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A REVIEW ON MORTAR-PESTLE GRINDING SYNTHESIS AND THERMAL PROFILING OF HYDRAZONE-BASED COMPLEXES AS BIOCIDAL AGENTS

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ABSTRACT

Mortar-pestle is a simple and ancient tool that offers an alternative method for chemical transformations with numerous benefits such as safe and clean reaction profile, time-efficiency, high atoms economy, simplicity of operation, and non-purification of products. The ability to relate thermal parameters of hydrazone-based complexes to their biological activities and to alter the parameters in needed direction leads to the successful biocidal activity. This review covers the benefits and limitations of mortar-pestles synthesis and thermal profiling of hydrazone-based complexes as biocidal agents. An overview of mortar-pestle grinding and the effect of operational parameters on the synthesis of hydrazone-based complexes are included.

Keywords: Biocidal Agents, Hydrazone-based Complexes, Mortar-pestles, Grinding, Thermal profiling

INTRODUCTION

Solvent-free mortar-pestle (grinding) synthetic method is the preparation of chemical products by using environmentally safe procedures that decrease the production of harmful substances, as well as the cost [1-2]. Grinding synthesis has demonstrated efficiency in shortening time and increasing yield [3-4]. This environmentally benign approach is pollution-free, eco-friendly, low-cost, high-yield, and simple [5-6]. Avoiding solvent-based in the development of potent chemicals possessing biocidal activities is emerging as an active area of scientific research in Coordination chemistry.

Hydrazones and their complexes are compounds in curative chemistry owing to their broad spectrum of biological activities [7-9] and these properties have inspired interest in developing methodologies for their synthesis. However, there is still a problem in finding a simple and

efficient approach for their selective preparation [10]. Hydrazones are typically formed by condensing hydrazides with different carbonyl compounds (aldehydes or ketones) in various organic solvents [10, 11]. Another condensation synthesis of hydrazones [12] and their complexes has been reported [10, 13-14]. However, Pisk *et al* reported an ineffectiveness of synthesizing hydrazones by condensing pyridine-2-carbaldehyde with 2-aminobenzoylhydrazide [10]. On account of the futility of conventional synthesis of hydrazones reported by Gudasi *et al*. [15], researches have been carried out more recently on the improvement and development of environmentally friendly synthetic methods [16-18]. Several innovative approaches have been reported to include more friendly solvents like water [16]. Recently, solvent-free techniques such as microwave irradiation, solid-state synthesis (grinding), and water suspension medium techniques have been reported with improvement in the synthetic process [19-20].

Though mortar-pestle is a component of "Green Chemistry" and thermal profiling which could be used for selecting hydrazone-based complexes as biocidal agents, not much importance has been given to them in recently published articles. In this review article, attempt is made to highlight the literature available on the benefits and limitations of mortar-pestle synthesis, effects of operational parameters on the synthesis of hydrazone-based complexes and their thermal profiling as biocidal agents.

