

REVIEW ON MECHANO-CHEMICAL APPROACHES IN DRUG DESIGN

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ABSTRACT

Mechanochemistry is becoming more widespread as a technique for molecular synthesis with new mechanochemical reactions being discovered at an increasing rate. All the mechanochemical methods are solvent free and can therefore lead to improved sustainability metrics, it is more likely that the significant differences between reaction outcomes, reaction selectivity and reduced reaction times will make it a technique of interest to synthetic chemists. Many mechanochemical reactions of organic compounds take place at low milling energy that is not sufficient to break primary bonds, but the gentle mechanical grinding can influence the relative position of macromolecules, leading to the formation of unique co-crystals and compounds. In inorganic systems, unusual products form due to forced mixing and the high defect density generated by intense milling. This article provides an overview of mechanochemical reaction examples by direct comparison to solvent based reactions, which collectively seemingly show that solid state grinding can lead to reduced reaction times, different reaction outcomes in product selectivity and in some instances different reaction products, including products not accessible in solution.

KEY-WORDS:

Mechanochemistry, Green chemistry synthesis, mechanochemical reactions, milling energy, organic compounds.

INTRODUCTION

Mechanochemistry^[1] is characterized by the application of mechanical energy to achieve chemical transformation e.g. includes either by compression, shear or friction^[2]. Mechanochemistry is the recurrence technique for organic synthesis, in the well known areas of crystal engineering and polymorphism^[3,4]. It is a long-established method for synthesizing solids & molecules. Wilhelm Ostwald, a Russian-German chemist who received a Nobel prize in 1909 for mechanochemical synthesis, termed the mechanochemistry as like a branch of Physical chemistry i.e., thermo chemistry, photochemistry & electrochemistry^[5,6].

DEFINITION: Mechanochemistry provided unique phases and microstructures in inorganic materials. In a more general way, a mechanochemistry is defined as “a branch of chemistry which deals with physico-chemical changes of substances of all states of aggregation due to the influence of mechanical energy”. IUPAC states, a formal definition for mechanochemical reaction, “a chemical reaction that is induced by the direct absorption of mechanical energy” and Shearing, stretching, & grinding are typical methods for the

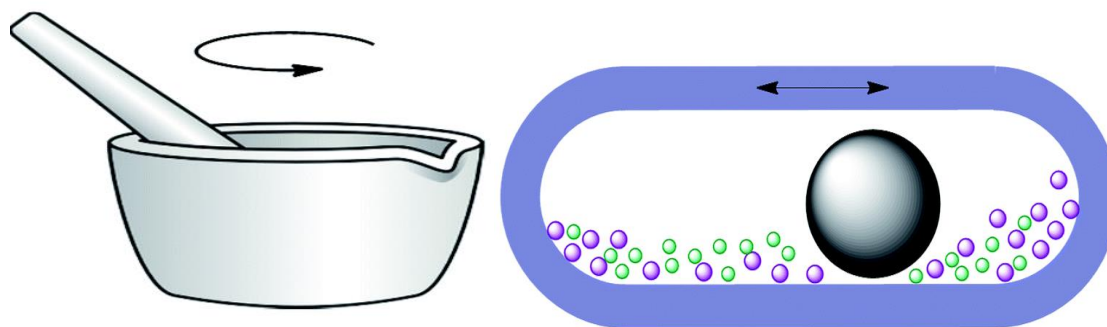
mechano-chemical generation of reactive sites, usually macro radicals, in polymer chains that undergo mechano-chemical reactions^[7]. It is interconnected to tribochemistry, within chemical reaction occur on the boundary/surface between different environment^[8,9]. Several mechanochemical approaches that have been synthesized include catalysts, magnet, nano particles, nickel-vanadium carbide and molybdenum-vanadium carbide nano composite powders^[10]. The examples of both classical and modern mechanochemical routes to compounds comprising S- and p-block elements, these have not yet been comprehensively addressed^[11].

AN OVERVIEW OF MECHANOCHEMICAL SYNTHESIS

The mechanisms of mechanochemical synthesis are often complex and differ from thermal or photochemical mechanism. Factors that permit improved reaction rates include: 1) Reactions performed at very high reagent concentrations, owing to the absence of solvents. These remarkable conditions may lead to alterations in product selectivity. 2) Working under solvent-free conditions, solvation phenomena are not relevant; this may lead to acceleration. 3) It is worth mentioning that volatile organic solvents comprise the main type of residue from synthetic chemistry, both at laboratory & industrial scale.

