



Non-conventional Approaches towards Various Organic Reactions

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Abstract

Chemical transformations frequently involve time-consuming processes that can occasionally be achieved by employing different techniques and media. New methods allow us to explore new reaction profiles while saving time and solvents. As a result, new solvent classes for processing chemicals have been introduced. Supercritical fluids, fluorinated solvents, and solvents made from biomass, in addition to ionic liquids and the closely related deep eutectic solvents, have all attracted significant interest. From the perspective of green chemistry, sonochemistry, microwave, mechanochemistry, and catalysis are crucial strategies to enhance organic synthesis since they can encourage better yields and selectivities in addition to quicker reaction times than traditional procedures. This feature article describes the progress made in creating appealing sustainable approaches to synthetic organic chemistry and includes a recent survey of novel solvents and techniques used in a range of organic processes.

Key words: Green chemistry, Sustainable approaches, Organic reactions

1. Introduction

Chemistry is a science that is focused on the transformation of matter and energy. From this point on, chemists are uniquely qualified to offer a molecular-level approach to our society's sustainable growth. Sustainability is the ability to provide a happy, healthy, and high-quality living for everyone on Earth, both today and for future generations. In the past two decades, environmental challenges related to the chemical and related industries, such as the pharmaceutical business, have gained more significance. Numerous imitative synthetic approaches are typically linked with energy-intensive processes, the use of solvents that are frequently not environmentally friendly, and expensive and time-consuming procedures for the synthesis and isolation of sizable volumes of waste [1]. More recently, both academic and industrial chemistry have placed a high priority on the search for ecologically friendly procedures. Therefore, it is crucial in the industrial

field to apply green chemistry to the production of active medicinal components and manufacturing intermediates [2].

Anastas and Warner developed the idea of "Green Chemistry" in the 1990s, which refers to the design of procedures and goods associated with the removal or reduction of pollutants that are hazardous to the environment or life. A respectable number of chemists in both the industrial and academic fields have concentrated their efforts on the development of procedures that satisfy those criteria because this conception is based on the 12 principles advanced by them [1] followed by postulation of the twelve Green Chemistry principles (Figure 1) so a respectable number of chemists in both industrial and academic fields have converged their efforts on the development of processes that agree those criterions.

Avoiding or reducing the use of solvents is one evident approach to realize more sustainable processes, since this strategy diminishes the

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employment of chemical additives and with one another decreasing the generation of waste [3].



Figure 1: Green chemistry principles

The danger of most conventional solvents lies in their hazard as a function of their volatility. For example, chlorofluorocarbons (CFCs) which have been widely used as aerosol propellants, refrigerants, and solvents contribute to ozone depletion in the upper atmosphere, because they catalyze the conversion of ozone into O_2 . Other solvents are volatile enough to have a concentration in the air sufficient for humans to respire so they show manifest danger to human health. Indeed, Sheldon argued in 2005, that “the best solvent is no solvent” but if a solvent is required then water has a lot to advise it [3]. Water is the credible reaction medium for the outlook of organic chemistry. Ionic liquids, deep eutectic solvents and Glycerol are also considered as convenient-salient examples for reaction medium activators. Ionic liquids (ILs) are powerful solvents and also used in many applications. Deep eutectic solvents (DESs), a novel class of ionic liquid (IL) mimics, are already well known. Glycerol has a wide range of uses in the food, drug, and explosive industries.

Lowering the activation energy linked to the chemical reaction is another factor that is crucial for implementing the concepts of green chemistry. Conventional techniques state that heating for extended periods of time is necessary for chemical reactions involving high activation energy. This has a high intrinsic cost and the attendant danger of reagent and/or product breakdown. Organocatalysis, mechanochemical activation, microwave irradiation, ultrasounds, and photocatalysis are some of the most successful solutions for efficient activation under

environmentally friendly circumstances in the last two or three decades. A sizable number of review articles and monographs on green chemistry have lately been published, defining effective strategies to enable the activation of chemical transformations in sustainable processes [3-12]. This review deals with non-conventional trends to mildly and efficiently manipulate organic transformation.

I. Unconventional reaction media

Solvents are incredibly important in many different domains, but synthesis is one of them. Due to the growing importance given to “greenness,” solvents in general are a clear subject for interest and concern [13]. They make up the greatest single component in the majority of reactions. The usage of green solvents continues to be a difficulty due to the well-known environmental and safety issues produced by traditional hazardous volatile organic solvents (VOCs) [14]. In contrast to VOCs [5-7], however, low vapor pressures [15], low volatility, and less toxicity enable for greener synthesis with less environmental harm [16, 17]. Many alternative solvents such as water, supercritical fluids, room temperature ionic liquids (RTILs), and fluorosolvents have been proposed [13]. Due to their potential to address both environmental and economic issues, ILs is a relatively new class of promising solvents. As a result, both the scientific and industrial communities are becoming more and more interested in them. Deep eutectic solvents (DESs) are a brand-new family of environmentally friendly solvents that are preferred because of their low cost, low toxicity, low volatility, biodegradability, non-flammability, and appropriateness for a variety of industrial applications [13]. In a number industrial and laboratory processes, supercritical fluids are used as another treatment alternative. Fluorous techniques offer strategic new choices for introducing solution phase organic reactions and for separating the products.

1. Free solvent media

To obtain the stereoselective products and speed up the reaction, the reactants can be mixed with clays, zeolites, silica, alumina, etc. or used alone to produce a solvent-free reaction [18]. Through the avoidance of typical volatile organic solvents, this useful reaction reduces the production of trash or byproducts. Additionally, this environmentally

benign reaction is notable for its excellent product purity, high yield, economic effectiveness, and little to no harmful effects. By creating new chemical entities without using up all the solvents, clever approaches have been used to create diverse pharmacological compounds [19]. To carry out the chemical reactions, two experimental conditions are used without the need to use solvent such as:

(a) Reaction on solid support

The reactants in this reaction are initially adsorbed either on a mineral support (alumina, silica clays), a polymer support (polystyrene, polyethylene glycol), or via their solution in a suitable organic solvent of low boiling [20]. For instance, clays and modified or supported clays stand out for their simple structural activation, eco-friendliness, low cost, ready availability, and capacity to act as acidic or basic catalysts without being corrosive, making them some of the most commonly used catalysts for different organic reactions (Figure 2, 3).



Figure 2: Catalyzed alumina

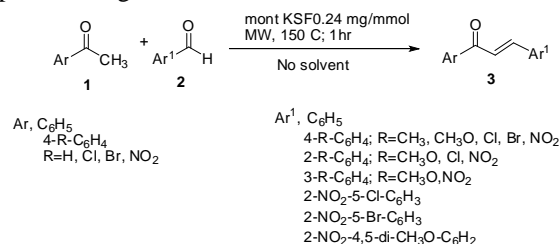


Figure 3: Catalyzed clay

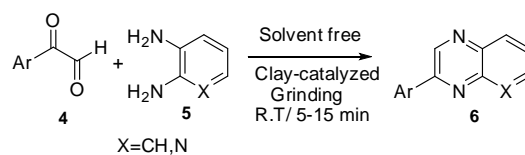
Merchant montmorillonite KSF clay was used as catalyst for synthesizing chalcones **3** in excellent yields beginning with, acetophenone derivatives **1**, benzaldehyde derivatives, 2-actylfuran, 2-acetylthiophene, furfural, and thiophene-2-aldehyde **2** [21] (Scheme 1).

By condensing aromatic 1,2-diamines **5** with arylglyoxals **4** under clay-catalyzed reaction conditions, a series of arylquinoxalines **6** were produced [22] (Scheme 2). This has led to respectable

reductions in reaction times and good yields, green, rapid and facile strategy in comparison with already reported using toxic solvents under reflux conditions.



