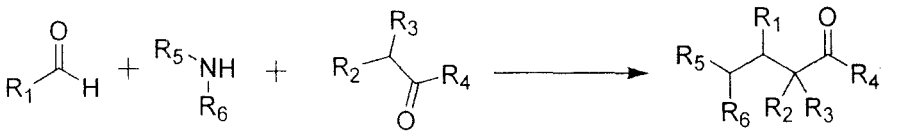
Scheme 25 Hantzsch multicomponent synthesis of pyrroles

A decade later, in 1891 Pietro Biginelli (Florence, Italy) discovered a three-component acid-catalyzed cyclocondensation of β-ketoesters, aromatic aldehydes and urea that produced substituted Dihydropyrimidinones (Scheme 26).[44]



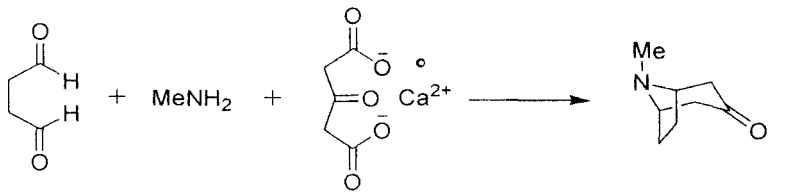
Scheme 26 Biginelli multicomponent synthesis of dihydropyrimidinones

The Mannich Reaction, discovered by Carl Mannich in 1912, is a condensation of amine derivatives, enolizable carbonyl compounds and non-enolizable aldehydes, like formaldehyde. The resulting optically active b-amino carbonyl compounds are valuable building blocks for the asymmetric synthesis of pharmaceutical agents and natural products (Scheme 27).[45]



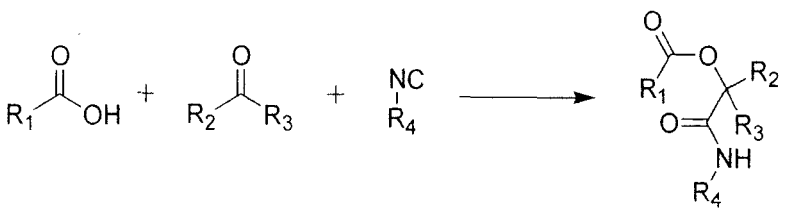
Scheme 27 Mannich 3-component reaction

The first important application of MCRs in natural product synthesis was the Robinson synthesis of the alkaloid tropinone from succinic dialdehyde, methylamine and calcium salt of acetonedicarboxylic acid, carried out in 1917 (Scheme 28).[46]



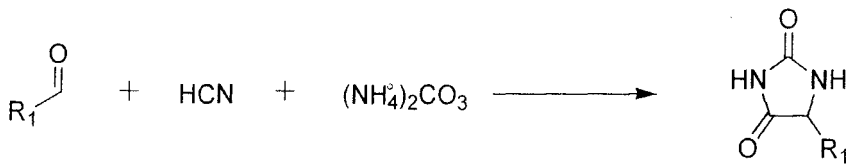
Scheme 28 Robinson synthesis of tropinone

In 1921 Mario Passerini (Florence, Italy) discovered the first MCR involving three component condensation of carboxylic acids, carbonyl compounds and isocyanides affording α-acyloxy carboxamides in a one-pot procedure. It was the first synthetically useful reaction involving isocyanides (Scheme 29).[47]



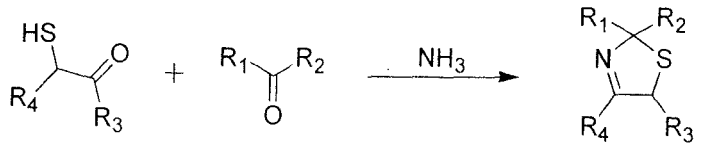
Scheme 29 Passerini 3-component reaction

In 1934 Bucherer and Bergs described a four-component reaction for synthesis of hydantoins. One-pot reaction of hydrogen cyanide, aldehydes, NH_3 and CO_2 afforded hydantoins, which can be easily transformed into α-amino acids by simple hydrolysis (Scheme 30).[48]



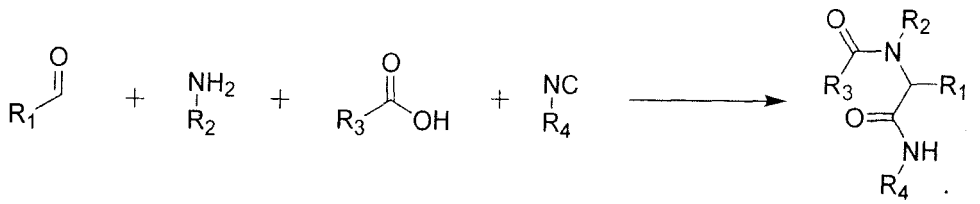
Scheme 30 Bucherer-Bergs multicomponent synthesis of hydantoins

The next important example is the Asinger reaction reported in 1956. Invented by Friedrich Asinger, the reaction is a multicomponent reaction and is classified as A-4CR (short for Asinger-4 component reaction). α-Halogenated carbonyl compounds and sodium hydrogen sulfide generated in situ thiols which reacted with carbonyl compounds and ammonia to afford thiazolines (Scheme 31).[49]