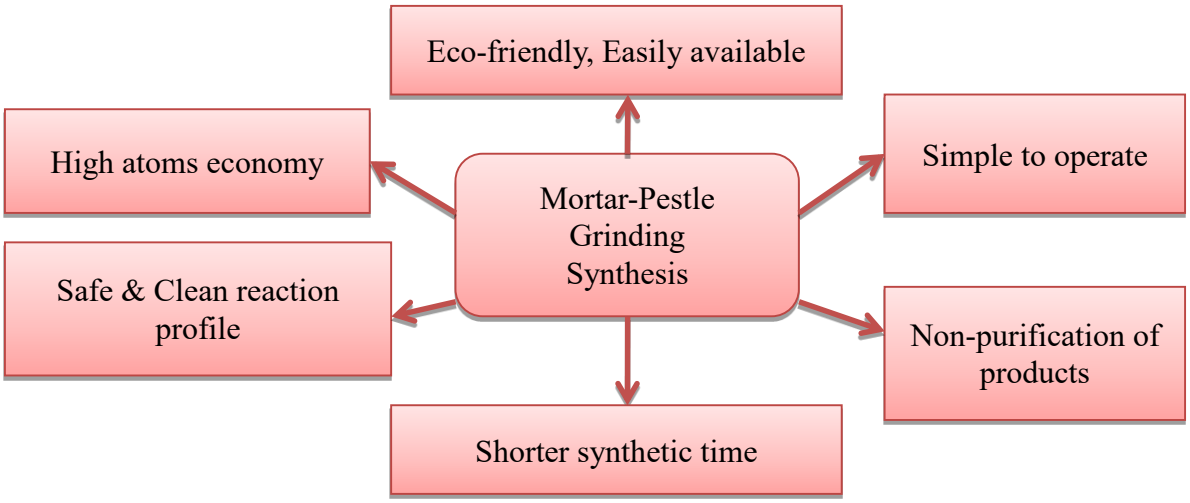


Figure 1: Advantages of Mortar-Pestle Synthesis [16 -18]

Mortar-Pestle Grinding Synthesis: An Overview

Grinding using mortar and pestle is a common process to achieve mechanochemical transformations [21]. It is the tool for particle size reduction and has been changed into a toolkit

for the synthesis and screening of different hydrazones and their complexes. It complements traditional strategies on solvent-based synthesis [10, 22]. The attractiveness of grinding-based synthesis lies in its success in forming metal-ligand coordination bonds, thus providing the means not only to activate otherwise inactive reactants but also incorporate them into final products [23]. Systematic studies of metal complexes structure-templating effects in a grinding synthesis lead to its application in the development of pharmaceutically important hydrazones and their complexes [4, 24].

Types of mortar-pestles used in grinding synthesis

As the grinding tool, a mortar pestle is obtainable in variable sizes and types. One of the applications of mortar and pestle is to transform ingredients into fine powder and paste. This use of mortar and pestle is only possible due to the dimensions, material quality, and texture of the mortar and pestle. The classes are:

i. **Granite mortars-pestles**, which are tools made from granite rock (quartz, feldspar, and mica**)**, ideal for grinding synthetic materials owing to their strength and coarse texture [25]. While they excel in grinding complex samples, their weight makes them challenging to handle and to clean. Granite mortar pestles are outstanding for bruises and keep the flavour of the ingredients. It is possible to grind synthetic materials into excellent powder via rough granite mortar-pestle sets, but they are fragile and discolour readily.
ii. **Agate mortar-pestle** is a typical stone, mainly, chalcozanide (a cryptocrystalline form of silica composed of very fine intergrowths of quartz and moganite) [26]. It is used for grinding different synthetic starting materials homogeneously to obtain products with desirable composition and structure [27]. The benefit of Agate mortar-pestle over other types is that it maintains the purity and texture of the sample.
iii. **Porcelain mortar-pestles** are generally made from porcelain (kaolinite as raw material. Others include feldspar, glass, ball clay, steatite, bone ash, quartz, alabaster and petuntse). They are robust and versatile, suitable for grinding different synthetic materials [28]. They are easy to clean and do not retain odours or colours from past samples. Though they can be brittle, using too much force may cause them to break off. These durable and reliable laboratory instruments are used for particle reduction and powder blending. The glazed exterior, deep bowl and defined

lip of mortars permit controlled pouring. To prepare porcelain mortars for usage, some sand is occasionally ground into a rougher surface that aids in particle reduction [29].

Mortar-pestle synthesis of hydrazone-based complexes: Benefits, opportunities, and limitations

Synthesis of hydrazone-based complexes by mortar-pestle grinding avoids limitations of solution-based chemistry, such as solvolysis and solvent complexation. Mortar-pestle grinding is a labour-intensive process, which often raises some concerns, like, does the reaction kinetics depend on the physical power or the grinding speed? how long the mortar-pestlegrinding can be sustained or what the scalability is? For manual grinding, gentle and steady grinding is generally adequate for a reaction to proceed in the forward direction and hardly affect the kinetics. However, exceptions are also seen [30]. Observations were raised by Castro *et al*. [31] on whether the rate of reaction depends on the force applied for grinding the reaction mixture; also, will fast and steady grinding yield product in a significantly reduced time compared to gentle grinding? These problems can be primarily addressed by automation in the grinding process [30].