Scheme 1: Aldol condensation reaction catalyzed by montmorillonite KSF

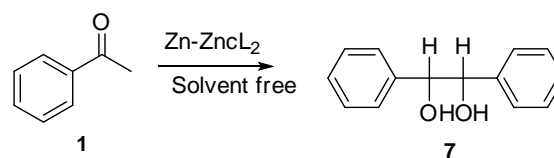


Ar=C₆H₅, 4-CH₃O-C₆H₄, 3-CH₃OC₆H₄, 3,4-(CH₃O)₂C₆H₃, 4-ClC₆H₄

Scheme 2: Synthesis of arylquinoxalines derivatives under clay-catalyzed reaction conditions

(b) Reaction without any solvent

Without any adduct, the reaction between neat reactants can be conducted in a quasi-equivalent amount without the use of any solvent [19]. In organic chemistry, the diols **7** are simple building blocks. When an electron donor and a free radical are present, a pinacol coupling reaction occurs, forming a carbon-carbon covalent link between the carbonyl groups of a ketone **1** [19] (Scheme 3).



Scheme 3: Formation of vicinal diol via pinacol coupling reaction

Quinazolinone derivatives are currently widely known as successful drug discovery scaffolds. Dihydroquinazolinone derivatives **9** were made using an enhanced multicomponent procedure using isatoic anhydride **8**, aldehydes **2**, and NH₄OAc in a solvent-free environment at 110 °C. SnCl₂ dihydrate served as the catalyst [23] (Figure 4).

One of the important classes of nitrogen heterocyclic compounds is acridine diones. It is generally known that acridine diones play a significant role in both biological chemistry and chemical synthesis. Using Cu-doped ZnO nanocrystalline powder as a catalyst in a one-pot

three-component condensation process with dimedone **10**, aromatic amines **11**, and aromatic aldehydes **2**, a new catalytic approach was created to produce N-substituted decahydroacridinediones **12** [24] (Scheme 4).

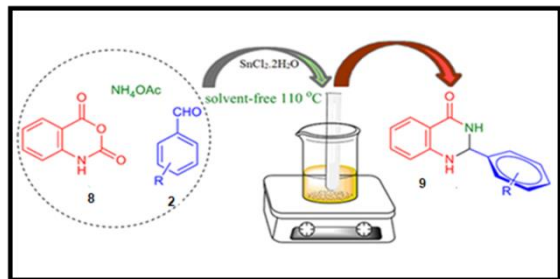
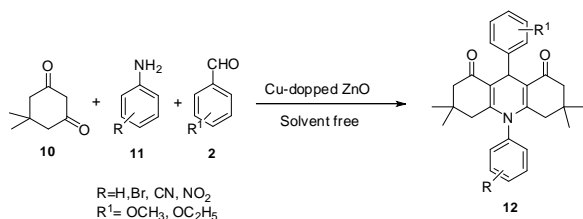


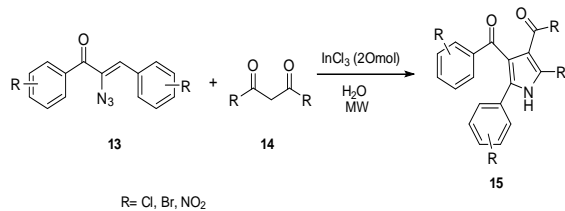
Figure 4: Dihydroquinazolinones are created without the need of any solvent



Scheme 4: Dioxodecahydroacridine is made without the use of any solvents

2. Water

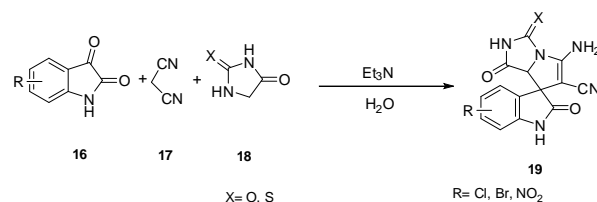
In the last two decades, the use of water as a solvent in chemical reactions has drawn a lot of interest. In addition to the advantage of utilizing a solvent that is inexpensive, non-toxic, and non-flammable, reactions in water are frequently accelerated and exhibit increased selectivity. Polysubstituted pyrroles **15** were obtained in good yields from reacted azidochalcone **13** with 1,3 diketone **14** in water [25] (Scheme 5).



Scheme 5: Synthesis of polysubstituted pyrroles

The development of a three-component procedure for the synthesis of novel spiro [indolinepyrrolo[1-c]imidazole] carbonitrile derivatives **19** is reported. Using isatin **16**, malononitrile **17**, hydantoin or thiohydantoin **18**, and Et₃N as the base, the reaction

was successfully accomplished in good yields [26] (Scheme 6).



Scheme 6: Synthesis of spiro[indolinepyrrolo[1-c]imidazole] carbonitrile derivatives in water as solvent

3. Ionic Liquids

Room temperature molten salts or Ionic liquids have piqued the researcher's interest to reduce potential risk to the environment and human health. The extremely low vapor pressures of room temperature ionic liquids have been characterized by many of the researchers as "having no vapor pressure" as they have been prepared such that the vapor pressure is so negligible.

Ionic liquids evolution is currently being obviously pursued in the design of the molecular structures with lower toxicity and isolating the products of a reaction by Green Chemistry techniques. There are many commercial and scientific challenges for radically changeable industrial chemical processes through the employment of ionic liquids [27]. Ionic liquids can be classified into four types according to their cationic species: alkylammonium-, dialkylimidazolium-, phosphonium- and N-alkylpyridinium- based ionic liquids [27] (Figure 5).

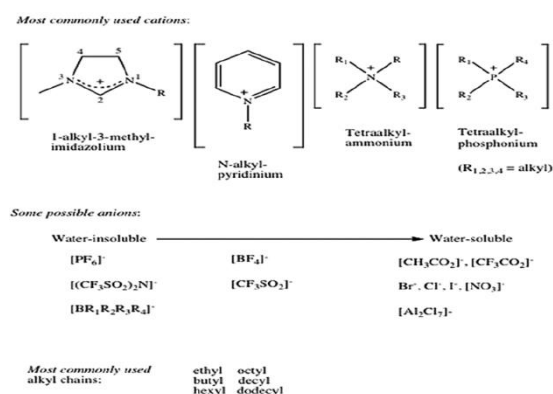
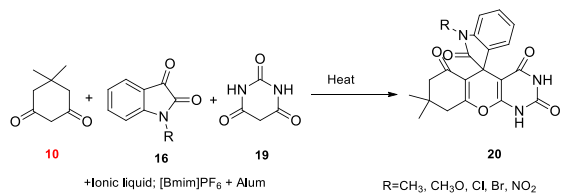


Figure 5: Types of ionic liquids

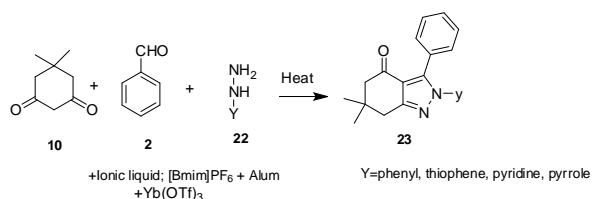
Dimedone **10**, isatin derivatives **16**, and barbituric acid **19** were combined with butylmethylimidazolium hexafluorophosphate and alum to

form the indoline tetraones **20** [28] (Scheme 7). The synthesized tetraones **20** derivatives were found to be important skeletal motifs for many pharmaceuticals.



Scheme 7: Synthesis of indolinetetraones derivatives in excellent yields

Dimedone **10**, variously benzaldehyde derivatives **2**, and hydrazine derivatives **22** were put through a one-pot multicomponent reaction in an ionic liquid with Yb(OTf)₃ acting as a catalyst to produce tetrahydroindazolones **23** [29] (Scheme 8). Due to their beneficial characteristics and biological activities, indazole- and indazolone-based compounds have recently attracted particular attention [30].