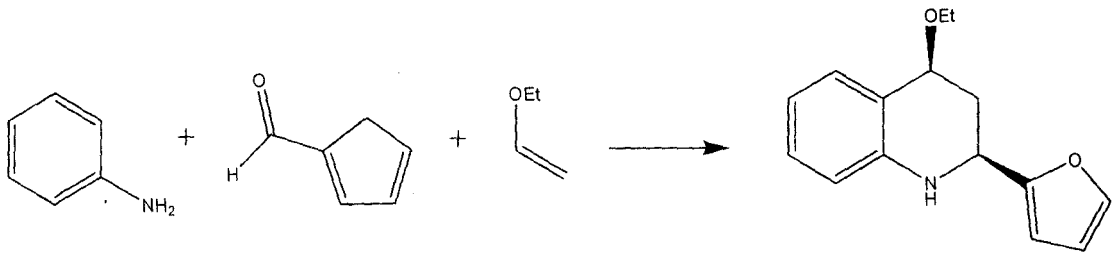
Scheme 31 Asinger reaction

One of the most utilized multicomponent reactions was discovered in 1959 by Ivar Ugi (Munich). Synthesis of α-acylamino amides was achieved by reacting aldehydes, primary amines, carboxylic acids and isocyanides (Scheme 32).[50]



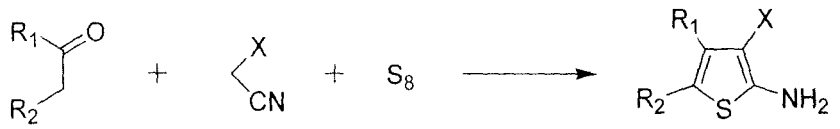
Scheme 32 Ugi-four component reaction

In 1965, L. S. Povarov discovered a Lewis acid-catalyzed cycloaddition between *N*-aryl imines and vinyl ethers which was basically a three-component synthesis of substituted tetrahydroquinolines (Scheme 33).[51]



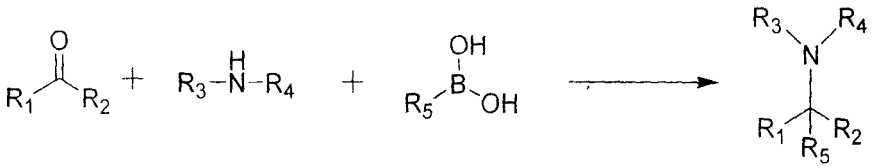
Scheme 33 Povarov's reaction

The following year, Gewald and co-workers (1966) described the synthesis of polysubstituted thiophenes via a one-pot multi-component procedure which includes the condensation of aldehydes, ketones or 1,3-dicarbonyl compounds with activated nitriles and sulfur in the presence of amine at room temperature (Scheme 34).[52]



Scheme 34 Gewald's reaction

A powerful synthetic tool that evolved in the last decade is the Petasis multicomponent reaction, developed by N. A. Petasis in 1993.[53] It involves the condensation of amines, carbonyl derivatives and aryl- or vinylboronic acids for the preparation of amine derivatives (Scheme 35).



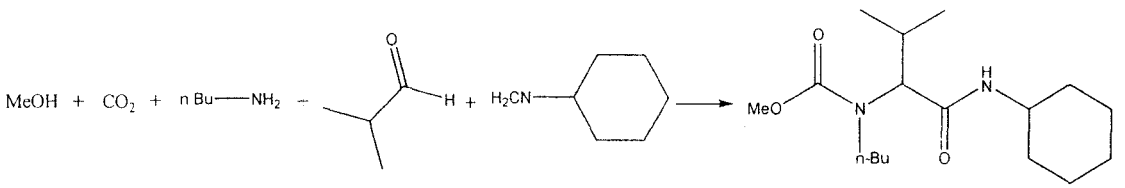
Scheme 35 The Petasis reaction

1.2.2.2. Recent Developments in Multicomponent Synthesis

In spite of the significant useful attributes of MCRs for modern organic chemistry and their suitability for building up large compound libraries these reactions were of limited interest in the earlier years for as nearly as fifty years. Though, multicomponent reactions have accompanied the field of organic chemistry since the early days, particularly in heterocyclic chemistry, they have not been recognized as a fundamental principle until Ugi's groundbreaking extension of the Passerini reaction and the

conclusions he drew from this. With tremendous foresight, Ivar Ugi recognized already in 1961 that MCR is ideally suited to probe structure-activity relationships via the synthesis of "large collections of compounds", which nowadays are referred to as libraries. However, in the last few decades, with the introduction of high-throughput biological screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. With a small set of starting materials, very large libraries can be built up within a short time, which can then be used for research on medicinal substances. This growing interest is stimulated by the significant therapeutic potential that is associated with many heterocycles.

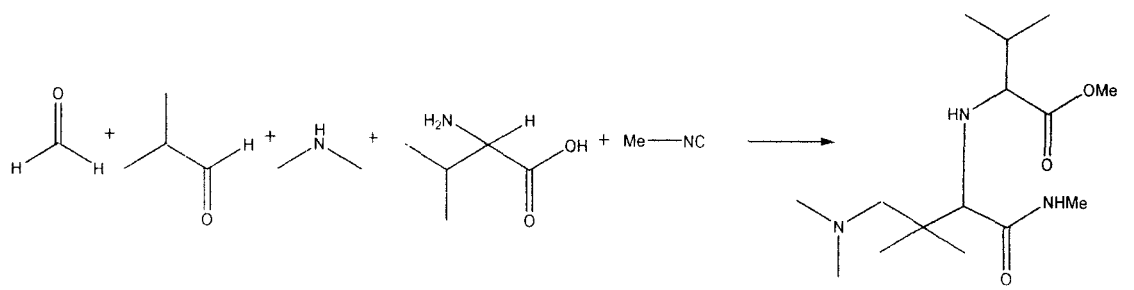
Over the years the development in multicomponent reactions have taken a rapid pace and MCRs are nowadays capable of condensing 3, 4, 5, 6, 7and even 8 reactant species in a single reaction mixture. A typical five-component reaction reported by Haslinger et al is shown below (Scheme 36).[54]