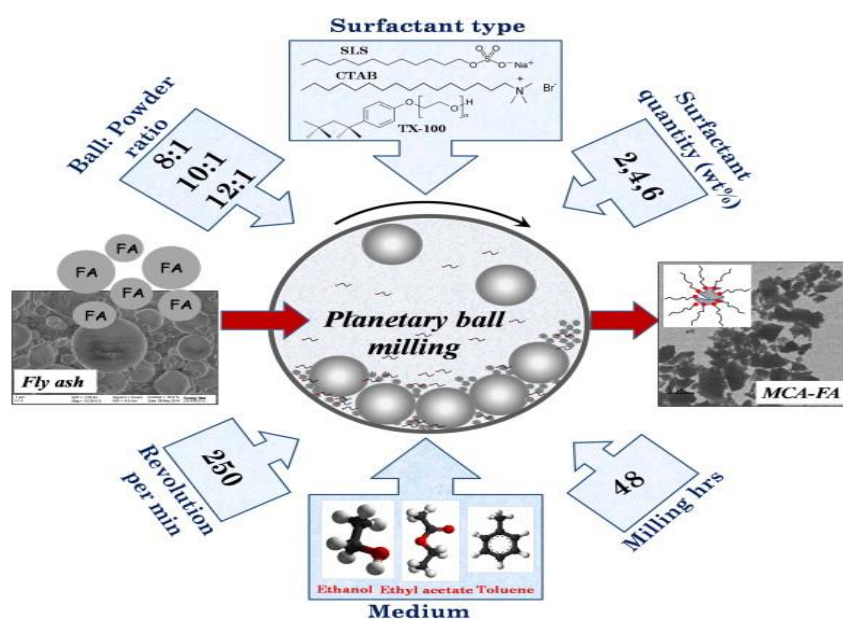
Historically^[12], the first mechanochemical reactions were accomplished by grinding reactants together with a mortar and pestle, this is an approach sometimes referred to as “grindstone activation”. This technique does not need exclusive equipment & consequently is easy to perform in any laboratory. Limitations include: not being practical unless reaction times are short & not being always easy to generate, as it is dependent on the physical strength of the operator. Recently, automated ball mills have been introduced for laboratory-scale synthesis. These instruments permit the control of energy input by adjusting the milling frequency, and therefore have better reproducibility. Moreover, these automated ball mills are safer as the reactions are performed in closed vessels & the operator is not exposed to the products, reactants or catalysts.

There are two main types of instruments that are available, namely planetary ball mills & mixer mills. Specifically, the ball and reactants experience two types of movements in the earlier stage i.e., friction with the inside walls of the jar as a cause of the centrifugal force and impact when they lift off and collide with the opposite wall. Whereas, in mixer mills the jar is placed horizontally and swings back and forth, a movement that causes the balls and reactants to collide with the opposite wall of the jar and generally described as high-speed ball milling (HSBM) or high-speed vibration milling (HSVM). These reactions are influenced by main factors which include the reaction time and milling frequency, the material of milling balls, jars and the number of balls.



(a)Grinding With Mortar And Pestle
("Grindstone" Activation)

(b)High Speed Vibration Milling In a Mixer



(c)Influence Of Planetary Ball Milling Parameter

Figure 1: Instruments that are used to achieve mechanochemical synthesis

MECHANOCHEMISTRY: WHY AND HOW?

The major creativity behind the rediscovery of mechanochemistry is green chemistry^[13], specifically microwave, ultrasound, sunlight and mechanochemical can be used to augment conventional lab techniques by applying these alternative means of activation the need of pharmaceutical and chemical industries is for cleaner, safer, and more efficient transformations^[14,15]. The characteristic of mechanochemistry is achieving chemical transformations by milling or grinding, without the need for bulk dissolution of reactants. Mechanochemical procedures are different from conventional laboratory work, as stirrers and heaters are replaced by automated ball mills and beakers and flasks are replaced by jars (FIG a) containing milling media. In contrast to manual grinding, which is open and susceptible to a range of environmental factors^[16], ball milling offers an enclosed solvent-free reaction environment with well-defined

parameters for optimizing reactivity, such as medium-to-sample weight ratio, frequency, etc. In the former, jars swing back and forth with a frequency that determines the milling intensity. Shaker and planetary mill ones are most popular among different mill designs. Shaker mills are often used for small samples, e.g., in screening of pharmaceutical solids. In a planetary mill, the jar rotates around a central axis, while spinning around its own axis. Milling jars and balls are usually made of stainless steel, zirconium, Teflon, or tungsten carbide. Jars of transparent poly(methyl methacrylate) (PMMA) are also used to facilitate *in situ* monitoring as seen in FIG a^[17]. *In situ* monitoring permits the investigation of fundamental aspects of reactivity that are well understood in solution, but have remained largely unexplored in mechanochemistry, e.g., reaction kinetics or the effect of temperature on reactivity.