Scheme 8: Synthesis of tetrahydro-indazolones

The circular bio economy is giving catalytic depolymerization of lignin to value-added chemicals due consideration. Utilizing butyl methylimidazolium tetrachloroferrate (III) [BMIM][FeCl₄] as a catalyst in an aqueous solution, metal-based ionic liquids (MBILs) were used to selectively depolymerize alkali lignin to vanillin with 85% selectivity at room temperature. (Figure 6) [31].

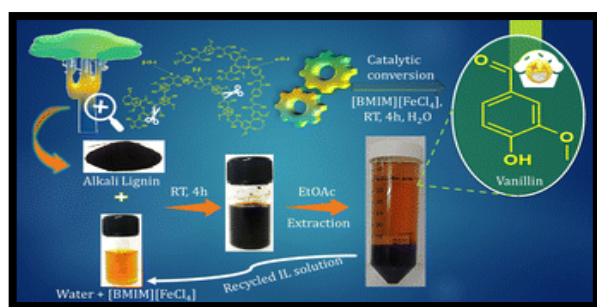


Figure 6: Efficient aqueous-based catalysts for the selective synthesis of vanillin

4. Deep eutectic solvent (DES) as dual solvent/catalyst

Deep eutectic solvents (DES) are ionic solvents and are a eutectic mixture of a base and a Brønsted or Lewis acid having lower melting point than the starting components [32] (Figure 7).

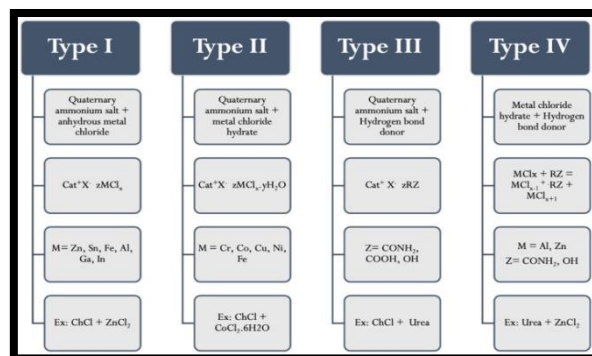
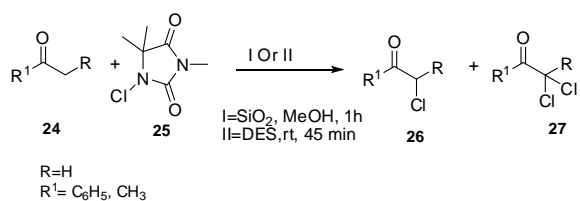


Figure 7: Types of deep eutectic solvents

Although, ILs and DESs are similar in their nature and applications, the making ready of DESs is 100% atom economic, highly pure, high thermal stability, less expensive and in chemical processes, they can act as catalysts and solvents [33]. The DESs are referred to as natural deep eutectic solvents when the components that make up the DES are primary metabolites, specifically organic acids, amino acids, sugars, or choline derivatives (NADES). Because of their complete environmental friendliness, NADES excellently exemplify green chemistry ideas that have attracted notable attention. A wide range of research topics, including manufacture drug solubilization vehicles, metal electrodeposition, metal electropolishing, an electrolyte for dye-sensitized solar cells, and synthesis implementation, have been addressed by the deep eutectic solvent approach.

The selective synthesizing of highly reactive α -mono **26** or α,α -dichloro **27** ketones have been received increasing concern as they are considered as building blocks for several classes of compounds due to their selective transformations. When a mixture of acetophenone **24** and dichloro dimethylhydantoin **25** at room temperature in a DES choline chloride/ p-toluenesulphonic acid gave excellent yield compared to the conventional procedure that uses methanol as the solvent under reflux and silica gel as the catalyst [34] (Scheme 9).



Scheme 9: preparation of α -mono or α,α -dichloro ketones in a choline chloride: p-TsOH DES

In the aza-Michael addition of maleimide and arylamines to obtain aminopyrrolidine dione derivatives, the effects of DES choline chloride/p-toluenesulfonic acid and DES choline chloride/p-toluenesulfonic acid-water were systematically investigated. Under relatively benign reaction conditions, the derivatives were produced with a good yield [35] (Figure 8).

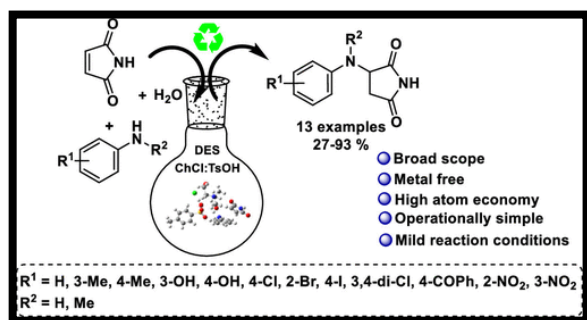
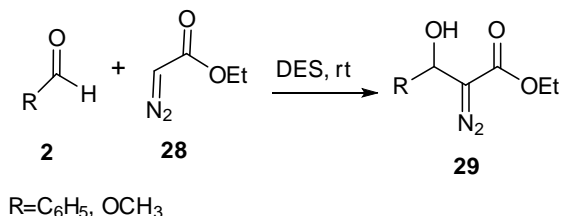


Figure 8: Aza-Michael addition in a choline chloride: p-TsOH DES-water

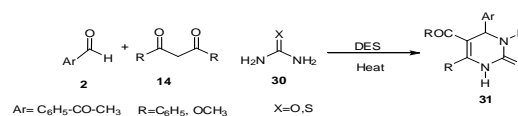
In order to create the crucial synthetic intermediates known as diazocarbonyl **29** compounds, by reacting aldehyde **2** and ethyl diazoacetate **28** and deep eutectic solvent (DES) potassium carbonate to glycerol in 1:5 molar ratio was used as both a solvent and a catalyst [13] (Scheme 10).



Scheme 10: Aldol-type coupling in DES at room temperature

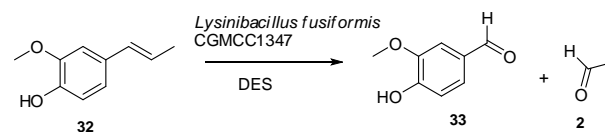
The Biginelli reaction is a multiple-component reaction that produce dihydropyrimidin ones/thiones

(DHPMs) **31** involving easily-accessible starting materials namely, an aryl aldehyde **2**, β -ketoester **14**, and (thio) urea **30**. The highest catalytic activity was catalyzed by P-toluene sulfonic acid (PTSA) and choline chloride-based DESs (ChCl) [36] (Scheme 11). (DHPMs) have high pharmacological and therapeutic activities and are increasingly finding implementations in the development of materials such as polymers, adhesives, fabric dyes [37]



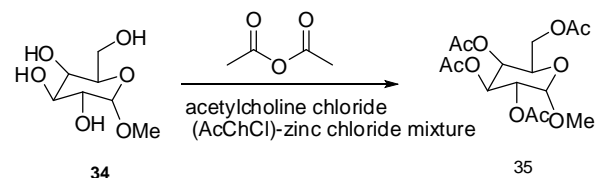
Scheme 11: Dihydropyrimidinones/thiones (DHPMs) synthesis

The application of DESs in biotransformations, a chemical alteration of a chemical substance by an organism or enzyme, is a developing study topic. It would be ideal if enzymatic alkene oxidative cleavage would take the place of more conventional processes like ozonolysis. Such a reaction was discovered to be catalyzed by *Lysinibacillus fusiformis* CGMCC1347, turning isoeugenol **32** into vanillin **33** [38] (Scheme 12).