Scheme 36 A typical five-component reaction

A recent example includes the efficient synthesis of functionalized tetrahydropyridines through a one-pot, five-component reaction. [55]

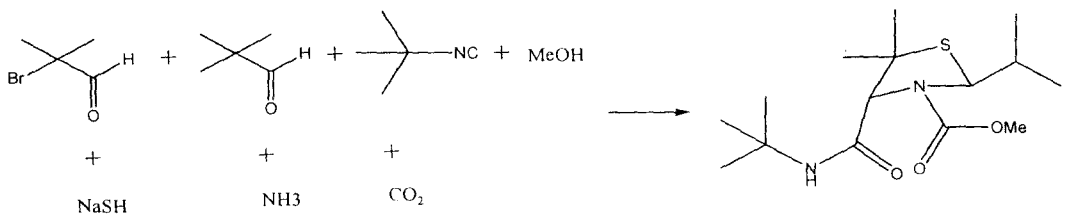
A typical six-component (seven–centre) reaction was reported by Mannich-Ugi (Scheme 37). [56]



Scheme 37 A typical six-component reaction

Recently Bonfield et al. has also reported an efficient method for the preparation of the isoindoline framework via a six component, tandem double A3-coupling and [2+2+2]-cycloaddition reaction .[57]

More than a decade back Asinger-Ugi also reported a seven-component reaction (Scheme 38).[58]



Scheme 38 A typical seven-component reaction

Very recently, Brauch et al. have extended MCRs to seven components by taking advantage of the different chemoselectivities of the Ugi-Mumm and the Ugi-Smiles reaction.[59]

Among notable recent efforts to develop new MCRs,[60] a one-pot reaction of up to eight components has also been developed by the Orru group that involves nine new bond formations and eleven points of diversity.[61]

In addition to the above, much of the work in MCRs over the past two decades has been devoted to extending the scope of the well known classical MCRs to newer systems.[62] Apart from these recent efforts two fields have stood out among others and are getting a lot of attention since the last decade. These are the multicomponent reactions carried under solvent free conditions and their applicability in diversity oriented synthesis (DOS). MCR strategies may be planned under *solvent free conditions*. Moreover, because of the ease with which a large variety of products may be formed via MCRs, they are very suited for any *Diversity Oriented Synthesis*. This ultimately relates to its significance in *drug discovery* efforts. All three being our topic of interest, have been discussed briefly.

1.2.2.3. Solvent-free Multi-Component Reactions

The literature on multicomponent reactions (MCRs) has experienced exponential growth over the last decade and the literature of MCRs under solvent-free conditions has expanded enormously, making it very difficult to keep up with the research reported in this field. The eco-friendly, solvent-free multicomponent approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently. That is why solvent-free protocols have been developed for almost all the classical multicomponent reactions namely the Strecker,[63] Hantzsch,[64] Biginelli,[65] Mannich,[66] Passerini,[67] Ugi,[68] Gewald,[69] Petasis,[70] Radziwenski etc,. The chemo-, regio- or stereoselective synthesis of high-value chemical entities and parallel synthesis to generate a library of small molecules will add to the growth of multicomponent solvent-free reactions in the near future. A thorough recent review on the advancement of these solvent free MCRs in the last ten years says it all for the scope and significance of such approaches in modern day organic synthesis.[71]

1.2.2.4. Multi-component reactions for Diversity Oriented Synthesis

Multi-component reactions fill an important role in library synthesis by providing direct access to library compounds and by serving as starting points for Diversity-Oriented Synthesis (DOS).[72] DOS represents the synthesis of relatively small libraries of organic molecules that are structurally more complex and have a greater variety of core structures. It tries to maximize the number of structures and scaffolds produced from a given synthetic scheme. In a way, it's the opposite of natural product synthesis, which focuses all its effort into producing one specific molecule at a time. Unlike traditional target-oriented synthesis (TOS) strategies, the DOS approach enables chemists to efficiently synthesize libraries of complex and structurally diverse small molecules in a small number of synthetic steps. Since biologically active molecules can be identified through the screening of small-molecule libraries, the point of this is to increase the diversity of compounds libraries for biological screening. The continuous decline in drug-

discovery successes point out to the deficiencies in current compound collections. Typically, such collections are comprised of large numbers of structurally similar compounds. But it is more important to have a smaller but a diverse library (in terms of structure and functionality) rather than a large library of compounds. Diversity-oriented synthesis (DOS) aims to generate such structural diversity in an efficient manner.

The advantages of using an MCR for DOS has been pointed out to be many (i) MCRs provide the highest number of compounds for the least synthetic effort. A 3CR will provide 1000 compounds when 10 variants of each component are employed in a full matrix of combinations. Second, MCRs provide an inherent measure of SAR (structure activity relationship) information within a screening library by providing sets of compounds with related core structures. Third, 'screening positives' or 'hits' that emanate from MCRs provide a valuable starting point for follow-up as the rapid preparation of 'focused' libraries and scale up are ensured. While there are obvious advantages, the use of MCRs for the preparation of diverse libraries may carry the potential liability of having one core structure that is over-represented within a collection. The diversity of a library of MCR products is, on some level, limited by the structure of the appendages attached to the core components. This liability is addressed by new variants of traditional MCRs that result in fundamentally different structures. Furthermore, the use of MCRs as a starting point for subsequent reactions that define the core connectivity of the components is a powerful approach to achieving efficiency and diversity. Many recent examples of diversity-oriented synthesis in which MCRs play key synthetic roles have been given by Schreiber in his recent review.[73]