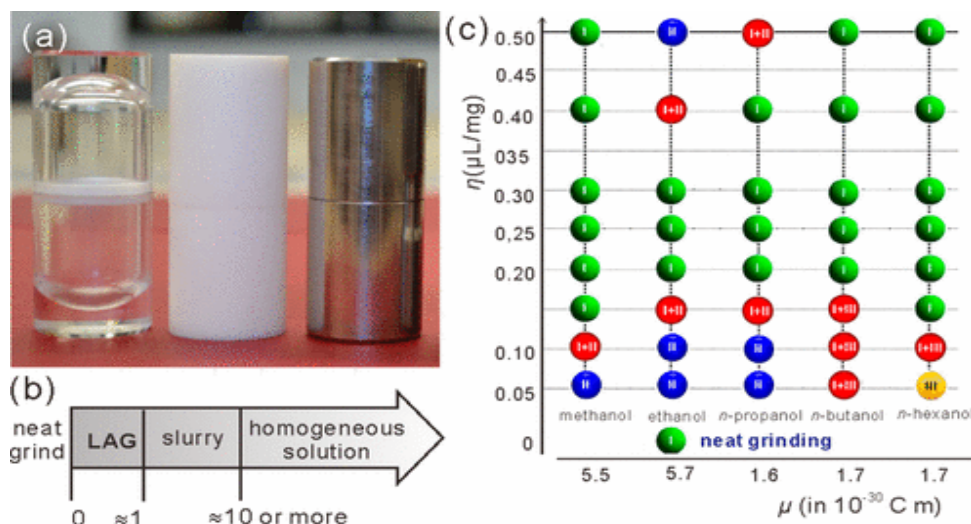


FIG:1(a)Milling jars of PMMA, polytetrafluoroethylene (Teflon), and stainless steel. (b)The weight of reactant-scale (expressed in $\mu\text{L}/\text{mg}$) (c) Effect of η and dipole moment (μ) on appearance of co-crystal polymorphs in LAG.

Crucial to the success of mechanochemistry are new techniques which use catalytic additives to control reactivity. So far unique *in situ* study of a LAG organic reaction revealed that the rate of a nucleophilic substitution may be correlated to the donor number (quantitative measure of Lewis basicity) of the liquid additive-this method was developed by Gutmann, thus this method was named as Gutmann donor number. Of these, liquid-assisted grinding (LAG)^[18] is particularly important for expanding mechanochemistry into a viable alternative to solution synthesis, as illustrated by the demonstrated concept of an elaborate multistep mechanochemical or solvent-free research laboratory routes to pharmaceutically and biologically relevant targets^[19-24]. The experimental definition of LAG is based on how mechanochemical reactivity is affected by the ratio of the liquid additive to the weight of reactants (η , FIG b)^[25]. LAG uses a small amount of a liquid to accelerate reactions, additionally to enable and direct transformations that do not take place by neat grinding.

Highly efficient LAG was shown in screening for salts, solvates, inclusion compounds^[26], co-crystals^[27],

polymorphs^[28] and also in organic mechanochemistry^[29]. Changing the liquid additive in LAG is a simple, powerful route to control mechanochemical reactions^[30], which is especially attractive in screening for solid forms of drugs^[31,32]. Solubility-independent reactivity in LAG has been explained in different ways, e.g., by formation of mobile surface layers, or the amount of liquid is slight continuously saturated with reactants. The origination of the structure-directing effect in LAG is unclear, research signifies liquid polarity, η , and there is a specific interaction between the liquid and the reactants^[33-35]. The three main variables that affect how mechanochemical reactions perform: the kinetic energy of the balls prior to collision (maximum amount of energy that can be transferred to the reagents per collision), how that energy is transferred to the reagents (effects whether or how a reaction occurs) and the frequency of collisions (the easiest variable to control and can be changed simply by adjusting the settings on the mill).

REACTIONS THAT ARE BEST SUITED TO MECHANOCHEMISTRY:

Numerous mechanisms operating mechanochemically remain elusive; it is difficult to decide when to use mechanochemistry. The most obvious advantages are that reactions can be performed under solvent-free conditions. This leads to several cases where it is worth attempting mechanochemical reactions. Firstly, reactions between solids that are not soluble (or not all components are soluble in the same solvent) are well suited to mechanochemistry. Such class of reactions can be very challenging, or even impossible in solution. Reactions in which the solvent can interfere are also interesting candidates for mechanochemical investigations. For example, many catalysts and reagents can be very sensitive towards water, or solvents with Lewis basic sites. Indeed, great lengths are often taken, with expense, to dry solvents. Although the solvent is not required in mill. By using solvent-free conditions eventually, reactions that require hazardous solvents could be made safer, such as mechano chemistry.

Only reactions between solid reagents have been discussed, but reactions between solids and liquids, or even liquids can be performed. These usually require the addition of a solid material referred to as a grinding agent or grinding auxiliary.

ROLE OF MECHANO-CHEMICAL SYNTHESIS IN RELEVANCE TO GREEN CHEMISTRY:

Mechanochemical synthesis is a hypothetical chemical synthesis, in which reaction outcomes are determined by the use of mechanical constraints to direct reactive molecules to specific molecular sites. Mechanochemistry is an upcoming branch of solid chemistry for achieving Green Chemistry goals. Mechanochemical treatment is a typical example of non-conventional solid-state process, used for a synthesis of new materials characterized by new properties; it can change the thermodynamic potentials of reagents and diminish the temperature of the chemical reactions. Milling is very practical, convenient and rational tool for providing chemical reaction especially in solid-state without heating and in large quantities. By keeping potential apart, it is visualize that Mechano-chemical synthesis ignores the undesired reactions of

the molecules. This is the synthesis which automatically obtains the best reaction of the reactant under processing. Ball-milling or hand grinding are the 2 mechanochemical techniques that are considered to be promising candidates in solvent-free synthesis.

