Tetrahedron 112 (2022) 132753

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report 1261

Grindstone chemistry: A “green” approach for the synthesis and derivatization of heterocycles

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ARTICLE INFO

Article history:
Received 7 December 2021
Received in revised form
17 March 2022
Accepted 23 March 2022
Available online 2 April 2022

Keywords:
Grindstone
Mechanochemistry
Liquid assisted grinding
Neat grinding
Mortar-pestle
Heterocycles

ABSTRACT

The famous quote by ancient great philosopher Aristotle, “No Coopora nisi Fluida” means “No reaction occurs in the absence of solvent.” Chemistry till the last century was developed based on this philosophy. In the current century, with the growing environmental concerns and global warming, it has become imperative to minimize the usage of hazardous chemicals and solvents. Over a few decades, the application of mechanical energy for reactions, called “mechanochemistry,” has emerged as a solvent-less and alternative technique for chemical transformations. The simple and ancient tool for “mechanochemistry,” a pair of mortar and pestle, also called “grindstone chemistry,” is revitalized in recent years for a myriad of reactions from simple two-component condensation reactions to multicomponent reactions even to the synthesis of materials. Many of these reactions by grinding in a mortar-pestle led to the construction of various heterocycles. The method has benevolent characteristics such as clean and safe reaction profile, high atom economy, time-efficiency and over a period of time, it proved as a viable alternative to traditional solution-phase reactions. While the main focus of this review article is to cover the literature available on the use of mortar-pestle for the construction and derivatization of heterocycles, a brief overview of “grindstone chemistry” is included to give readers an out-and-out idea on its potential as a sustainable technology for the future.

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https://doi.org/10.1016/j.tet.2022.132753
0040-4020/

1. Introduction

"Sustainability" is no longer a fancy term but a deliberation for chemical transformations in the current scenario. Sustainable chemistry must meet the present needs without compromising future generations and the ecosystem [1]. A chemical transformation under solvent-less or neat conditions minimizes toxicity, reduces pollution and energy demands, and lowers the overall cost of the process [2–4]. This has inspired a large group of researchers to adopt green and contemporary technologies such as sonochemical synthesis [5–7], microwave irradiation [8,9], flow-chemistry [10], mechanochemistry [11,12] as potential alternatives to conventional "organic media" based chemical transformations [13,14]. Notably, mechanochemistry, in which the activation energy of a chemical reaction is provided by sheer frictional force, has been recognized by IUPAC as one of the ten leading world-changing technologies [15]. Although known for years, mechanochemical reactions were mostly ignored by chemists of the 20th century, but it has brought in a revolutionary change in the 21st century towards achieving sustainability [16]. In a typical mechanochemical process, the reactions are induced by the input of mechanical energy, most commonly by grinding in a mortar-pestle or by milling in a planetary ball-mill/mixer-mill/shaker-mill. Although mechanical milling with higher energy input is a superior and versatile technique for organic transformations [17–21], the grinding in a mortar-pestle with features like simple instrumentation and easy operation is an equally useful method in the paradigm of synthetic organic chemistry [17,22,23]. The use of a mortar-pestle for organic transformation, more popularly known as grindstone chemistry, was introduced by Toda et al. in the last century [24,25]. The technique offers solvent-free or solvent-less reactions, often works in the absence of a catalyst, avoids an extensive work-up step in addition to faster reaction kinetics and better regio- or stereo-selectivity [26]. Gradually, it became an effective tool for a variety of organic reactions including Michael addition [27] aldol condensation [28], Claisen-Schmidt condensation [29], Wittig reaction [30], Horner-Wadsworth-Emmons reaction [31], organocatalysis [32], peptide synthesis [33] etc. More importantly, this method is found to be equally effective for the construction of heterocyclic compounds of biological interest in the last few years [34–37]. The early developments of grindstone chemistry have been pioneered and reviewed by Tanaka and Toda [22]. Later, this segment of mechanochemistry was only partly covered by Wang in 2013 [17], Menendez in 2018 [23], Friščić in 2020 [21], Su in 2020 [38].