In recent times, the diversity of products is increasing by both versatile and smart MCRs and many consecutive further reactions like versatile domino-reactions and post-condensation-cyclization (PCCs).[74] This can also be achieved by an increase of the number of components, as in 5CR,[75] 7CR,[76] and 8CR,[60]transition metal catalyzed MCRs[77] and evolutionary chemistry aided MCRs.[78] Several recent diversity oriented reviews demonstrate the high innovation and creativity in this seminal field of chemistry.[79]

1.2.2.5. Multi-component reactions in Drug discovery

During the last 10 years pharmaceutical companies have invested significant efforts in developing robotics and miniaturization for biological screening purposes. As a result of these efforts, the capacity of biologists to perform in vitro high-throughput screening of chemicals for drug discovery has dramatically improved.[80] The main limitation of this new screening technology lies in the capacity of the chemists to furnish biologists with a great diversity and number of products. Traditionally, drug discovery involved the optimization of lead structures, most likely derived from biological sources, through a multistep process of serial synthesis and screening. This approach is extremely costly, as each compound will have to be individually synthesized in solution by a synthetic chemist. So there is a need to find more cost-effective methods of drug development. With the recent advances in robotic screening that enable the testing of hundreds of thousands of products per year, pharmaceutical companies are being driven to examine MCR synthetic strategies with DOS approaches along with combinatorial synthetic strategies as means of accelerating drug discovery programs and increasing the chemical diversity of their compound libraries. Chemists from academia are presently conscious and significant efforts are being made in order to meet the increasing requirements of the high-throughput biological screening technology. For this purpose, the use of MCRs with the DOS approach over and above the combinatorial synthetic approach may significantly improve the diversity of synthetic libraries.

By their nature, MCRs are by no means restricted to a particular application, but rather they can be used advantageously in any area of modern chemistry-based technology. In recent years, asymmetric multicomponent reactions have been applied to the total synthesis of various enantiopure natural products and commercial drugs, reducing the number of required reaction steps significantly.[81]

Recent applications of MCRs unrelated to drugs include EPR-spin labeling, biocompatible materials, e.g. for artificial eye lenses, polymers with novel properties, chiral phases for HPLC, natural product synthesis, peptide-nucleic acids and

agrochemicals. Many groups have leveraged their projects in natural product total synthesis with the power of MCR, e.g. Ugi, Jouille, Fukuyama, Hofheinz, Banfi, Semple, Armstrong, Hatanaka, Schmidt, etc. The only limitation in total synthesis is that the more components that a MCR employs, the more complex the target it generates. The more complex the target, the less generally applicable it becomes in total synthesis.

The library of known multicomponent reactions is far from complete. New combinations of existing reactions are always possible and a firm understanding of reaction mechanism can lead to the discovery of novel modes of reactivity. Most advantageously and practically, MCR can often be extended into combinatorial, solid phase or flow syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule-based materials.

1.3. Thermal Analysis

Thermal analysis constitutes a set of analytical methods which trace their origin back almost 500,000 years to the first controlled use of fire by humans. Thermal methods of analysis may be defined as a group of analytical techniques in which changes in physical and/or chemical properties of a substance are measured as a function of temperature. Methods that involve changes in weight or changes in energy come within this definition.[82] The International Confederation for Thermal Analysis and Calorimetry (ICTAC) and IUPAC define thermal analysis as "a group of techniques in which a physical property of a substance, and or its reaction products, is measured as a function of temperature whilst the subject is subjected to a controlled temperature program" (Gallagher, 1993).[83]

True thermo-analytical techniques began in the 18th century with the acceptance of the Fahrenheit temperature scale. The use of thermal and calorimetric methods has shown rapid growth over the last two decades, in an increasingly wide range of applications. Calorimetry is very well suited for analysis of chemical reactions. In

particular, the heat of exothermic and endothermic reactions can be determined. In this context, thermal analysis is a versatile group of techniques which can be used to aid preparatory studies.

Thermal analysis is becoming useful in different fields of study such as inorganic and organic chemistry, polymer science, and the biological and medical sciences.[84] Thermo-analytical techniques, although not routinely used in biological investigations, when applied to biochemistry and biology have yielded some interesting results.[85] In polymer production, it is very important to determine the thermal stability of the material because in this way we can achieve the temperature range in which the material can be used without degradation.[86] It is a very important characterization method used for the control of the reaction process and of the properties of the materials obtained.[87] DTA and particularly DSC have been used in pharmaceutical chemistry for the investigation of product purity,[88] the identification of optical isomers, polymorphism[89] and eutectic formation. In the food industry, edible fats and oils have been characterized by differential thermal methods. It is also of great interest for characterization of foodstuffs, as it relates relevant foodstuff data to the industrial process, decreasing analysis time and the sample quantity required for obtaining the kinetic parameters.[90] Thermal analysis is widely used in combustion research for both fundamental and practical investigation.[91]

A variety of techniques fall under this definition. Thermogravimetry, differential thermal analysis, and differential scanning calorimetry are the three principal thermo analytical methods. Thermogravimetry (TG) is concerned with a change in weight in response to changing temperature, or time at a constant temperature. Differential scanning calorimetry (DSC) measures either the heat, or the heat flux of a sample. This method is used widely to study the dehydration of minerals and the combustion of coals. Differential thermal analysis (DTA) is similar to DSC, but instead of measuring the heat associated with the sample, it measures the temperature of the sample with respect to the furnace temperature or the temperature of an inert standard. This method may detect any changes which cause a change in the enthalpy, conductivity, or heat capacity of the sample. The weight changes monitored by thermogravimetry invariably involve the

absorption or release of energy; hence they can be measured by either DSC or DTA. But there are many changes in energy that are not accompanied by a gain or loss in weight. For example, melting, crystallization, fusion and solid-state transitions do not involve weight changes.