Benefits of mortar-pestle grinding as a solvent-free synthesis

The method is sustainable. Grinding affords all-around chemical processes that does not require the use of reaction solvents, thereby, drastically reducing the generation of waste and pollution while simultaneously cutting down economic costs [32-33]. Grinding processes often give rise to larger yields than similar reactions in solution and typically involve significantly reduced reaction times [33], excellent stoichiometry control, and improved product selectivity [34]. Additionally, sometimes they lead to products not obtainable from solutions or other synthetic methods [35] in terms of structures, stereochemistry, stoichiometry, or mixture compositions [36]. These observations point to the chemical mechanisms involved in grinding, which sometimes appear to be considerably different from those reactions in solution [37]. Also, grinding synthesis maximizes incorporating all the starting materials used in the process into the final product [38]. Its reactivity depends on the mechanical-induced breaking of molecular bonds and reduction of particle size through friction in the process leading to more efficient mixing and close contact [39-40]. Thus, new paths are enabled to fine-tune mechanochemical reactions and obtain new products.

Opportunities

Presently, there is an increasing understanding that grinding synthesis is not just a synthetic method of making chemistry ‘‘greener’’ but can also be a tool for discovery, enabling access to products that are not obtainable in solution [41]. For example, solution-based synthesis generally relies on using liquid organic solvents to dissolve the reactants. Therefore, reactions of insoluble substrates are challenging and often ineffective [42]. The development of grinding synthetic overcomes this long-standing solubility concern and would afford opportunities to new areas of making chemicals [43].

Limitations

Currently, grinding synthesis is only in its early stages. Consequently, physicochemical knowledge of grinding processes and how this relates to thermodynamics and kinetics knowledge is yet to be fully demonstrated. Most variables used to study and control chemical reactions in thermodynamics and kinetics studies, such as temperature and pH, are not yet routinely measured or controlled in the grinding synthetic method [44]. Remarkably, the energy of mechanochemical reactions, how much energy is transferred or available to the reactants due to the combined effects of the temperature and the mechanical treatment applied, how it flows through the chemical system to form products, and why particular products are obtained (chemical selectivity), the chemical mechanisms (what atoms or molecules are doing at the atomic/molecular level during a reaction, how the elementary response steps combine in complex chemical mechanisms leading to the observed products); and overall how mass transfer occurs, since most often mechanochemical processes are heterogeneous phase reactions-all remain poorly understood, and only recently have inspired an increasing interest from researchers [45-46].

Other limitations of the grinding synthetic method are the possibility of non-homogeneity [39], formation of structural amorphous products and the formation of unwanted products as a result of the competing reactions [47], reaction with mortar/pestle, difficulties in separating the phases after synthesis, and volatility of one or more of the components [48].

Effect of operational parameters on the synthesis of hydrazones-based complexes

The synthesis of hydrazone-based complexes depends on some operational parameters. Irrespective of the methods used to synthesize hydrazone-based complexes, certain factors such as pH, reaction duration, temperature, and solvent nature influence the yield, size, and shape of

crystals obtained. These parameters could be varied to control the work, general morphology, efficiency, and applicability. A review of the influence of these parameters is examined in this section.

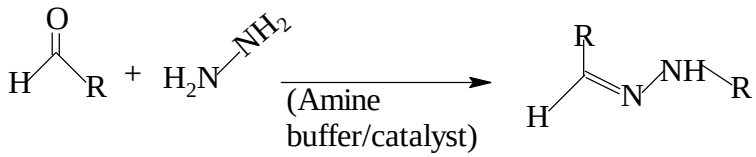
pH

Hydrazone formation is convenient and is widely applied in multiple fields of research [49]. However, pH is one of the parameters that plays a significant role in hydrazone synthesis through carbonyl reaction with hydrazine and hydrazone-based complexes [50-51]. These reactions happen quickly under slightly acidic pH < 7, proceeding under common acid catalysis, and the reaction rate increases as pH decreases. Conversely, at pH < 3 and neutral pH, the reaction rate slows down, limiting the utility of these reactions [52-53]. Furthermore, reactions occurring at a pH < 3 slow significantly requiring a catalyst to drive the response rapidly to completion at a neutral or higher pH. This necessitates using an efficient catalyst for solvent-based hydrazone synthesis to achieve high yield and produce stable products [54-55].