Scheme 12: Biocatalytic alkene oxidative-cleavage converting isoeugenol to vanillin

It is also favorable to transmute some organic molecules in these liquids, such as cellulose and unprotected sugars. cellulose's selective O-acetylation **34** to the acetylated one **35** has been reported [39] (Scheme 13).



Scheme 13: Selective O-acetylation of cellulose in DESs

5. Glycerol

Glycerol, an organic waste product of the biodiesel industry, has a great deal of potential as a green solvent alternative for a variety of organic

catalytic and non-catalytic reactions. High stereoselective product yields, catalyst and reactant solubility and easy separation of the product were noticed while usage glycerol. The benefits of water (low toxicity, low cost, wide availability, and renewability) and ionic liquids may be combined with glycerol (high boiling point, low vapor pressure) (Figure 9).

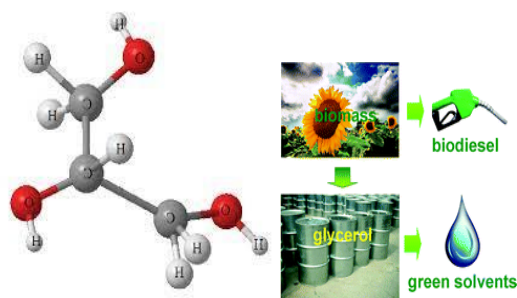
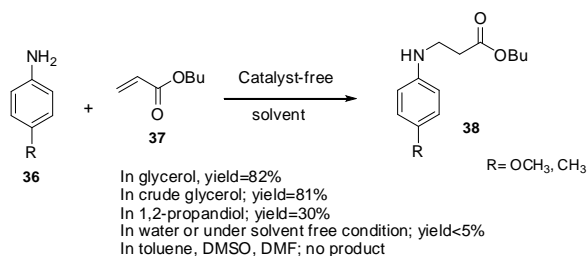


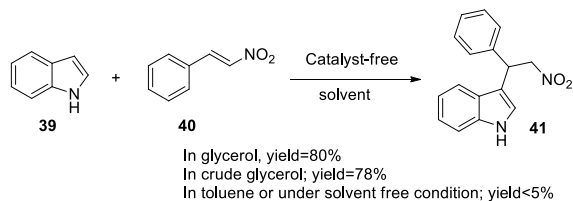
Figure 9: Glycerol

Without the aid of a catalyst, Aza-Michael P-anisidine **36** and n-butyl acrylate **37** can be added forward satisfactorily using glycerol as the optimum solvent [40] (Scheme 14).



Scheme 14: Aza-Michael reaction under several solvent systems

The Michael addition of indole **39** and nitrostyrene **40**, where alone glycerol was shown to be capable of giving the desired product **41** in outstanding yield without assistance from any catalyst, followed the same trend [40] (Scheme 15).



Scheme 15: Michael reaction of indole in different solvent systems

6. Supercritical carbon dioxide (SC-CO₂)

When carbon dioxide is kept at or above its critical temperature and critical pressure, it is said to be in the supercritical state (SC-CO₂). It has been demonstrated that it can replace a number of solvents

in an environmentally friendly manner. Supercritical CO₂ is considered as an important industrial and commercial solvent due to its relatively low toxicity and environmental impact and its role in chemical extraction [41] (Figure 10).

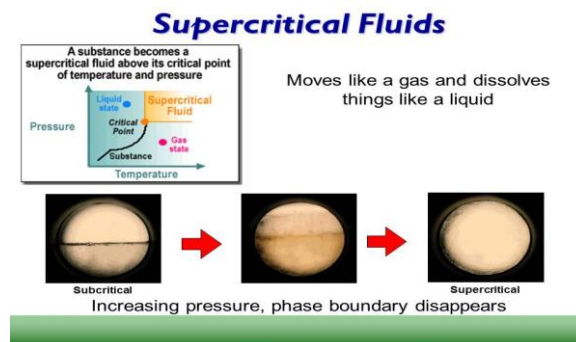
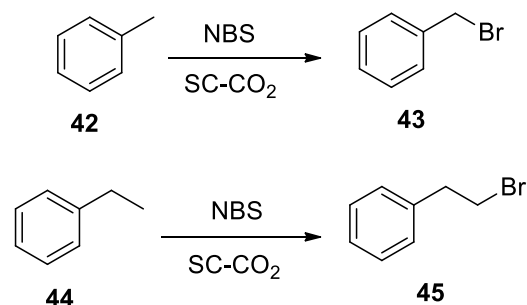


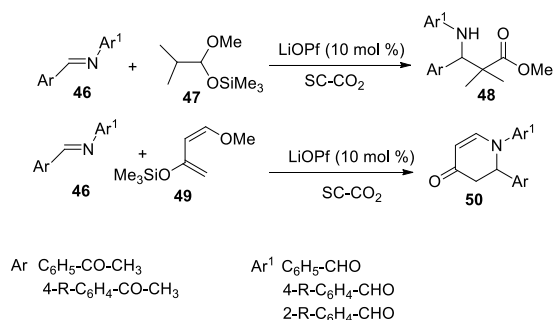
Figure 10: Supercritical carbon dioxide (SC-CO₂)

By using SC-CO₂ with the brominating reagent, N-bromosuccinimide, a free-radical side-chain bromination of (methyl, ethyl) benzene **42** or **44** was successfully performed respectively, to produce bromobenzene derivatives **43** or **45** [41] (Scheme 16). SC-CO₂ can successfully substitute common reaction solvents like benzene or the chlorinated compound carbon tetrachloride.



Scheme 16: Side-chain bromination of alkylaromatics using SC-CO₂

Lithium heptafluorooctanesulfonate acts as a catalyst in Mannich-type reaction using imines **46** and trimethylsilane **47** to afford amino carbonyl compounds **48**. Also, in Diels - Alder reaction of imines **46** with Danishefsky's diene **49** to produce nitrogen-containing six-membered ring compounds **50** [42] (Scheme 17).



Scheme 17: The Mannich-type and Diels–Alder reactions under environmentally benign conditions

7. Fluorous Solvents

Solvents with a significant amount of fluorine in their molecules are known as fluorous solvents. Most fluorous solvents have strong chemostability and thermostability and low toxicity [43] (Figure 11).

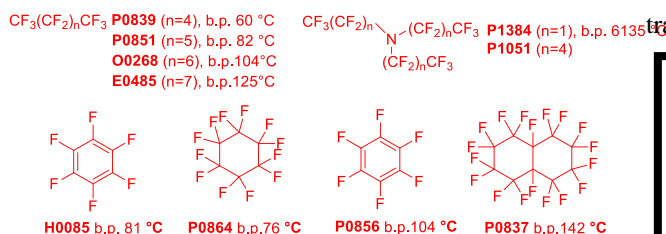
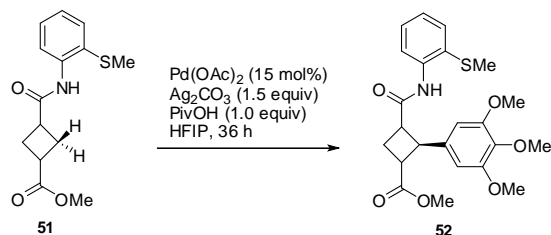


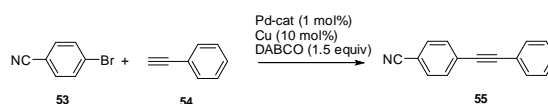
Figure 11: Examples of fluorous solvents

Using of hexafluoroisopropanol jointly with the pivalic acid additive was crucial parameter allowing for effective arylation of the cyclobutane derivatives **51** for furnish the piperarborenine cores **52** [44] (Scheme 18).