The modem trend is to use two analytical methods concurrently, TG/TM, DTA/DSC, TG/DTA, and others. These multiple method instruments are collectively known as simultaneous instruments, and allow for more accurate knowledge of the sample temperature and furnace conditions. Notably, by coupling a thermobalance with an FTIR spectrometer, the gaseous decomposition products can be identified and assigned to the respective temperatures and TG steps.[92] Differential scanning calorimetry (DSC) coupled with thermogravimetry (TG) have been extensively used to carry out thermal analysis of forest fuels in the presence of fire retardants, under air or inert gas flow.[93] The simultaneous thermal analysis techniques have been extensively used in studying of the thermal behavior of metal complexes.[94] There is no doubt that thermal analysis is extremely versatile and able to address a wide variety of analytical problems. Only two of the important techniques for thermal analysis, the TGA and the DSC, used in our present study have been discussed further.

1.3.1. Thermogravimetric analysis (TGA)

It is a thermal analysis technique in which the mass of a substance, typically a solid, is monitored as a function of temperature or time as the sample specimen is subjected to a controlled temperature programme. TGA measurements are used primarily to determine the composition of materials and to predict their thermal stability up to elevated temperatures.

Any type of physiochemical process which involves a change in sample mass may be observed by using thermogravimetry. Mass losses are observed for dehydration, decomposition, desorption, vaporization, sublimation, pyrolysis, and chemical reactions with gaseous products.[95] Mass increases are noted with adsorption, absorption, and chemical reactions of the sample with the atmosphere in the oven, such as the oxidation

of metals. This is accomplished by placing the entire experimental chamber on a balance, that continuously measures the sample mass during the heating process. Thus the basic instrumental requirement for thermogravimetry is a specially designed thermobalance, a precision balance with a furnace programmed for a linear rise of temperature with time. Although limited in scope to those reactions taking place with a change in mass, TG gives results that are intrinsically quantitative. Thus the measured mass losses will fully reflect the overall reaction taking place. Heating is performed under strictly controlled conditions and can reveal changes in structure and other important properties of the material.being studied.

The results may be presented as a thermogravimetric (TG) curve, in which the weight change is recorded as a function of temperature or time; or as a derivative Thermogravimetric (DTG) curve, where the first derivative of the TG curve is plotted with respect to either temperature or time. Since the TG curve is quantitative, calculations on compound stoichiometry can be made at any given temperature. The first derivative of the TG curve (DTG) is effective in highlighting the onset and termination of individual reactions.

If the rate of change of weight with time dW/dT is plotted against temperature, a derivative thermogravimetric (DTG) curve is obtained. In the DTG curve when there is no weight loss then dW/dT = 0. The peak on the derivative curve corresponds to a maximum slope on the TG curve. When dW/dT is a minimum but not zero there is an inflexion, i.e. a change of slope on the TG curve. Inflexions may imply the formation of intermediate compounds. Derivative thermogravimetry is useful for many complicated determinations and any change in the rate of weight loss may be readily identified as a trough indicating consecutive reactions; hence weight changes occurring at close temperatures may be ascertained. Apart from directly measuring chemical reactions, one can also analyze materials by exposing them to a temperature sweep, either in an inert atmosphere (nitrogen or helium) or in an oxidizing atmosphere. Then, all effects — such as glass transition, crystallization, melting, evaporation, decomposition, and even oxidation — can be detected. For this, a DSC is again utilized. In the more expensive

analysis systems, DSC instruments often offer the possibility of incorporating other techniques.

Quantitative gravimetric analyses may be performed due to the precise measure of the mass change obtained. Rates of mass change have been used to evaluate the kinetics of a process and to estimate activation energies. Fine details of these thermograms may also be used to deduce reaction intermediates and reaction mechanisms.

Basically, the occurrence of physical or chemical changes upon heating a sample may be explained from either a kinetic or thermodynamic viewpoint. Kinetically the rate of a process may be increased by raising the temperature as shown by the Arrhenius equation (1),

$$\text{Rate} = Ae^{-Ea/RT} \qquad (1)$$

where A, E_a, and R represent the pre-exponential factor, activation energy, and the gas law constant, respectively. At some point the rate becomes significant and readily observable. Similarly an increase in temperature can change the Gibbs free energy [Equation (2)],

$$\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ} \qquad (2)$$

where ΔG° is the Gibbs free energy, ΔH° is the reaction enthalpy, and ΔS° is the entropy change for the process to a more favorable (that is, more negative) value. In particular, ΔG° will become more negative if ΔS° is positive and the temperature is increased. In many cases a combination of these factors causes the observed physiochemical process. Primary applications of thermogravimetry are to deduce stabilities of compounds and mixtures at elevated temperatures and to determine appropriate drying temperatures for compounds and mixtures. Evaluation of polymers,[96] food products, and pharmaceuticals[97] is a major application of thermogravimetry. The technique has been applied with great success not only in chemistry but also in other areas such as ceramics and metallurgy.

1.3.2. Differential Scanning Calorimetry

In Differential scanning calorimetry (DSC)- the energy necessary to establish a zero temperature difference between the sample and a reference material is measured as a function of temperature or time. Thus, when an endothermic transition occurs, the energy absorbed by the sample is compensated by an increased energy input to the sample in order to maintain a zero temperature difference. Because this energy input is precisely equivalent in magnitude to the energy absorbed in the transition, direct calorimetric measurement of the energy transition is obtained from this balancing energy.