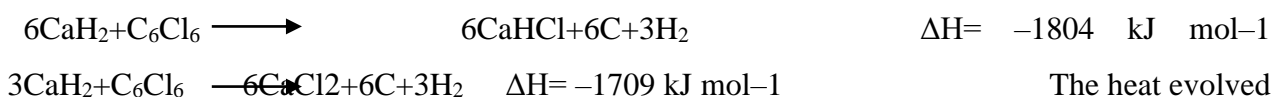
Whereas, the term dealing with the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Thus, a new branch of chemistry termed as Green Chemistry, industry is adopting it because, it gives economic benefits mainly due to decreasing operating costs. It is also known as Sustainable Process, deals with environmentally kindly chemical synthesis with a view to devise pathways for the prevention of pollution and absolutely brought about revolution (e.g., synthesis of drugs etc). According to Paul T Anastas^[36], the following twelve principles of green chemistry have been formulated and few of them are: atom-economical synthesis, minimizing of chemical-waste/energy, avoiding the use of volatile and toxic solvents, reducing the quantity of catalyst and reagents, prevention of waste, using environmentally benign chemicals, prevention of wastes, etc. To address one of the major issues of green chemistry, i.e., minimizing chemical-waste/energy, solvent-free syntheses have become a popular research topic. Microwave, mechanical mixing, visible-light and ultrasound are Non-conventional energy sources for chemical reactions that are becoming surge of interest to the chemist as alternative energy sources in laboratories. By imposing these techniques innumerable chemical transformations have been documented and thereby developed many existing protocols with superior results are further anticipated.

PRACTICAL EXAMPLES OF MECHANOCHEMICAL PROCESS RELATED TO PRINCIPLES OF GREEN CHEMISTRY:

Specific features of the mechanochemical processes clearly differentiate from thermally activated ones. For many solid-phase chemical reactions, the limiting stage is the diffusion in the solid state while mechanical treatment escalates transport of the reagents. Conventional synthesis could mechanochemical processing are differentiated as mechanical milling, mechanical alloying and reactive milling. Mechanical milling refers to the milling of a pure metal or compound, which is in a state of thermodynamic equilibrium at the start of milling. Mechanical alloying is the formation of alloys from elemental precursors during processing in a ball mill. Reactive milling uses mechanical processing to urge on chemical reactions. Mechanochemical technology covers a wide range of important reactions in industrial processes such as faster decomposition and synthesis, escalation of dissolution and leaching processes, preparation of substances and improvement in sintering properties. Green chemistry principles are important because, chemical products should be designed so that at the end of their function they breakdown into non-toxic degradation products and do not persist in the environment. Green Chemistry principles like less hazardous chemical synthesis, Designing safer chemicals, safer solvents and Auxiliaries are Inherent safer chemistry for Accident prevention guide designers to reduce the hazards of chemicals.

EXAMPLES: MECHANOCHEMICAL DEGRADATION OF POLLUTANTS: Mechanochemical degradation of polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins and furans, chlorinated

pesticides is one of the useful mechanochemistry in environment protection, which make a serious problem for environment^[37]. Traditional methods of their degradation based on incineration at high temperature often lead to formation more harmful congeners. Therefore, an effective method of utilisation this kind of substances is searching. Scientist, Rowland's^[38] developed Methods based on mechanochemical activation which led to transformation of the reactants to hydrogen, graphite, calcium halide, and/or calcium hydride–halide mixed salt. Monaghedu^[39] modified this method by providing mechanochemically induced combustion process in which dioxins are mixed with hexachlorobenzene and calcium hydride. The last ones react to each other with evolving high amount of heat according to the equations:



The heat evolved in above reactions burns dioxins. Whole process had realized in one single milling operation (e.g. using Spex Mixer–Mill operated at 875 rpm, in argon atmosphere). The improvement on reactivity of cementations waste materials had realized by mechanochemical treatment^[40]. Such waste defined as a cement kiln dust (CKD) forms during cement manufacturing. CKD is used as a supplementary cementitious material that owing mechanical treatment has increased surface free energy making material more reactive. Other waste, which is very hazardous for environment and difficult to treat due to their variability, is asbestos containing wastes (ACWs)^[41]. These wastes have mechanically treated using a ring mill equipped with a tungsten carbide bowl. The results of this experiment show that milling of asbestos involves complete disappearance of asbestos fibres after several minutes. This method is easy to perform and additionally gas and dust pollution from mechanochemical reactors is low, because whole process is realised in a closed milling vial. In such case, thermal treatment of material could be eliminated.

GREEN SYNTHESIS OF NANOMATERIALS:

NANOMETALS:

In the synthesis of metal nanoparticles i.e., the reduction of the corresponding metal ion salt solutions, there are three areas of opportunity to engage the green chemistry principles: (I) choice of solvent, (ii) the reducing agent employed, and (iii) dispersing agent. In this context, it would of great interest to identify environmentally friendly materials that are multifunctional. The synthesis of noble non-metals are carried out by reacting respective metal salts with vitamin B2 dissolved in solvents of varying densities, such as ethylene glycol, acetic acid, N-methyl pyrrolidinone, water, isopropanol, acetone, and acetonitrile at room temperature. The vitamin B2 used in this study functions both as a reducing as well as a dispersing agent for Au and Pt metals. In addition to its high water solubility, biodegradability, and low toxicity compared to other reducing agents, such as sodium borohydride (NaBH₄) and hydroxylamine hydrochloride,

it appears to be an ideal multifunctional agent for the production of nonmaterials. The reason for using vitamin B2 is that it is the most frequently encountered organic cofactor in nature and it can assume three different redox states: fully oxidized, one-electron reduced, fully reduced, and these redox states exists in a cationic, neutral, and anionic form, depending on the pH of the solution, and can transfer electrons. This approach provides simplistic entry in producing multiple shaped noble nanostructures that could find widespread technological and medicinal applications. Environment compliance costs go down, when less waste is generated.

