REVIEW ARTICLE

Solvent-free Mechanochemical synthesis of organic compounds

Vijaya Durga Neelam [1]*, Adhi Kesava Naidu Neelam [2]

[1] *Asst. prof, B. Pharmacy, A.K.R.G College of Pharmacy, Nallajerla, Andhra Pradesh, India*

[2] *Student, B. Pharmacy, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India*

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Abstract: Solvents are extensively used in large quantities for organic processes. Often, volatile organic compounds (VOCs) are used as solvents. The environment is seriously threatened by their toxicity and volatility. Additionally, they are frequently extremely combustible and can have a variety of harmful health impacts, such as allergic skin responses, headaches, and irritated eyes. It is also known or believed that some VOCs cause cancer. Minimizing the use of toxic solvents in research, both in academia and industry, is crucial. Organic synthesis has seen a significant increase in advancements in green procedures without the use of solvents due to their many benefits, which include high efficiency and selectivity, ease of separation and purification, gentle reaction conditions, less waste, and significant advantages for the environment as well as the industrial sector. Mechanochemistry, the use of mechanical energy for reactions, has been a popular solvent-free alternative method for chemical transformations for the past few decades. It is also called grind-stone chemistry because it uses a simple and ancient tool called a mortar and pestle. The synthesis of different heterocycles as well as multicomponent reactions and basic two-component condensation processes may all be accomplished using this method. Improved Claisen-Schmidt condensation can occur by grinding the reactants at ambient temperature without the need for solvents. Compared to traditional reactions, this technique is straightforward, inexpensive, efficient, and ecologically safe with a high yield economy. There may be potential contaminants from milling reactors, amorphization sometimes, and difficulty controlling the synthesis precisely.

Keywords: Mechanical energy; Grind-stone chemistry; Synthesis; Solvent free; Ecologically Safe; Amorphization.

1. Introduction

It is said that "No reaction occurs in the absence of solvent" in the well-known statement by the ancient great philosopher Aristotle, "No Coopora nisi Fluida"[1]. This idea served as the foundation for the development of chemistry up to the last century. Reducing the use of dangerous chemicals and solvents has become essential in the twenty-first century due to rising environmental concerns and global warming. Use safer solvents and auxiliaries is one of the 12 tenets of green chemistry. Solvents should be used as little as feasible, or if this isn't possible, we should attempt some alternatives [2]. These days, organic chemists aim to make use of many green chemistry resources. Mechanochemistry is a green alternative tool that achieves solvent-free conditions. Mechanochemical methods such as hand grinding (by using a pair of mortar and pestle) or ball milling are thought to be good options for solvent-free synthesis. Compression, shear, and friction are examples of mechanical energy-induced chemical changes that are studied using mechanochemical approaches. This review focuses on the solvent free mechanochemical synthesis of organic compounds and its importance in the new chemical entity development.

2. Mechanochemistry

It has been known since the end of the 1800s that certain chemical compounds respond differently when subjected to heat and mechanical force. Mechanochemistry was then established as a distinct field of chemistry because to the work of Carey Lea. Ostwald coined the word "mechanochemistry" in 1891 to refer to the related field of physical chemistry [3]. Mechanochemistry, therefore, ought to be taken into account in conjunction with other related fields such as thermochemistry, electrochemistry, photochemistry, sonochemistry, chemistry at high pressures, shock waves, or microwave effects.

2.1. Origin of Mechanochemistry

In order to take pictures, silver solutions were necessary, and Lea found the chemistry of photography to be rather fascinating. A novel type of silver colloid was created by Lea during his experiments with the metal. When it came into contact with light, it turned