Routine differential scanning calorimetric (DSC) and thermo gravimetric analysis (TGA) techniques, used to characterize polymer thermal stability, have been further employed for assessment of thermal properties of various bio-composites used in the packaging industry.[98] DSC is especially useful when one wants to obtain the thermal behavior of materials as a function of temperature. In turn, the temperature-dependent behavior of materials can tell a lot about their structure, their properties, and even their thermo-mechanical history. Since a typical DSC curve is a plot of heat capacity against temperature, thermal events which do not involve an enthalpy change, such as glass transitions can be detected. They appear as a change in the gradient or the position of the baseline.

DSC also provides a rapid yet reliable method for determining the purity of materials. The DSC technique allows the melting curve to be determined for the sample as it is heated through its melting point. It is well known that the higher the concentration of the impurity present in a sample, the lower its melting point and the broader its melting range. The data obtained by DSC includes the complete melting curve and the latent Heat of fusion (ΔH_f) of the sample.

References

1. (a) P. T. Anastas, J. C. Warner, Green Chemistry; Theory and Practice, Oxford Science Publications, Oxford, 1998
2. C. Jimenez-Gonzalez, D. J. C. Constable and C. S. Ponder, *Chem. Soc. Rev.* DOI: 10.1039/c1cs15215g
3. B. M. Trost, *Science*, 1991, **254**, 1471; (b) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259
4. W. Knowles, *Angew. Chem. Int. Ed.*, 2002, **41**, 1998; (b) R. Noyori, *Angew. Chem. Int. Ed.* 2002, **41**, 2008; (c) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974
5. M. Poliakoff and P. T. Anastas, *Nature*, 2001, **413**, 257
6. D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133
7. P. T. Anastas and I. T. Horvath, *Chemical Reviews*, 2007, **107 (6),** 2167
8. K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025
9. F. Wohler, *Ann.* 1828, **88 (2)**, 253
10. C. Lee and J. W. T. Spinks, *Canadian Journal of Chemistry*, 1953, **31(1),** 103
11. (a) L. Claisen, *Ber.*, 1912, **45**, 3157; (b) D. S. Tabell, *Org. React.*, 1944, **2**, 1
12. B. Satish, K. Panneersel-Vam, D. Zacharids and G. R. Desiraju, *J. Chem. Soc. Perkin Trans.*, 1995, **2**, 325
13. F. Toda, K. Tanaka and K. Hamai, *J. Chem. Soc., Perkin Trans.*, 1990, 3207
14. C. L. Raston and J. L. Scott, *Green Chem.*, 2000, **2**, 49
15. G. Kaupp, M. R. Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2003, **59**, 3753
16. K. Tanaka, T. Sugino and F. Toda, *Green Chemistry*, 2000, **2**, 303
17. G. W. V. Cave and C. L. Raston, *Chem. Commun.*, 2000, 2199
18. K. Yoshizawa, S. Toyota and F. Toda, *Green Chemistry*, 2002, **4**, 68
19. D. C. Waddell and J. Mack, *Green Chem.*, 2009, **11**, 79
20. D. Rajagopal, R. Narayanan and S Swaminathan, *Proc. Indian Acad. Sci. (Chem. Sci.)*; 2001, **113 (3)**, 197
21. K. Yoshizawa, S. Toyota and F. Toda, *Tetrahedron Letters*, 2001, **42**, 7983

22. K. Tanaka, S. Kishigami and F. Toda, *J. Org. Chem.* 1991, **56**, 4333

23. X. Ma, Y. Zhou, J. Zhang, A. Zhu, T. Jiang and B.Han, Green Chem., 2008, **10**, 59

24. J. Schmeyers, F. Toda, J. Boy, and G. J. Kaupp, *J. Chem. Soc. Perkin Trans. 2*, 1998, 989

25. (a) F. Toda, K. Tanaka and S. Iwata, *J. Org. Chem.*, 1989, **54**, 3007; (b) T. Higashizima, N. Sakai, K. Nozaki and H. Takaya, *Tetrahedron Lett.*, 1994, **35**, 2023

26. D. Huertas, M. Florscher and V. Dragojlovic, *Green Chem.*, 2009, **11**, 91

27. F. Toda and T. Shigemasa, *J. Chem. Soc. Perkin Trans.1*, 1989, 209

28. D. R. Palleros, *J. Chem. Edu.*, 2004, **81**, 1345

29. B. C. Ranu, A. Hajra and S. S. Dey, *Organic Process Research and Development*, 2002, **6**, 817

30. J. L. Scott and C. L. Raston, *Green Chem.*, 2000, **2**, 245

31. S. A. Sikchi and P. G. Hultin, *J. Org. Chem.*, 2006, **71**, 5888

32. J. O. Metzger, *Angew.Chem. Int. Ed*, 1998, **37 (21)**, 2975

33. Y. Bergman, P. Perlmutter, and N. Thienthong, *Green Chem.*, 2004, **5**, 539

34. T. R. van den Ancker, G. W. V. Cave and C. L. Raston, *Green Chem.*, 2006, **8**, 50

35. A. Kumar, M. K. Gupta and M. Kumar, *Green Chem*, 2012, **14**, 290

36. J. Zhu and H. Bienayme, Multicomponent Reactions, Wiley-VCH, Weinheim, Germany, 2005

37. (a)V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402; (b) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (d) A. Domling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168.