Scheme 18: Arylation of the cyclobutane derivatives using HFIP as solvent

The palladium-catalyzed Sonogashira coupling reaction between an aryl halide **53** and a terminal alkyne **54** was found to occur in FC-77-DMF 1:1 giving the corresponding aryl-substituted alkyne **55** in high yield. The palladium catalyst was recovered simply and reused three times with only slightly changing in catalytic activity [45] (Scheme 19).



Scheme 19: Synthesis of aryl-substituted alkyne in high yield in FC-77-DMF 1:1

II. Non-conventional methods and techniques

1. Mechanochemistry

The study of chemical reactions brought on by mechanical forces is known as mechanochemistry [46]. Energy mechanochemical methods are straightforward, adaptable, and sustainable. Organic synthesis depending on mechanochemical methods can be carried out in a variety of environments, including low temperatures, high gas pressures, reactive or inert atmospheres, solvents, or all-solid-state conditions (Figure 12). This pattern can be used to create novel processes for particular chemical reactions that are challenging to accomplish using traditional chemical synthesis [47].

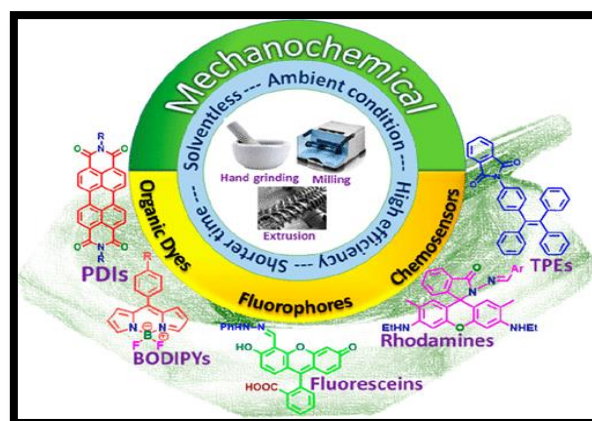


Figure 12: Mechanochemistry

From the first manual mortar and pestle to a range of new mechanical instruments, mechanochemical equipment has evolved. Various grinding machines are already available that are automated for their convenient and dependable use in laboratory (small scale) or industrial (large scale) applications [47] (Figure 13).

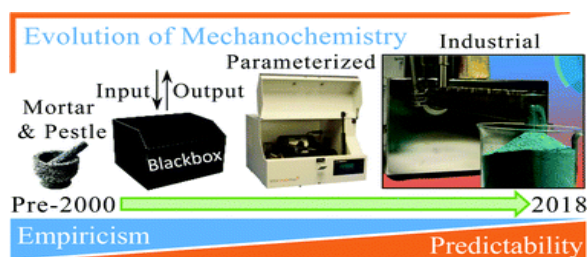


Figure 13: Evolution of mechanochemistry

Advanced functional materials for energy conversion and storage have been successfully prepared using mechanochemical processes such as grinding, ball-milling, and ultrasonic irradiation.

1.1. Grinding

At most, mechanical milling or manual grinding used to improve mechanochemistry. Typically, hand grinding is done in a mortar and pestle. The method of grinding organic compounds is practical and easily regulated. A successful grinding technique with excellent yields has been used to produce dihydropyrano[2,3-c]pyrazole derivatives from acetylene ester, hydrazine hydrate, aryl aldehydes, and malononitrile without the use of solvent [48]. Recent studies have proven that the unique class of heterocyclic compounds known as pyranopyrazole derivatives exhibits a wide range of biological functions [49] (Figure 14).

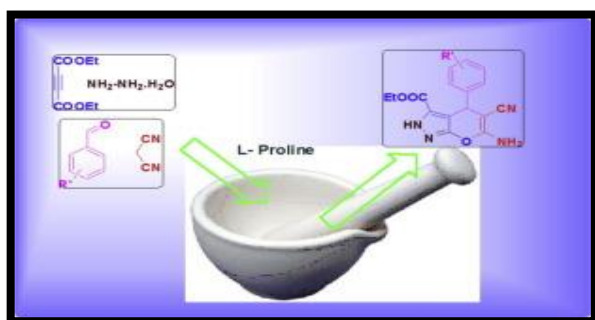
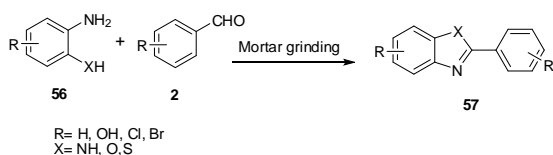


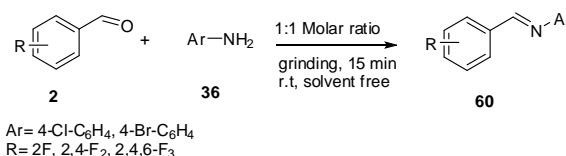
Figure 14: Synthesis of dihydropyrano[2,3-c]pyrazole derivatives by grinding protocol

It was mentioned that the mortar-and-pestle grinding method, with acetic acid as a catalyst, produced benzimidazoles **57** in excellent yields. Aldehyde **2** and *o*-phenylenediamine **56** were first condensed in this mechanochemical process, which was then followed by a cyclization reaction [50] (Scheme 20). Benzimidazole is served as a “privileged structure” in heterocyclic chemistry due to its association with a broad range of biological efficiency [51].



Scheme 20: Synthesis of benzimidazoles by mortar-pestle grinding technique

A manual solvent-free grinding process was used to create a variety of imines **60** from variably fluorinated benzaldehydes **2** and a variety of anilines or chiral benzylamines **36**. The yields were on par with or much higher than those for the imines synthesized using other traditional techniques as described in the literature [52] (Scheme 21).



Scheme 21: Mechanochemical approach to fluorine-containing imines formed

1.2. Ball-Milling-Induced Mechanochemistry

High speed ball mills (HSBMs), planetary mills, and screw mills are the most often utilised. The mill reactor's friction and banging of the spheres create stress that leads to high-temperature microsites that facilitate the substrate's bond cleavage and the creation of new bonds to produce the desired products [3] (Figure 15).

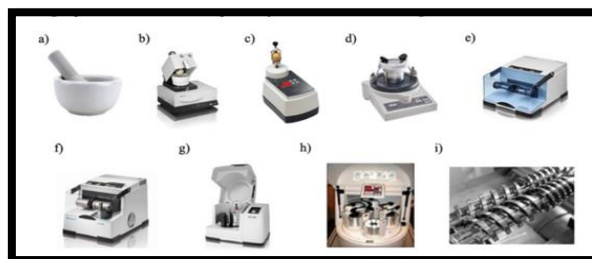


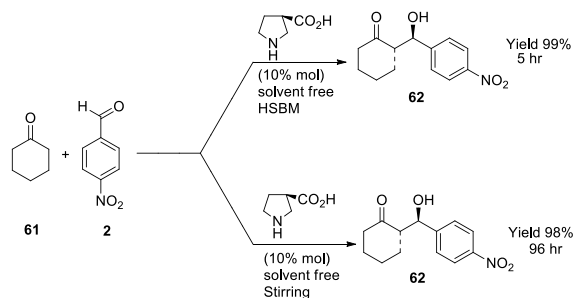
Figure 15: Common tools for grinding and milling include a) Mortar and pestle b) Automatic mortar c) Vertical vibrational and mini-mill d) Vibratory micro-mill e) Vibrational ball milling f) Vibrational ball milling with temperature control g) Planetary ball milling h) Multi-sample milling i) Twin-screw device for continuous mechanochemical process

1.2.1. Catalyzed Reactions under Solvent-Free Ball-Milling Conditions

Organocatalysis is a new field with benefits for the economy, environment, and science. In Organocatalysis and mechanochemical activation work together to provide efficient processes with high yields and observable chemo-, regio-, and stereoselectivities. This combination has been a potent synergistic tool in organic synthesis.