* Corresponding author: Vijaya Durga Neelam

from gold to white [4]. Three samples of what he referred to as "allotropic silver" were carried by him to his vacation home. Three samples were used: one was placed on paper, one on glass plates, and one was loosely packed within glass tubes. When the 600-mile jouncing journey by rail and riverboat began, everything had been perfect. However, the silver that was kept in the tubes had never been exposed to light and had instead become white upon arriving. Lea considered this strange metamorphosis. He reasoned that there had to be some form of mechanical force at work. Otherwise, all of the samples would have been impacted by the bounces and bumps from riding the rails. Instead, he guessed, the chemical shift had been triggered by the friction between the particles rubbing against one another. Three further samples were packed and sent on a 2,400-mile train journey in order to verify his theory. Lea was confirmed to be correct when the cargo was returned; a sample that was carefully packed with cotton wool kept its original gold color, while the two controls that were packed loosely went white [5]. This simple experiment served as the basis for "Mechanochemistry." Chemical reactions may be induced mechanically, by a process known as Mechanochemistry.

2.2 Mechanical energy and reactivity of organic molecules

Organic molecules on subjected to mechanical energy (milling or grinding) two surfaces slip each other resulting in a frictional force. The kinetic energy of the materials touching the slide is converted into their internal energy by frictional forces, which are non-conservative. In certain cases, friction and other mechanical actions can produce thermodynamically metastable states via raising enthalpy. A reaction between the mechanically triggered molecules' kinetics and equilibrium state are both impacted by this increase. This provides the same effect as liquid mixing [6]

3. Mechanochemical Synthesis of Organic Molecules

Mechanochemistry is a synthetic technique that involves manual grinding or ball milling to create both simple and complicated chemical compounds.

3.1. Chalcones

Chalcones are a significant family of naturally occurring substances that possess a range of biological actions such as antimicrobial, antifungal, anticancer, anti-inflammatory, antitubercular, antihyperglycemic and antimalarial properties. The preparation of chalcone derivatives can be done in a number of ways. The most popular technique is the base-catalyzed Claisen–Schmidt reaction, which involves the condensation of an aldehyde with a methyl ketone in presence of sodium hydroxide. Ma et al. proposed a green mechanochemical approach by just grinding solids (or liquid and solids) together [7]. The procedure entails combining equal parts of the relevant methyl ketones and various aldehydes in a porcelain mortar without the use of solvents while solid sodium hydroxide is present. After 3-5 minutes of grinding, a solid mass with a yellow color was obtained, and this turned out to be the desired chalcone. For a further five to ten minutes, grinding went on. The ultimate purification of the crude products was accomplished by crystallization from the suitable solvents, after they had been simply separated by Buchner filtering and washed in cold water [8].

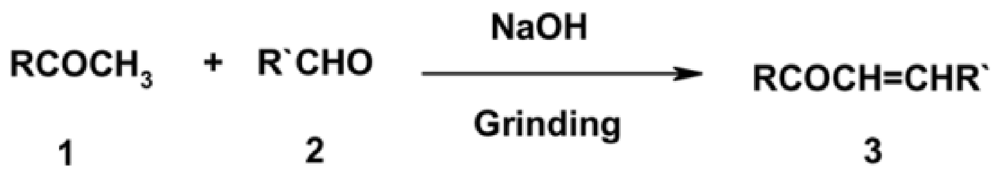


Figure 1 Mechanochemical Synthesis of Chalcones

We can make a number of chalcones using this method since it is efficient, and produces great yields with a short reaction time—all of which align with the green chemistry strategy. Room temperature is used, and no organic solvents are used at all throughout the reaction or the product's separation (except for recrystallization) [9]. The synthesis of chalcones by grinding technique is shown in Table 1.

Table 1 Synthesis of chalcones by Grinding

S No	R	R'	Time (minutes)	Percentage of Yield
1	Acetophenone	Benzaldehyde	10-15 min	80%
2	Acetophenone	4-Chlorobenzaldehyde	5-10 min	91%
3	2-Furyl methyl ketone	Benzaldehyde	15 min	50%
4	2-Furyl methyl ketone	4-Flurobenzaldehyde	3-6 min	80%
5	2-Furyl methyl ketone	4-Chlorobenzaldehyde	3-4 min	88%

Mechanochemical Synthesis of chalcones

3.2. Heterocyclic Compound

A range of heterocyclic compounds can also be prepared by use of mechanochemical techniques. Heterocyclic compounds are important biological agents. Heterocyclic compounds have a wide range of pharmacological and biological properties, including anticancer, antibacterial, pesticidal, insecticidal, and inflammatory effects. Additionally, heterocyclic compounds have antioxidant qualities, (prevent other molecules from oxidizing) anticonvulsant qualities. The grindstone method is an easy way to synthesize numerous heterocyclic systems efficiently and environmentally [10].