One can conclude that, Green Chemistry is an environmental, health and safety strategy that emphasizes pollution prevention. The green activity design process includes the selection of safer starting materials, avoiding the use of toxic solvents, using renewable materials, lowering the energy inputs and returning safe substances to the environment^[42].

“MECHANOCHEMICAL” SYNTHESIS COULD BOOST GREENCHEMISTRY:

“In recent years, ball milling begins to be increasingly popular in the production of highly complex chemical structures, steel balls are shaken with the reactants and catalysts in a rapidly vibrating jar. Chemical transformations take place at the sites of ball collision, where impact causes instant "hot spots" of localized heat and pressure. Mechanochemistry remained poorly understood because, it is difficult to model and, without access to real time reaction monitoring. When these reactions was started to study Tomislav Friscic, a professor at McGill university in Montreal says that, the challenge was to observe the entire reaction without disturbing it, in particular the short-lived intermediates that appear and disappear under continuous impact in less than a minute. While mechanical action can break chemical bonds-for e.g., in the wear and tear of textile fibers-the mechanical force can also be used to synthesize new chemical compounds and materials . In the chemical industry, solvents are ubiquitous and are a major environmental and safety concern. Accordingly the large growing interest in avoiding their use relies on mechanochemistry: an energy-efficient alternative that avoids using bulk solvents and uses high-frequency milling to drive reactions. Milling is achieved by the intense impact of steel balls in a rapidly moving jar, which hinders the direct observation of underlying chemistry. Currently, scientists have studied for the first time studied that a milling reaction in real time, using highly penetrating X-rays to observe the surprisingly rapid transformations as the mill mixes, grinds and transforms simple ingredients into a complex product. Scientists choose to study mechanochemical production of the metal-organic framework ZIF-8(sold as Basolite Z1200)from the simplest and non-toxic components.ZIF-8 is such a material that rapidly gain popularity of capturing large amounts of carbon-dioxide, suppose manufactured cheaply could become widely used for carbon capture, catalysis and even hydrogen storage.

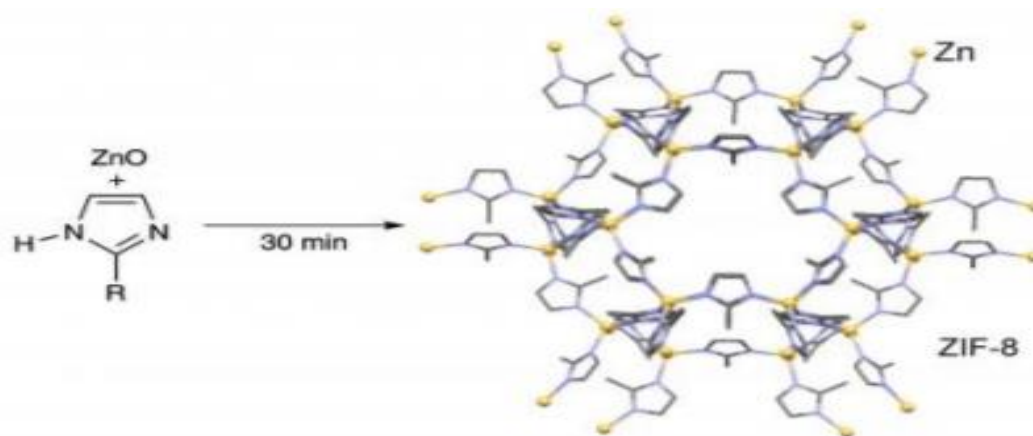


Figure 2 : Role of ZIF-8 in mechanochemical production of various organic compounds

ADVANTAGES OF MCHANOCHEMISTRY:

Mechanochemistry has two noteworthy advantages. The initial one is environmental. Unlike conventional chemistry, mechanochemical reactions do not require the reactants to be dissolved in a solvent. Thus, mechanochemistry offers a green alternative to conventional chemical processes, and in fact, this was one of the main triggers for its improvement. Following, more exciting benefit of mechanochemistry is that, it achieves reactions previously considered impossible, and in this process yields unique molecules and compounds. There are many reports of mechanochemical transformations that either do not occur or occur only with great difficulty in conventional solution-based chemistry. Mechanochemical reactions produce compounds and microstructures that are essentially different from conventional chemical reactions. This has huge implications for pharmaceutical and solar energy industries^[43].