Excellent results were reported for asymmetric

aldol reactions using chiral organocatalysts in a ball mill [53, 54] (Scheme 22). Proline catalysis has produced anti-aldol compounds from cyclohexanone **61** and p-nitrobenzaldehyde **2** in excellent yields under straightforward experimental solvent-free circumstances to produce compound **62**. One of the most advantageous methods for creating C-C bonds is the aldol reaction.



Scheme 22: Novel methodologies for chemical activation in asymmetric aldol reactions

Using butylenebis(sulfo-3H-imidazolium) hydrogen sulphate as a recycled Brønsted acid ionic liquid in a ball milling process at room temperature under solvent-free conditions is a new and effective method for producing pyrrolidinones. It shows how to combine a synthetic benefit of a one-pot multicomponent reaction with environmental advantages and the appropriateness of a mechanochemical process [55] (Figure 16).

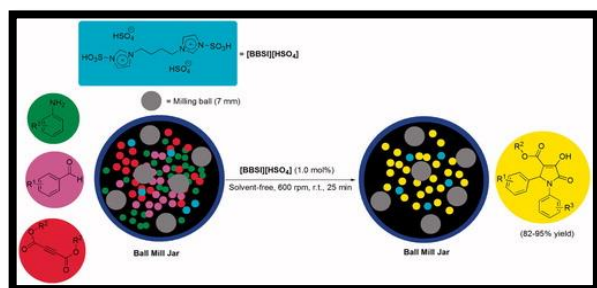
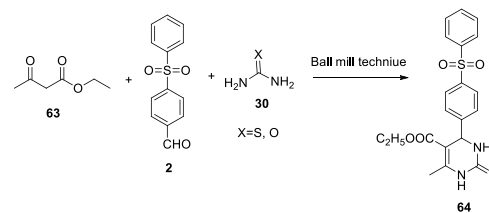


Figure 16 : Efficient protocol for the synthesis of pyrrolidinones

Dihydropyrimidinones (DHPMs) derivatives **64** were created by a ball-milling three-component, environmentally friendly, one-pot reaction using β -ketoester derivatives **63**, aldehyde **2**, and urea or thiourea **30** over the alkali-treated H-ZSM-5 zeolite [56] (Scheme 23).

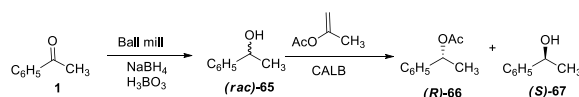


Scheme 23: A ball-mill, solvent-free technique for synthesis of DHPMs

1.2.2. Under Solvent-Free Ball-Milling Conditions, Enzymatic Reactions

Enzymes are extremely selective, operate at room temperature, and facilitate a range of reactions, making them an ideal choice for high efficiency catalysts [57, 58]. The processes utilising them are considered environmentally friendly and sustainable because they are made up of naturally occurring compounds that serve as non-toxic reagents and are biodegradable. [59] Enzymes tolerate unconventional media such as ionic liquids [60], deep eutectic solvents [61] and ball-milling apparatus. We'll give some examples of how enzymes and mechanochemistry have been used together to convert diverse organic compounds below.

Racemic secondary alcohols *rac*-**65** were enzymatically resolved by acylation with isopropenyl acetate, which was catalysed by *Candida antarctica* lipase B. (CALB) [60] (Scheme 24). The catalyst under ball milling conditions, showed high stability and a high enantioselectivity hydrolysis affording acetates (*R*)-**66** and the residual alcohols (*S*)-**67** [62].



Scheme 24: Acylative kinetic resolution of secondary alcohols

Only a half equivalent of water and 0.2 mL of 2-methyl-2-butanol served as the liquid grinding assistance during the ball milling enzymatic resolution of *N*-benzylated-3-amino esters in the absence of solvent (LAG). The enantiomeric products can be maintained in spite of the usage of the recovered enzyme [63] (Figure 17).

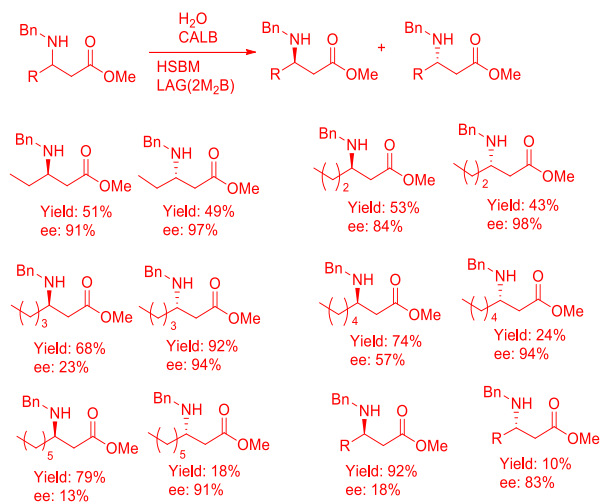


Figure 17: Enzymatic resolution of N-benzylated-3-amino esters in HSBM conditions without the use of solvents

Chemoenzymatic oligomerisation of L-amino acids was introduced by utilizing a mixer ball mill or twin-screw extrusion technology must be able to produce the matching in excellent to outstanding yields depending on the type of amino acid [64] (Figure 18).

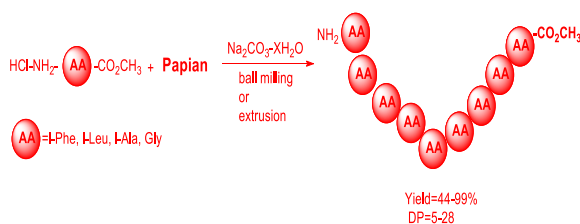


Figure 18: Papain-catalyzed synthesis of oligopeptides by milling and twin- screw extrusion

2. Sonochemistry

Sonochemistry is the study of how ultrasound causes liquids to create acoustic cavitation, which starts or intensifies chemical activity in the solution. Similar to mechanochemistry, sonochemistry offers novel reaction conditions and prohibitive heat activation barriers, giving it an unmatched position in comparison to other activation techniques (thermal, microwave, photochemistry, etc.) [65]. There is no direct interaction between chemical species and ultrasound at the molecular level. The effect of pressure waves on liquid medium leads to the formation of cavities in liquid which undergo continuous compression and rarefactions. This goes on until the cavities reach a critical radius, which is

determined by the frequency of ultrasound [66] (Figure 19).

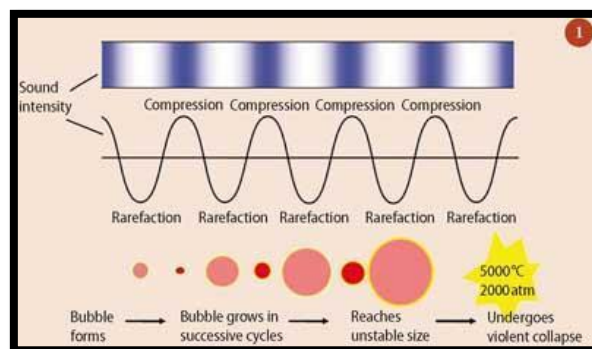
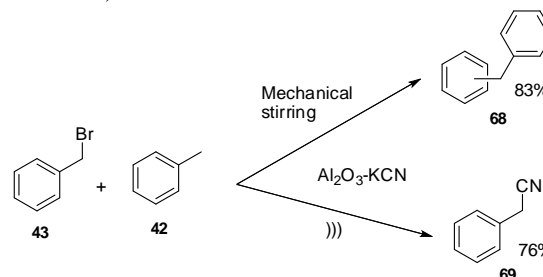