38. (a) R. Shapiro, *Origins of Life and Evol. Of the Biosphere*, 1995, **25**, 83; (b) J. Oro, *Biochem. Biophys. Res. Commun.*, 1960, **2**, 407; (c) J. Oro and S. S. Kamat, *Nature*, 1961, **190**, 442

39. A. Strecker, *Annalen der Chemie und Pharmazie*, 1850, **75** (1), 27

40. H. Debus, *Ann.*, 1858, **107**, 204

41. B. Radziszewski, *Ber.*, 1883, **16,** 747

42. A. Hantzsch, *Chem. Ber.*, 1881, **14 (2)**, 1637

43. A. Hantzsch, *Ber.*, 1890, **23**, 1474

44. (a) P. Biginelli, *Ber.* 1891, **24**, 2962; (b) P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23,** 360

45. C. Mannich and W. Krosche, *Arch. Pharm. (Weinheim, Ger.),* 1912, **241**, 647

46. R. Robinson, *J. Chem. Soc.,* 1917, 762

47. M. Passerini and co-workers *Gazz. Chim. Ital.* 1921, **51**, 181

48. H. T. Bucherer, H. T. Fischbeck, *J. Prakt. Chem.,* 1934, **140**, 69

49. F. Asinger, *Angew. Chem.*, 1956, **68**, 413

50. (a) I. Ugi, et al, *Angew. Chem.* 1959, **71**, 386; (b) I. Ugi, *Angew. Chem.* 1960, **72**, 267

51. (a) L. S. Povarov, *Russ. Chem. Rev.,* 1965, **34**, 639; (b) L. S. Povarov, *Russ. Chem. Rev.,* 1967, **36**, 656

52. K. Gewald, E. Schinke and H. Bottcher, *Chem. Ber.,* 1966, **99**, 94

53. N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, 1993, **34**, 583

54. E. Haslinger, *Monatsh. Chem.,* 1978, **109**, 749

55. Hong-Juan Wang, Li-Ping Mo, and Zhan-Hui Zhang, *ACS Comb. Sci.*, 2011, **13**, 181

56. I. Ugi, A. Domling and W. Horl, *Endeavour* 1994, **18**, 115

57. E. R. Bonfield and C. J. Li, *Adv. Synth. Catal.*, 2008, **350**, 370

58. S. Brauch, L. Gabriel and B. Westermann, *Chem. Commun.* 2010, **46**, 3387

59. K. Kumaravel and G. Vasuki, *Curr. Org. Chem.* 2009, **13**, 1820

60. N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter and R. V. A. Orru, *Angew. Chem., Int. Ed.* 2009, **48**, 5856

61. G. Byk, H. E. Gottlieb, J. Herscovici, and F. Mirkin, *J. Comb. Chem.* 2000, **2**, 732

62. (a) B. V. S. Reddy, A. S. Krishna, A. V. Ganesh and G. G. K. S. Narayana Kumar, *Tetrahedron Lett.*, 2011, **52**, 1359; (b) J. Zhang, Z. Cui, F. Wang, Y. Wang, Z. Miao and R. Chen, *Green Chem.*, 2007, **9**, 1341; (c) B. C. Ranu and A. Hajra, *Tetrahedron*, 2001, **57**, 4767; (d) O. A. Attanasi, G. Favi, F. Mantellini, G. Moscatelli and S. Santeusanio, *J. Org. Chem.*, 2011, **76**, 2860

63. (a) B. Karimi and D. Zareyee, *J. Mater. Chem.*, 2009, **19,** 8665; (b) H. Wang, X. Zhao, Y. Li and L. Lu, *Org. Lett.*, 2006, **8 (7)**, 1379; (c) P. Galletti, M. Pori and D. Giacomini, *European Journal of Organic Chemistry*, 2011, **20**, 3896

64. (a) M. A. Zolfigol, E. Kolvari, A. Abdoli and M. Shiri, *Molecular Diversity*, 2010, **14(4)**, 809; (b) V. Sivamurugan, R. S. Kumar, M. Palanichamy, V. Murugesan, *Journal of Heterocyclic Chemistry,* 2005, **42 (5)**, 969; (c) G. V. M. Sharma, K. L.

Reddy, P. S. Lakshmi and P. R. Krishna, *Synthesis*, 2006, 55

65. (a) F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, *Tetrahedron Letters*, 1999, **40 (17)**, 3465; (b) J. Peng and Y. Deng, *Tetrahedron Letters*, 2001, **42 (34)**, 5917; (c) R. Wang and Z. Liu, *J. Org. Chem.*, 2012, **77 (8)**, 3952
66. (a) L. el Kaim, L. Gautier, L. Grimaud, L. M. Harwood and V. Michaut, *Green Chem.*, 2003, **5**, 477; (b) Y. Hayashi, T. Urushima, S. Aratake, T. Okano and K. Obi, *Org. Lett.*, 2008, **10 (1)**, 21
67. (a) D. Koszelewski, W. Szymanski, J. Krysiak and R. Ostaszewski, *Synthetic Commun.*, 2008, **38 (7)**, 1120 (b) T. Bousquet, M. Jida, M. Soueidan, R. Deprez-Poulain, F. Agbossou-Niedercorn L. Pelinski, *Tetrahedron Lett.*, 2012, **53 (3)**, 306
68. (a) N. Liu, S. Cao, J. Wu, J. Yu, L. Shen, X. Feng and X. Qian, *Tetrahedron,* 2008, **64,** 3966; (b) L. El Kaim, L. Grimaud and S. Hadrot, *Tetrahedron Letters*, 2006, **47 (23)**, 3945; (c) M. Jida, S. Malaquin, R. Deprez-Poulain, G. Laconde and B. Deprez, *Tetrahedron Letters*, 2010, **51 (39)**, 5109
69. J. S. B. Forero, E. M. de Carvalho, J. J. Junior and F. M. da Silva, *Heterocyclic Letters*, 2011, **1 (1)**, 61; (b) K. Wang, D. Kim, and A. Domling, *J. Comb. Chem.* 2010, 12, 111
70. P. Nun, J. Martinez and F. Lamaty, *Synthesis*, 2010, **12**, 2063
71. M. S. Singh and S. Chowdhury, *RSC Adv.*, 2012, **2**, 4547
72. H. Eckert, *Molecules,* 2012, **17**, 1074
73. (a) T.E. Nielsen and S.L. Schreiber, *Angew Chem Int Ed.*, 2008, **47**, 48; (b) S. L. Schreiber, *Nature*, 2009, **457**, 153
74. M. D. Burke and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.* 2004, **43**, 47; (b) J. D. Sunderhaus and S. F. Martin, *Chem. Eur. J.*, 2009, **15**, 1300
75. M. Li, F.-M. Gong, L.-R. Wen and Z.-R. Li, *Eur. J. Org. Chem.*, 2011, 3482
76. A. Doemling, E. Herdtweck and I. Ugi, *Acta Chem. Scand.*, 1998, **52**, 107
77. D. M. D'Souza and T. J. J. Mueller, *Chem. Soc. Rev.*, 2007, **36**, 1095
78. L. Weber, *Drug Discov. Today,* 2002, **7**, 143
79. (a) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (b) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (c) J. E. Biggs-Houck, A. Younai and J. T. Shaw, *Curr. Opin. Chem. Biol.*, 2010, **14**, 371; (d) B. Jiang, T. Rajale, W. Wever, S.-J. Tu and G.