MECHANO-CHEMICAL REACTIONS SIMILAR TO CONVENTIONAL SYNTHESIS:

Conventional synthesis is also known as chemosynthesis. A Conventional method is one that has been used for a long time. Whereas, in a hypothesized process of mechanochemical-synthesis, a chemical reaction is induced by the direct absorption of mechanical energy. Synthesis was carried out using modified reported procedures for conventional synthesis and reactions were modified to improve the yield and purity of products. Mechano-synthesis offers advantages over conventional chemical synthesis usually occurring in solution or in gas phase. The possibility of reducing side reactions leading to higher yields or better conversions. Mechanochemical phenomena have been utilized since time aeons ago, the best and simplest example is making fire, oldest method of making fire is to rub pieces of wood against each other, creating friction and hence heat, allowing the wood to undergo combustion at a high temperature. Secondly, another method involves the use of flint and steel, during which a spark (i.e., a small particle of pyrophoric metal) spontaneously combusts in air, starting fire instantaneously. For comparison, microwave-assisted synthesis was also carried out.

UNIQUENESS ABOUT MECHANOCHEMICAL REACTIONS:

In many practical processes, mechanical action usually ball milling is used to induce reactions in the solid state at ambient temperature. Usually the products are similar to those obtained by conventional methods and mechanochemistry is used only to make the process greener or faster. But mechanochemical reactions can also be unique, and their products can be essentially different from the compounds and phases obtained by conventional chemistry. In most of those cases the reaction begins with the direct mechanical breaking of a primary bond. Mechanochemistry therefore enhance the conventional methods of activation: heat, irradiation and electrochemistry.

EXAMPLES OF MECHANO-CHEMICAL REACTIONS:

Solid-state chemistry is a rapidly developing frontier, and several technological applications are appearing .Wherein, mechanochemical forces are successfully utilized in accomplishing the chemical reactions. Such reactions between two macroscopic solid particles have currently well studied and are believed to proceed via phase transition where eutectic mixture exists. Some oxidative transformations by mechanochemical mixing of substrates with non-metallic hypervalent iodine reagents which enables the syntheses of relatively complex molecules, such as quinoxaline derivatives , b-ketosulfones , and a-tosyloxy b-ketosulfones .

1. OXIDATIVE TRANSFORMATIONS: These are important in organic synthesis and several reagents are available to accomplish the task. The oxidative transformation of arenecarbaldehyde 3-methylquinoxalin2-yl-hydrazones to 1-aryl-4-methyl-1,2,4-triazolo[4,3a]quinoxalines^[44] occurs readily by a simple grinding process using a friendlier non-metallic oxidant, iodobenzene diacetate,. This protocol simply involves grinding of the two solid substrates using a pestle and mortar; a mildly exothermic reaction results in the formation of a yellowish eutectic melt and the reaction is completed in a few minutes.

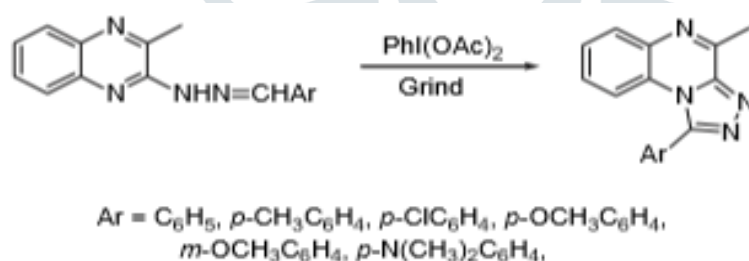


Figure 3: Synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines The work has now been extended to the synthesis of b-ketosulfones in high yields^[45] from ketones employing another hypervalent iodine reagent, hydroxytosyloxy iodobenzene (PhI(OH)OTs), which involves in situ generation of a tosyloxyketones followed by nucleophilic substitution with sodium arene sulfinate in the presence of tetrabutylammonium bromide at room temperature (Scheme-2).

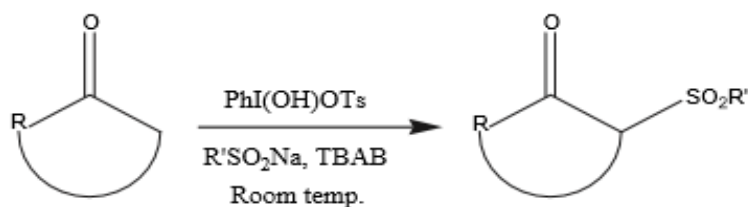


Figure 4: One-pot solvent free synthesis beta-keto sulfones from ketones. Similarly, novel α -tosyloxy β -ketosulfones, valuable precursors for heterocyclic compounds of therapeutic interests, have been prepared under solvent-free conditions by a simple mechanochemical mixing of β -ketosulfones with [hydroxyl (tosyloxy) iodo] benzene^[46]. The research activity in this fruitful area continues, as recently exemplified by a facile and environmentally benign solvent-free protocol described for the preparation of boronic esters from the corresponding boronic acids by simply grinding the two components together^[47].