Figure 19: The effect of pressure waves on liquid medium

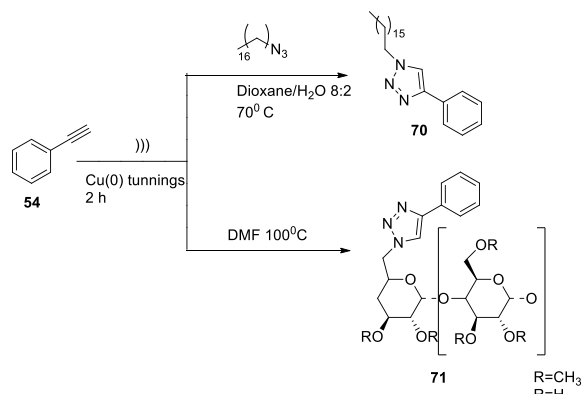
It's interesting how changing the chemical reaction's selectivity and pace may be accomplished by employing US as the energy source. Ando and his coworkers made the initial observation of this phenomena. When benzyl bromide **43** was sonicated in a potassium cyanide toluene suspension supported on alumina, a mixture of regioisomer phenyl-tolyl methanes **68** from a Friedel-Crafts reaction was produced under the usual oil-bath conditions, while benzyl cyanide **69** was produced in good yield as the result of an aliphatic nucleophilic reaction [66] (Scheme 25).



Scheme 25: Reaction modified by ultrasound activation

2.1 Acoustics in liquid media

To aid the cavitation process, a liquid medium needs to be added to a system that is being exposed to ultrasonic irradiation. Another remarkable benefit of US irradiation is the activation of surfaces made of hard metal. Application of metallic copper in the synthesis of disubstituted triazole derivatives **70** and **71** from azides and alkynes **54** proved successful [66] (Scheme 26).



Scheme 26: Metal surface activation in the azide-alkyne cycloaddition process

It was explained how to assemble aminodihydropyrano pyrancarbonitrile **73** scaffolds using a three-component reaction involving kojic acid **72**, malononitrile **17**, and aromatic aldehydes **2** in water while being exposed to ultrasound. This green process differs significantly from conventional procedures in that it is experimentally simple, has good functional group tolerance, excellent yields, a quick routine, and selectivity [67] (Figure 20).

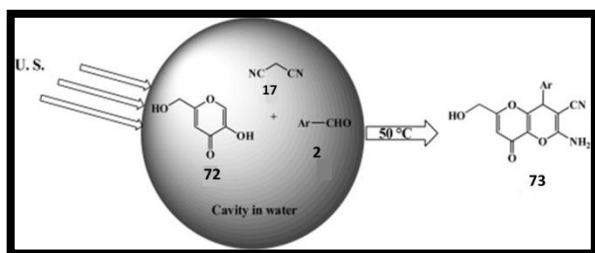


Figure 20: Kojic acid, malononitrile, and aromatic aldehydes reacting in three components as a green approach

2. 2. Solvent-free sonochemistry

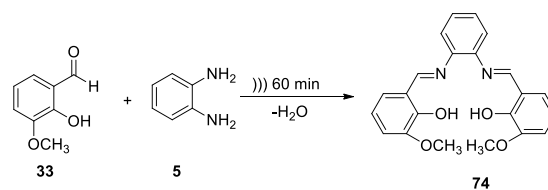
Recently, ultrasonic irradiation was used to successfully perform condensation reactions between solid reagents in the absence of any solvent (Figure 21).



Figure 21: Typical laboratory employed planetary ball mill and ultrasonic bath

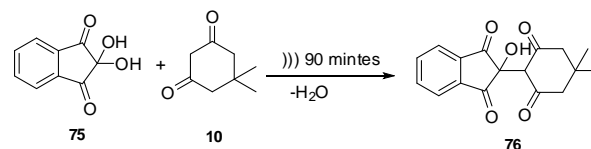
In the total absence of any solvent and without the

use of any grinding medium, the ball milling reaction to create salen ligand **74** by sonicating O-vanillin **33** and phenylenediamine **5** was studied [66] (Scheme 27).



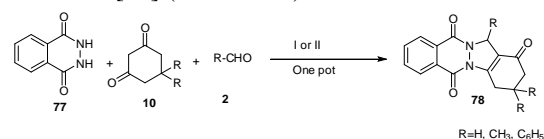
Scheme 27: O-vanillin and phenylenediamine subjected to an ultrasonic irradiation reaction

The successful formation of indandione **76** (Scheme 28) from ninhydrin **75** and dimedone **10** by ultrasound irradiation in the absence of solvent suggests that organic synthesis could continue by using sound waves as an appropriate form of mechanical energy [68].



Scheme 28: Aldol reaction between ninhydrin and dimedone

A quick and effective three-component one-pot procedure for 2H-indazolo[2,1-b]synthesis]'s By domino coupling phthalhydrazide **77**, diketones **10**, and aldehydes **2** under solvent-free circumstances at 80 °C as well as under solvent-free ultrasonic irradiation at room temperature supported by (S)-camphorsulfonic acid, phthalazine-1,6,11-triones **78** were created [66] (Scheme 29).



Reaction conditions: I: (S)-CSA (20 mol%), solvent free
II: (S)-CSA (20 mol%), r.t.,))) solvent free

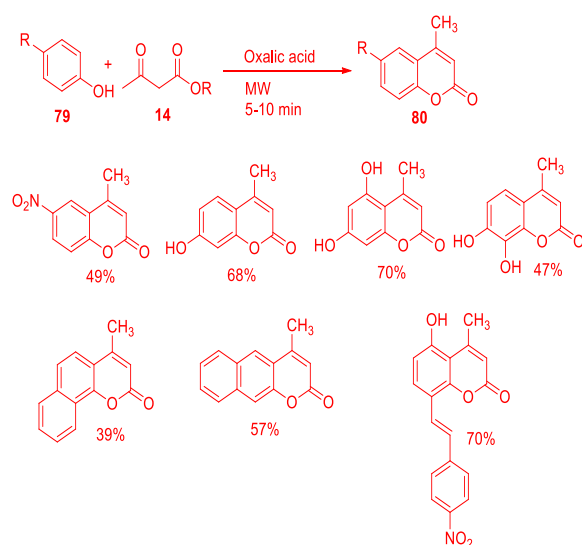
Scheme 29: Domino coupling under solvent-free ultrasound irradiation

3. Microwave activation under solvent free conditions

For more than two decades, microwave irradiation has been transforming organic chemistry. Better yields and higher purity of the reaction products, energy savings, homogeneous heating, and strong repeatability are a few benefits of using microwaves in organic synthesis [69, 70]. The occasional

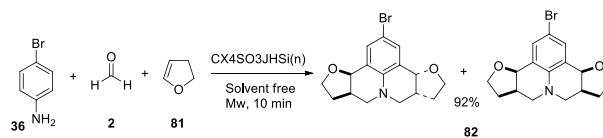
explosion of the reactor flasks or tubes due to pressure put on them by the reaction solvent during irradiation is one of the potential issues with using microwave reactors. This is why it's become quite crucial to get rid of the solvent, which actually results in faster reaction times and higher yields [70].

Monga *et al.* reported the microwave-based, solvent-free synthesis of coumarins **80** [71]. Coumarin derivatives **80** are compounds found in a variety of plants and have interesting therapeutic properties. This procedure uses β -Ketoester **14**, substituted phenols **79** and oxalic acid in catalytic amounts to allow the preparation of a variety of products that demonstrate the scope of the method (Scheme 30).