3.2.1. Synthesis of Pyrazoline Derivative by Mechanochemical Grinding

Pyrazolines are 5 membered heterocyclic rings consisting of two nitrogen atoms in their structure. Chemists have modified the ring's structure in a number of ways to create a range of compounds with distinct pharmacological properties since pyrazolines are extremely stable. For neurodegenerative illnesses including Alzheimer's disease (AD), Parkinson's disease (PD), and mental disorders, pyrazolines have long been recognized as beneficial treatments [11].

It is thought that α,β-Epoxy ketones provide a special framework for the production of stable hydroxy azoles Grinding α,β-epoxy ketones in a porcelain mortar without the use of a solvent at room temperature with hydrazine hydrate (shown in Table 2) and/or phenyl hydrazine resulted in stable pyrazoline-4-ol derivatives in a shorter reaction time (5-7 min) and higher yields (80-93 %) [12].

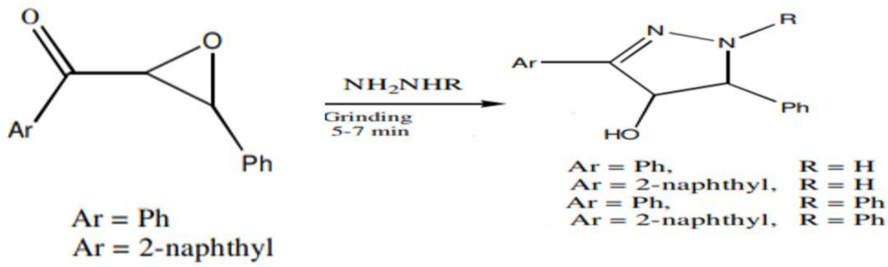
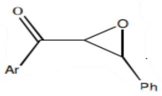


Figure 2 Mechanochemical Synthesis of Pyrazoline Derivatives

Table 2 Synthesis of Pyrazoline Derivatives by grinding

SN.	α, β-epoxy ketone 	phenyl hydrazine NH2NHR	Time (minutes)	Percentage of yield
1	Ar= Ph	R= H	5 min	93%
2	Ar= 2-naphthyl	R= H	7min	90%
3	Ar= Ph	R= Ph	7min	85%
4	Ar= 2-naphthyl	R= Ph	6 min	80%

Mechanochemical synthesis of Pyrazoline Derivatives

3.2.2. Synthesis of 5-acetylThiazoles

Tiazofurin an (anti-tubercular medication) Ritonavir an (antiretroviral medication) and sulfathiazole an (antibiotic) are just a few examples of the very active chemicals that belong to the significant class of heterocyclic compounds known as thiazoles. Among the substituted thiazoles, 5-acetylthiazoles are a fascinating starting point for creating a variety of bioactive substances [13].

The process includes using a ball mill to grind equimolar amounts of aniline derivatives with potassium thiocyanate and 3-chloro-2,4-pentanedione in presence of silica sulfuric acid under ideal circumstances (shown in Figure 3) with a quicker rection time and higher yields (80-93%).

1b-h 2 3 4b-h

Figure 3 Mechanochemical Synthesis of 5-acteylThiazoles

3.3. Mechanochemical Synthesis of Dyes

In many different sectors, such as textiles, cosmetics, paint, printing, medicines, and food organic dyes are extensively utilized. Using common scaffolds such as BODIPYs, PDIs, rhodamines, Coumarins etc. Mechanochemical methods have been widely used recently to achieve the syntheses and modifications of organic dyes and fluorophores in a more environmentally friendly manner [14].