Li, *Chem. Asian J.*, 2010, **5**, 2318; (e) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem. Int. Ed. Engl.*, 2011, **50**, 6234; (f) J. Yu, F. Shit and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156

80. F. H. Zenie, *Bio/Technology*, 1994, **12**, 736
81. C. Kalinski, M. Umkehrer, L. Weber, J. Kolb, C. Burdack and G. Ross, *Mol. Divers.*, 2010, **14**, 513
82. Vogel's textbook of Quantitative Chemical Analysis, 6th Edition
83. (a) P. K. Gallagher, Advances in Analytical Geochemistry., 1993, 1, pp 211- 257.
84. (a) J. L. Ford, *Thermochim. Acta*, 1995, 248; (b) I. Donova and D. I. Koceva, *J. Therm. Anal.*, 1995, **44**, 597; (c) I. O. Figura and M. Epple, *J. Therm. Anal.* 1995, 44; (g) M. A. A. Al- Meeshol, *J. Pharm. Soc.*, 1994, **8**, 51
85. L. A. Collett and M. E. Brown, *Journal of Thermal Analysis*, 1998, **51**, 693
86. (a) D. Stawski, *Polymer Testing*, 2009, **28**, 223; (b) N. Agullo and S. Borros, *Journal of Thermal Analysis and Calorimetry*, 2002, **67**, 513; (c) B. Wunderlich, *Journal of Thermal Analysis*, 1996, **46**, 643
87. G. V. Kunte, S. A. Shivashankar and A. M. Umarji, *Meas. Sci. Technol.*, 2008, **19**, 7
88. H. Nyqvist, T. Wadsten, *Journal of Thermal Analysis*, 1988, **33**, 1027
89. R. Barbas, R. Prohens and C. Puigjaner, *Journal of Thermal Analysis and Calorimetry*, 2007, **89 (3)**, 687
90. M. M. Conceicao, J. C. O. Santos, P. A. Filgueiras, R. O. Macedo, V. J. Fernandes and A. G. Souza, *Journal of Food Technology*, 2007, **5 (3)**, 265
91. V. Leroy, D. Cancellieri and E. Leoni, *Thermochimica Acta*, 2006, **451**, 131
92. E. Post, S. Rahnera, H. Miihlerb and A. Rager, *Thermochimica Acta*, 1995, **263**, 1
93. S. Liodakis, D. Bakirtzis, A. P. Dimitrakopoulos, *Thermochimica Acta*, 2003, **399**, 31
94. (a) A. A. Soliman, *J. Therm. Anal. Cal.*, 2001, **63**, 221; (b) G. G. Mohamed, F. A. Nour El-Dien and Nadia E. A. El-Gamel, *J. Therm. Anal. Cal.*, 2002, **67**, 135; (c) G. G. Mohamed and Z. H. Abd El-Wahab, *J. Therm. Anal.Cal.*, 2003, **73**, 347; (d) H. A. El-Boraey, *J. Therm. Anal. Cal.*, 2005, **81**, 339; (e) F. Carrasco, *Thermochim. Acta*, 1993, **213**, 115; (f) S. H. Patel, P. B. Panasuriya, M. R. Chhasatia, H. M. Parekh and M. N. Patel, *J. Therm. Anal. Cal.*, 2008, **91**, 413
95. P. Miranda Jr., J. Zukerman-Schpector , J. R. Matos , M. F. Maduar , E. M. Arico, M.

Linardi , L. B. Zinner and G. Vicentini, *Journal of Thermal Analysis and Calorimetry*, 2004, **75**, 577; (b) S. Gunasekaran and G. Anbalagan, *Bull. Mater. Sci.*, 2007, **30 (4)**, 339

96. W. Xiel, W.-P. Pan and K. C. Chuang, *Journal of Thermal Analysis and Calorimetry*, 2001, **64**, 477

97. M. G. Klous, G. M. Bronner, B. Nuijen, J. M. van Reeb and J. H. Beijnen, *Journal of Pharmaceutical and Biomedical Analysis,* 2005, **39**, 944

98. B. Tajeddin, *European Journal of Scientific Research*, 2009, **32 (2)**, 223