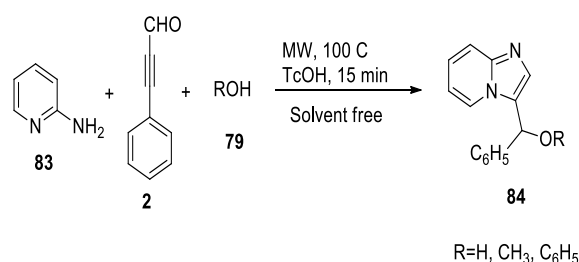
Scheme 30: Solvent free synthesis of coumarins under microwave irradiation

The respectable value of Julolidines **82** is due to their application as antivirals, antidepressants [72]. Using a microwave-assisted supported catalysis, Julolidines **82** were created by the reactions of bromoaniline **36**, aldehyde **2** and dihydrofuran **81**, without the use of a solvent [73] entails a many component reaction as demonstrated in (Scheme 31). The supporting catalyst is a Calix[4]arene, which when used in conjunction with microwave activation in a solvent-free procedure, demonstrated significant catalytic activity.



Scheme 31: Microwave assisted solvent-free synthesis of julolidines

Under solvent-free conditions, pyridine amine **83**, 3-phenylpropionaldehyde **2**, and alcohol **79** were combined in a microwave-assisted three-component reaction, which was catalyzed by TsOH. The reaction proceeded with high efficiency and good functional group tolerance to produce the corresponding imidazo pyridines **84** in good yields [72] (Scheme 32).



Scheme 32: An effective procedure for making functionalized imidazo[1,2-a]pyridines

3. Organocatalysis

Because it is used in so many different disciplines, such as industry, energy, the environment, and life sciences, catalysis continues to be a strategic area of chemistry. Catalysis, whether homogeneous or heterogeneous (or even enzymatic), is fundamentally a molecular phenomenon since it involves the chemical conversion of one type of molecule into another. Homogeneous catalysis is related to molecular organometallic chemistry, while heterogeneous catalysis is more closely related to surface science and solid-state chemistry. At the beginning of the 21st century, despite numerous attempts to completely close the gap between these two significant fields of chemistry, they still belong to different scientific communities (Figure 22).

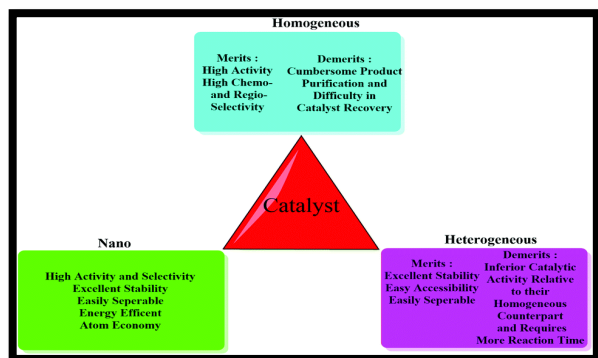
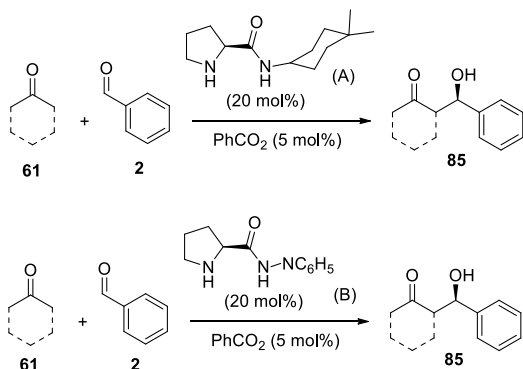


Figure 22: Types of catalyst

a) Organocatalysis in Free solvent media

Because the production of fine chemicals, pharmaceuticals, and minerals has a negative impact on the environment, the development of catalytic techniques is a topic of current concern. The utilisation of solvent-free processes in organic chemistry is becoming more and more important, with a major influence on both environmental and human health protection.

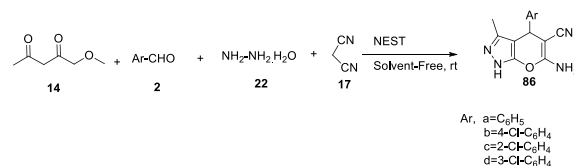
Two new prolinamide catalysts A and B for stereoselective and aldol reaction of aldehydes **2** and ketones **60** have recently reported to produce the corresponding β -hydroxy carbonyl compounds **85** under neat conditions [74] (Scheme 33).



Scheme 33: Two approaches of solvent-free

In the presence of nano-eggshell/Ti(IV) (NEST) as a very effective nanocatalyst, a successful one-pot four-component method was reported. Under mild circumstances, hydrazine hydrate **22**, ethyl acetoacetate **14**, malononitrile **17**, and aldehydes **2** combine to form dihydropyrano pyrazoles (DHPPs) **86** in good to outstanding yields (Scheme 34). Pyranopyrazoles derivatives are significant class of heterocyclic compounds because of their wide implementations in medicinal and pharmaceutical chemistry [75] (Scheme 34).

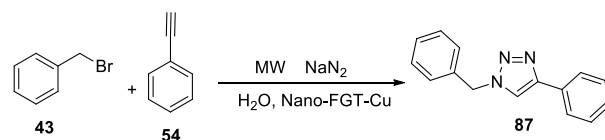
enantioselective aldol reactions



Scheme 34: In the presence of nano-eggshell and Ti(IV), DHPPs are synthesized (NEST)

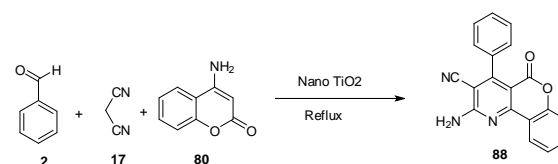
b) Organocatalysis in Water

Azide alkyne cycloaddition (AAC) process could be carried out using a magnetically separable nano-FGT-Cu catalyst. Through in situ azide production **87** and cycloaddition in aqueous media, this general reaction is carried out in a single pot [76] (Scheme 35). The use of magnetically recyclable nanocatalysts in benign media with microwave activation is the perfect combination for the development of environmentally friendly processes for organic transformations [76].



Scheme 35: Azide alkyne cycloaddition (AAC) reaction using nano-FGT-Cu catalyst

A sustainable formation of chromen pyridines has been accelerated by applying a mixture of aminocoumarin **80**, aromatic aldehydes **2**, chrome pyridine **88** and malononitrile **17** in the presence of TiO₂ NPs congeald, on carbon nanotubes in H₂O under ultrasonic irradiation [77] (Scheme 36).



Scheme 36: Efficient catalytic preparation of chrome pyridine

Conclusion:

The range of unconventional approaches for dealing with different organic reactions is developing at an unpredicted rate. The understanding of solvents and how they affect chemical processes has undergone a revolution. This has mostly been

motivated by the realization that solvent wastes provide a significant obstacle to the synthesis of sustainable compounds. As a result, new solvent classes for processing chemicals have been introduced. Ionic liquids, closely related deep eutectic solvents, supercritical fluids, switchable solvents, and solvents made from biomass have all attracted a lot of attention. Additionally, modern synthetic chemists' main objective is to come up with environmentally friendly ways to do chemical synthesis. To make a synthetic reaction "green," a number of factors must be taken into consideration. The energy source needed to complete a reaction is one of the crucial elements. Utilizing unconventional energy sources, such as microwave, ultrasound, and mechanochemical techniques, is one way to accomplish this. In order to speed up the reaction time and prevent or minimize the production of side products, new chemical processes for the synthesis of pharmaceuticals, fine chemicals, polymers, and other materials have been developed. These processes use alternative energy inputs in combination with non-toxic solvents, which helps to promote sustainable chemistry. By merging two different forms of unconventional energy sources, chemical activation has the potential to develop a new field of study in chemistry and add a fresh perspective to sustainable synthesis. The field of merchant applications is utterly astounding, both in terms of its sheer size and the wide range of applications that have resulted from industry and academic cooperation. Therefore, extrapolating from where we are today, it makes sense to forecast that non-traditional approaches will be used commercially in an uncountable number of disciplines.

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