3.3.1. Synthesis of BODIPY Dyes

The fluorescent boron-pyrrole complexes known as BODIPY dyes have a range of uses in imaging, photodynamic treatment, sensing, and other fields. They display high quantum yields and adjustable fluorescence characteristics [15].

A few BODIPY dyes were synthesized in low to moderate yields by Dzyuba and colleagues using a hand-grinding process. BODIPY dyes were obtained at 10−32% yields by condensing a few pyrrole derivatives with aromatic aldehydes in the presence of p-chloranil, triethylamine, and $BF_3 \cdot OEt_2$ for just five minutes in a mortar and pestle. It is also possible to create the BODIPY skeleton by condensing pyrrole with aromatic acid chlorides in comparable circumstances. The solvent-free mechanochemical transformation yielded a yield that was similar to that of solution-phase synthesis, but it required far less time to complete—just a few minutes instead of hours [16].

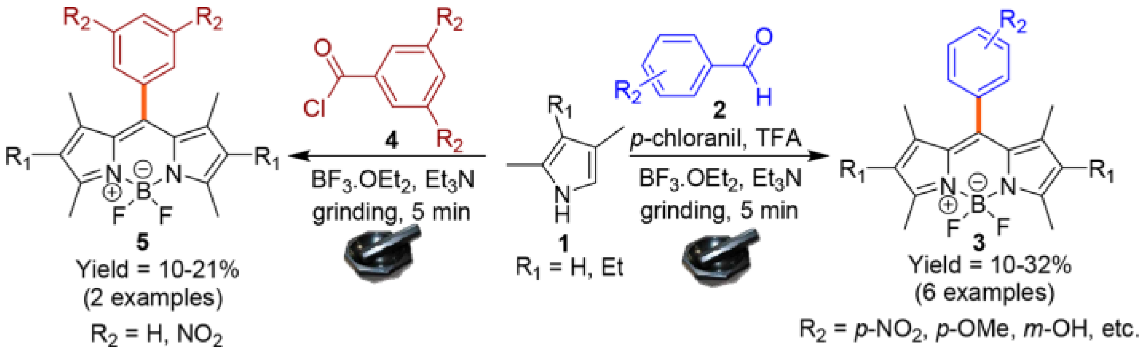


Figure 4 Mechanochemical Synthesis of BODIPY Dyes

3.4. Synthesis of Thiazole based Barbituric Acid Derivatives

A straightforward, catalyst-free mechanochemical process was used by Mahata et al. to synthesize a range of diphenyl-1,3-thiazoles connected to the barbituric acid moiety. High yields of matching trisubstituted thiazole-barbituric acid were obtained in 30 minutes by hand-grinding aryl glyoxal, barbituric acid and aryl thioamides in a mortar with the use of a tiny quantity of water for LAG [17].

Figure 5 Synthesis of Trisubstituted Thiazole-Barbituric Acid Derivatives by Hand Grinding

3.5. Synthesis of Schiff Bases

Schiff bases, often known as SBs, are widely employed in organic synthesis as pigments and dyes, catalysts, polymer stabilizers and luminescence chemo sensors [18].

Using a porcelain mortar and pestle, Garcias-Morales and colleagues reported a mechanochemical synthesis of six distinct Schiff bases with 76–96% yields by grinding salicylaldehyde and various aromatic and heteroaromatic amines for thirty minutes.