Hydrazones, once formed, is very stable hydrolytically. Adjusting the pH to acidic conditions with water in excess, hydrazones will rapidly hydrolyze and result in bond splitting of the functional group. The hydrolytic stability of hydrazones is due partly to the α-effect of the heteroatom (N or O) adjacent to the sp^2 nitrogen and partly due to inductive effects that reduce the basicity of the sp^2 nitrogen [51, 54].The mechanism of hydrolytic stability of hydrazones is used for pH-controlled drug delivery systems. Addition of water to hydrazones reaction occurs in the exact opposite manner beginning with protonation of the imide nitrogen and then nucleophilic substitution by water.

To address the pH drawback, researchers have developed ways to speed up hydrazones formation reaction. Kool *et al*. [55] reported on fast alpha nucleophiles: structures that undergo rapid hydrazone/oxime formation at neutral pH. Kinetics studies were carried out for a range of structurally diverse hydrazines, and a large variation in reaction rate was observed. The carbonyl compounds with acid/base groups near the reactive center formed products rapidly, even without added catalyst. Another research was carried out by Larsen *et al*. [49] on exceptional rapid oxime and hydrazones formation promoted by catalytic amine buffers with low toxicity accelerated the construction of hydrazones bond formation between hydrazines and carbonyl compounds. This was achieved by using bifunctional buffer compounds that not only control pH but also catalyze

the reaction at pH 5-9. The result showed that the reaction rates were higher below neutral pH, with a maximum near pH 5.5 in most cases, yielding second-order rate constants of $> 10\ M^{-1}s^{-1}$. The new buffer amines have low toxicity to human cells, and can be used to promote reactions in cellular applications.



(1)

However, for complexes, an investigation carried out by Majdecki *et al*. [56] on mono-substituted hydrazone β-cyclodextrin derivative for pH-sensitive complex formation with aromatic drugs was found to depend on the pH of the solution. The stability constants at pH 7.4 were higher than those at pH 5.5, indicating the pH sensitivity of hydrazone-based complex formation. This could be attributed to the ionization of the functional groups at higher pH and the slow rate of reduction observed in the acidic medium to the electrostatic repulsion of anions present in the reaction mixture.

Effect of contact time and temperature

An important factor influencing the synthesis of hydrazones alongside their complexes is the contact time, also known as reaction time. This was verified by varying the time taken for the formation of synthesized hydrazones alongside their complexes. Generally, the change in colour to yellow or brown is evidence of the shape of the hydrazones alongside their complexes. The transformation reactions of the various substituted organic hydrazines and phenol aldehydes could reach transformations ≥ 99 % by changing the grinding time from 1, 2, and 4 h as demonstrated by Oliveira *et al*. [57]. The study was monitored with the use of the Raman spectra with the peak intensity as function of the contact time and the intensity decreases with an increase in time [58]. Contact time is one of the parameters that control the crystal size of hydrazones alongside their complexes formed because of the blue shift of the adsorption peaks. Pisk *et al*. [59] showed *Ex-situ* X-ray diffraction intensity analysis of the 1:1 reaction between salicylaldehyde and isonicotinic hydrazine broadened from 10 min to 50 min because of the increase in conversion of reactants to hydrazones. Increasing the contact time enhances yield because many reactants have been converted to hydrazones [60].

Temperature is another factor that should be considered in synthesizing hydrazones alongside their complexes because it controls the reaction kinetics of the synthetic process. An increase in temperature is known to increase the reaction rate because there will be an increase in the collision and the frequency factor of the reacting species. Studies showed that an increase in temperature leads to a significant reduction in the impurities, enlarges the crystal unit cells, and reduces particles [61-62].