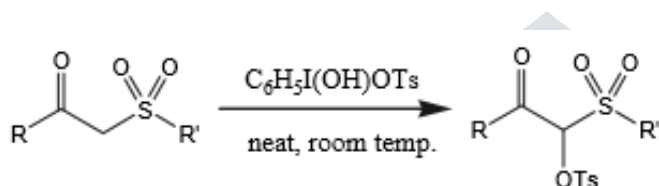


Figure 5: Solvent-free synthesis of alpha-tosyloxy beta-keto sulfones

2. FORMATION OF Cu-NHC COMPLEXES:

REDUCED REACTION TIME: Reduction in reaction times is the only way in which mechanochemistry offers apparent advantages over solution based reactions. There is a temperature difference between the solution based reactions and the mechanochemical processes, it may also be true in such case. There are many reactions where the comparison to running a solvent based reaction to an ‘ambient’ mechanochemical reaction demonstrates significant reductions in reaction time. The synthesis of Cu-NHC complexes (NHC=N-heterocyclic carbene) is an example of an inorganic reaction with increased reactivity. These are widely used as organometallic catalysts for a variety of reactions and various methods have been developed for this synthesis. Under solvent-based conditions, Cu-NHC complexes^[48] can be synthesized by the reaction of metallic Cu(O) with imidazolium salts, although these reactions require a large excess of insoluble Cu(O) and long reaction times^[49]. Recently, scientist named Lamaty and co-workers reported that Cu-NHC complexes(2) could be synthesized from imidazolium salts(1) metallic copper using a planetary ball mill(FIG 6)^[50]. The rate of reaction was enhanced due to the high concentrations of reagents and highly efficient mixing under mechanochemical conditions. Using this novel method, five Cu-NHC complexes with different counter ions(Cl, BF₄, PF₆) were successfully synthesized in improved yields compared to the analogous reactions in solution.

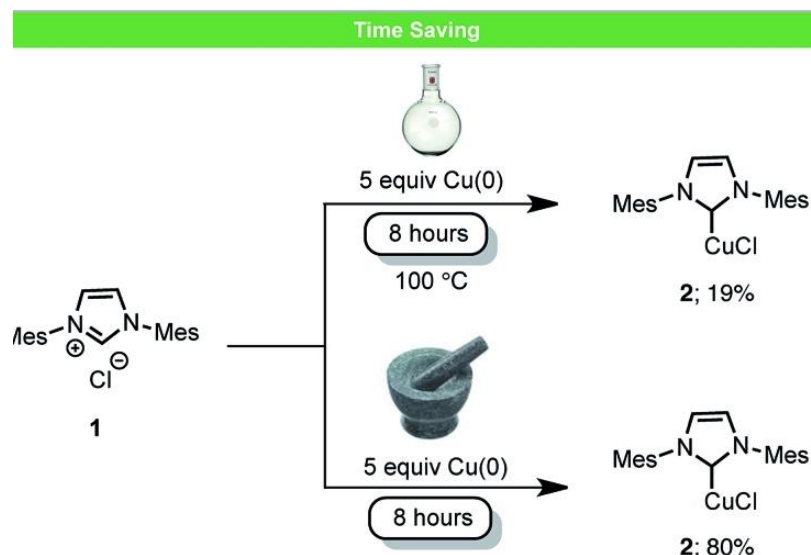


Figure 6: FORMATION OF Cu-NHC COMPLEXES

3. MECHANOCHEMICAL ORGANIC SYNTHESIS OF C-C BOND: A Common belief till last few decades “No Coopora nisi Fluida” means ‘No reaction is possible in the absence of solvent’ stated by Aristotle’s, a famous philosopher However, during the 1980s the pioneering works of Toda and co-workers proved that many organic reactions of solution chemistry would be reproducible in solid state too. In the solid state reactions the ingredients are mixed to finely powdered form for better mixing. The ball-milling chemistry can better be conceived as the updated and sophisticated version of traditional grinding chemistry^[51]. Mechanochemical synthesis of C–C bond More atom economic, energy efficient, time efficient and mild syntheses of C–C bonds are always desired. Many solution-based C–C bond synthesis methods are reproducible under mechanomilling conditions with improved time and energy efficiency^[52]. The solvent-free mechanomilling technique can also be an important alternative to replace traditional hand grinding methods. In this section some of the most important C–C bond forming reactions and their advantages are discussed.

ALDOLREACTION:

Raston and

Scott first reported the aldol condensation reaction using veratraldehyde, 4-phenylcyclohexanone and 1-indanone in the presence of NaOH in a vibrating ball mill and the products were obtained in the yield up to 98% within 10 min^[53].

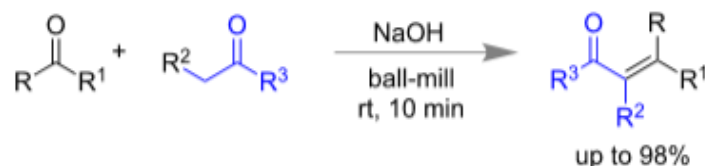
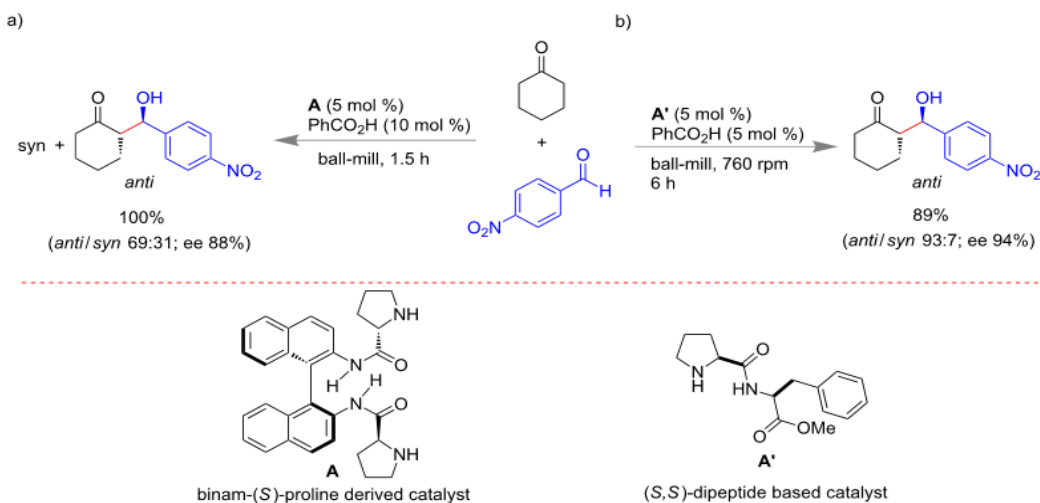