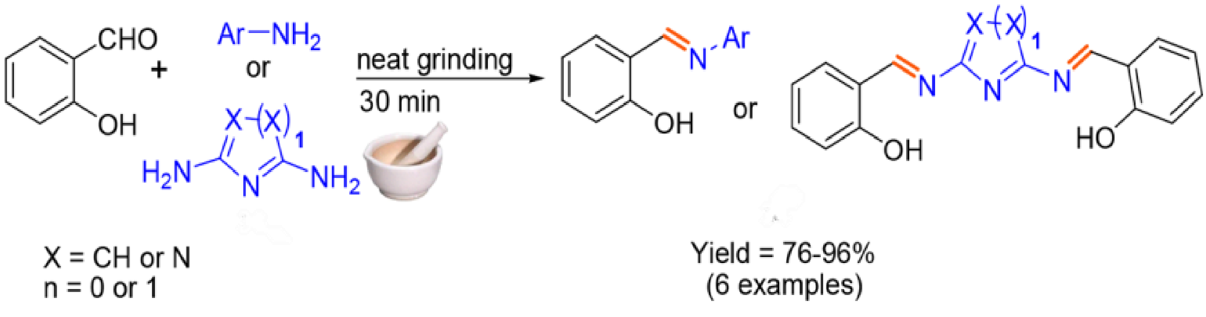


Figure 6 Synthesis of Schiff Bases by Hand Grinding

3.6. Synthesis of Nanoparticles by Hand Grinding

Metallic nanoparticles have attracted attention Because of their special qualities Particularly, there has been a rise in interest in nanoparticles composed of noble metals, such gold or silver, because of their high plasmon resonance. Silver nanoparticles have the ability to self-clean and may be used in cosmetic and cosmetics applications.On the other hand gold nanoparticles have also several potential uses. For example, they may be used in biomedicals for a broad range of cosmetic and beauty applications and can be an excellent drug delivery system in malignant tumors [19].

A basic hand grinding technique was also used to create gold and silver nanoparticles. These methods usually demand for the use of stabilizers to keep the nanoparticles from clumping together. In an agate mortar, 1.0 grams of silver, de-ionized water, 99% ethylene glycol, and manual grinding were used to create silver nanoparticles and 5%wt polyvinyl alcohol for stabilizing. The process of creating gold nanoparticles involved manually grinding 0.1 grams of 3.5 × 3.5 cm (96.5%) gold foil using poly vinyl alcohol with 5% weight as stabilizer. The reduction in size of silver nanoparticles is indicated by a change in color from clear to light yellow or brown, and for gold nanoparticles, from yellow to light blue (particle size can relate on the color of solution according to Mie theory). [42] Also, it was found that the longer the grinding time, the higher the number of nanoparticles can be obtained [20].

3.7. Mechanochemical oxidation and reduction

Mechanochemical methods may also be used to carry out a broad range of oxidation and reduction processes.

3.7.1. Reduction

Good yields of the corresponding alcohols were produced after five days of periodic mixing and grinding with an agate mortar and pestle in a combination of the powdered ketones and a ten-fold molar quantity of $NaBH_4$. The mixture was maintained in a dry box at room temperature.

Figure 7 Reduction of Ketone to Alcohol by Grinding

3.7.2. Oxidation

A combination of powdered ketone and m-chloroperbenzoic acid is ground with an agate mortar and pestle at room temperature to facilitate the oxidation of ketones to esters (Bayer-Villiger reaction) [1].

Figure 8 Oxidation of Ketone to Esters by Grinding

4. Conclusion

For the synthesis of a large range of organic molecules, mechanochemistry is an easy and efficient method to use. Grindstone chemistry exhibits a number of characteristics that make it a viable substitute method for chemical transformations. The main benefits of this procedure are (i) in expensive and environmentally friendly (ii) the moderate reaction conditions, and (iii) the reactions occur in clean or solventless environments(iv) the simplicity with which the product may be isolated in high yield. All of the synthesizes described above were done so utilizing mechanochemical techniques, and the products produced had high yields and comparable activities to those of the compounds synthesized using conventional techniques.

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Author's short biography

Vijaya Durga Neelam

Vijaya Durga Neelam completed her master's in Organic Chemistry and now, she is an Asst. Professor of Organic Chemistry, with a one year of experience. Her research interests broadly include the facts behind the chemical reactions.

Adhi Kesava Naidu Neelam

Adhi Kesava Naidu Neelam has a lifelong fascination with science. Because of his success in scientific studies in high school, he decided to pursue a degree in pharmacy. He went on to obtain his pharmacy bachelor's degree and working towards it. Following graduation, he plans to further his education to enhance both public health and pharmacy. With an eye on becoming a pharmacist, he hopes to use his curiosity and drive for self-improvement to further his career.