The effect of solvent

Solvent stabilizes the complexation process [63-64]. Solvent effects on complex formation vary and can be complicated. Their study may offer insight into the nature of the intermolecular interactions responsible for the construction of the complex. A quantitative theory of solvent effects on complex formation has been developed [65]. The solvation contribution to the total free energy of complex shapes can be either stabilizing or destabilizing [66-67].

Thermal Profiling of Hydrazone-based Complexes as Biocidal Agents

Thermal (kinetic and thermodynamic) profiling of bioactive compounds has the binding activity to the biological target known as hit and a compound with a pharmacological activity that still needs to be optimized for therapeutic effect and safety profile (hit and lead compound [68]. Kinetic analysis revealed that compound cellular activity showed a relationship with both association (k_1) and dissociation (k_2) whereas the thermodynamic signatures of the studied bioactive compounds were established to be mainly enthalpy driven with improved enthalpic contributions. According to Tonge [69], determination of binding interactions plays a vital role in drug break through, where structure-activity relationships guide the selection and optimization of drug leads. Hence, understanding the molecular interactions between bioactive compounds and their target is essential to the drug discovery process [70]. It is not sufficient to evaluate and optimize through 50 % inhibitory concentration (IC_{50}) values, as these values may change according to the assay conditions [71-73]. Instead, a characterization of the binding affinity, the binding and dissociation rates must be related to the molecular mechanism to improve efficacy and selectivity [74]. Conventional biocidal compound finding pattern has focused principally on optimizing biocidal compound-target binding affinities and *in-vivo* pharmacokinetics while developing lead compounds against a validated biocidal compound-target [75-77]. Nevertheless, in the last decade,

it has been proposed that kinetic and thermodynamic profiling of compounds may be better predictors of compound selectivity and *in vivo* efficacy [78-79].

The connection between thermal parameters of hydrazones-based complexes and biocidal activity can be represented by Equation 2 [80, 81] and 3 [82, 83]. Consequently, they are interconnected by structural features of the hydrazone-based complexes, target, and the hydrazone-based complex-protein in different ways [84, 85]. It is believed that, in general, slow k_2 offers benefits on compound efficacy and safety profile while k_1 is controlled by the diffusion limit [86]. This came from retrospective analyses indicating that any best-in-class bioactive compound possessed the lowest k_2 in their class [78].

$$Re + L \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ReL \quad K_D = k_2/k_1 \qquad [80, 81] \qquad (2)$$

$$\Delta G = \Delta H - T\Delta S = RT\ln K_D \qquad [82, 83] \qquad (3)$$

Where K_D is dissociation equilibrium constant of the kinetic interaction between receptor (R) and hydrazone-base complexes (L) to form the complex ReL. ΔG represents Gibbs energy of binding, ΔH represents the heat related to the making and breaking noncovalent bonds in going from the free to the bound state and ΔS reports on the overall change in the degree of freedom of a system. Migliore *et al*. (87) reported on the complex species and thermal parameters for the binding reactions of hydrazones derived from pyridoxal-5′-phosphate (PLP) with bovine and human serum albumin (BSA and HSA) in neutral aqueous solution. The result showed that the PLP-hydrazone derivatives were able to successfully interact with both BSA and HSA and facilitated the determination of the driving forces for the molecular recognition process. The formation of the 1:1 complex was found to be always enthalpy favoured and driven due to the insertion of the hydrazone moieties into the hydrophobic pockets of BSA or HSA. Thus, thermal profile contributions to binding provide a suitable parameter for hydrazone-based complexes selection as biocidal agent as it maximizes the influence of forces other than hydrophobicity [74, 88-89].

CONCLUSION

Mortar-pestle synthesis is observed from this review to have numerous benefits of becoming a regular tool in the synthesis of hydrazone-based complexes. Alongside its role in promoting

sustainable chemistry, mortar-pestle synthesis features simple instrumentation and easy availability. This will stimulate researchers to take it as a promising pathway towards the design of new synthetic methods and the development of more efficient and sustainable chemical transformations. Some parameters were noted to influence the synthesis of hydrazone-based complexes. Thermal profile parameters were also seen to contribute to the selection of hydrazone-based complexes as biocidal agents.

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