Figure 7: Aldol condensation by mechanochemical synthesis

MECHANOCHEMICAL ALDOL CONDENSATION REACTION

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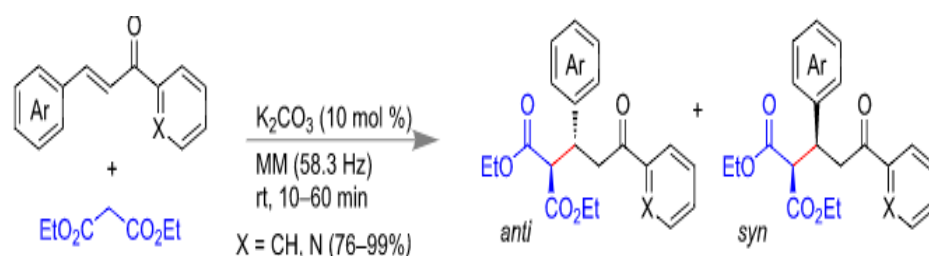
Najera with co-workers reported, the asymmetric version of a mechanochemical aldol condensation (Figure 8). Reactions between various ketones and aldehydes under solvent-free conditions were performed using a combination of (S)-binam-L-Pro (A, 5 mol %) and benzoic acid (10 mol %) as organocatalyst^[54].

**Figure 8:**

Enantioselective organocatalyzed aldol reactions under mechanochemical conditions.

a) Based on binam-(S)-proline derived catalyst. b) Report using α,α -dipeptide-based catalyst. Juaristi and co-workers investigated the mechanistic aspects of α,α -dipeptide derivatives of a (S)-proline- (A)-catalyzed asymmetric aldol reaction (Scheme 6b) under solvent-free mechanochemical conditions^[55]. By varying the electron density on the aromatic aldehydes, it was observed that electron deficient aldehydes provided a better yield with excellent stereo selectivity over electron rich systems. Apparently the solvent-free system enhances the rigidity of the transition state for more selective reactions under mechanochemical activation.

MICHAEL ADDITION REACTION: Wang and co-workers first reported a mechanochemical Michael reaction of 1,3-dicarbonyl compounds with chalcones and azachalcones using the mild base K_2CO_3 (Figure 9). Generally strong bases like NaOH, KOH, NaOEt etc., have been used as catalyst for the Michael addition of 1,3-dicarbonyl compounds to unsaturated ketones. Michael adducts were isolated with good to excellent yield (76–99%) in a high-speed vibration mill (HSVM) within 10–60 min^[56].

**Figure 9:** Michael Addition by mechanochemical synthesis

MECHANOCHEMICAL MICHAEL REACTION: Bolm and co-workers reported, an organocatalytic asymmetric version of Michael addition reaction under planetary-milling conditions. Differently substituted

thiourea-based organ catalysts were screened for the reaction to achieve stereoselective adducts through hydrogen bonding. Only with 2.5 mol % of thiourea-based catalyst B, nitrocyclohexanone and nitroalkene derivatives could undergo a Michael addition to yield up to 95% of the desired product within 30 min (Figure 10).

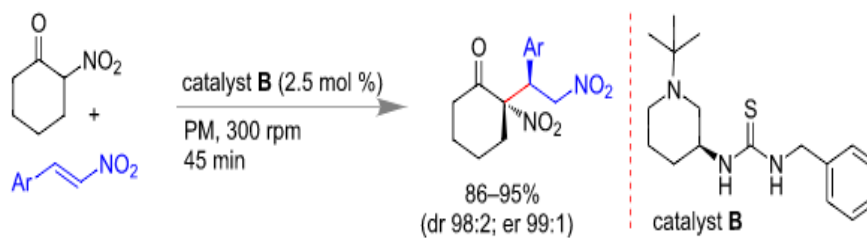


Figure 10: Mechanochemical Organocatalytic Asymmetric Michael Addition

CONCLUSION:

The understanding of the mechanism of mechanochemical reactions is still unclear and requires significant advancement in this research area. Improvement in new synthetic methodologies under mechano milling conditions with better results are always demanding, rather than “greening” the solution phase synthesis. In this context, we hope that this Perspective article, by critically summarizing the progress made so far in the area of mechanochemical multi component chemistry, will stimulate researchers to take this promising pathway towards the design of new synthetic methods and the development of more efficient and sustainable chemical transformations.

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