Heterocycles are the most privileged class of compounds for their wide spectrum bioactivities [39–41]. Heterocycles feature in a large number of pharmaceutical products (APIs) and are often the targets for new drug design and discovery [42–44]. The synthesis of heterocycles is one of the most commonly explored chemical transformations [45]. Simple heterocycles can be classified in terms of ring size and the number of hetero-atoms in them. Especially, nitrogen-containing heterocycles are vastly abundant among natural products. The porphyrin rings constitute chlorophyll, heme, and vitamin B12; drugs of natural origin like reserpine, morphine, penicillin are *N*-containing. The heterocycles present in RNA and DNA play important roles in the biochemical processes of living organisms [41]. These electron-rich compounds with high

coordinating abilities also feature in broad areas of applications in various agrochemicals [46], fragrance industry [47], polymers [48,49], dyes [50], material synthesis [51–53], and several other spheres [41]. An enormous number of methodologies have been developed targeting common heterocycles like five-members pyrroles, indoles, pyrazoles, oxazole, benzimidazole, or six-membered pyridines, pyrans, quinolones, quinazolines, quinoxalines, coumarins, etc. [54–58]. Again, complex heterocycles including fused heterocycles (e.g. imidazopyridine) or spirocycles (e.g. indolopyrroles), are of medicinal interest or marketed drugs and thus, are common synthetic targets [59–64]. Grindstone chemistry has been widely employed in the synthesis of several of these heterocycles and often in solvent-free and catalyst-free approaches in much economical and eco-friendly ways than conventional methods. Although grindstone chemistry is a part of "mechanochemistry" and is growing at an appreciable pace, not much emphasis has been given in any of the recently published excellent review articles. In this review article, we attempt to comprehensively cover the literature available on the construction and derivatization of heterocycles using a simple "mortar-pestle." Meanwhile, we felt it would be legitimate to provide a brief update on the entire spectrum of "grindstone chemistry" to give readers a wholesome idea of the potential of this "green" technology as a viable alternative to conventional methods to achieve "sustainability" in the future.

1.1. Simple instrumentation

The grindstone chemistry developed using "mortar-pestle" as the grinding tool, which are usually made of Agate, granite or porcelain and are available in variable sizes. Agate is the commonly used material because of its hardness and low porosity (Fig. 1). However, manual grinding, carried out by a person, is a labor-intensive process, which often raises some concerns like, does the reaction kinetics depend on the physical power or the grinding speed? Other pertinent questions are how long the hand-grinding can be continued or what is the scalability? For manual grinding, steady and gentle grinding is usually enough for a reaction to proceed in the forward direction and hardly affects the reaction kinetics, however, exceptions are also seen. Bhutia et al. observed that the rate of reaction is dependent on the force applied for grinding the reaction mixture, wherein, fast and steady grinding yields product in a substantially reduced time compared to gentle grinding [65]. These problems can be largely addressed by automation in the grinding process. The electrical grinders are available (e.g. Retsch mortar-grinder, RM200), wherein, reactants in a mortar are ground by an electrically operated pestle. Again, mortar/pestle is made of various hard materials like porcelain, Agate, zirconia, stainless steel, etc. A monitor can measure the grinding speed and a timer can be set for a reaction. A large automated grindstone apparatus can be envisaged for industrial-scale synthesis.

1.2. Features of grindstone chemistry

Apart from the fact that grindstone chemistry is sustainable as most of the reactions are carried out under neat or solvent*less* conditions, it displays numerous features that establish it as a promising alternative technique for chemical transformations. Often frictional force provided by "grinding" is good enough to complete the reactions in a time- and energy-efficient manner. The reactions are set in "open-air" making aerial oxidation a common feature of several transformations [34,66]. However, exposure to moisture may be detrimental to moisture-sensitive reactions. Additionally, the use of volatile reactants is avoided unless the reaction is very fast. The "open-system" also offers easy and effortless ways for monitoring the progress of a reaction. For instance, the synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles in a mortar-pestle by Bhutia et al. was monitored by recording IR spectra at regular intervals to check the conversion of the intermediate nitrones and the cyclized products [65].

Interestingly, grindstone chemistry is often assisted by additives and in many cases, it results in faster reaction kinetics and better yields. For example, Banerjee and coworkers reported **sluggish** reaction for benzimidazole formation as unreacted starting materials were trapped inside the solid mass of intermediate imine and product under neat condition, which was boosted by the addition of a little amount of EtOH [66]. This technique is commonly known as liquid assisted grinding (LAG) or solvent-drop grinding, evolved from kneading, in which a small volume of a liquid is added to the reaction mixture, measured by the ratio ofliquid volume to reactant weight (η) [67]. This provides a liquid-solid dual-phase for free interaction of the reactants facilitating product formation. Based on the parameter, η a method can be termed as neat grinding ($\eta = 0$), LAG (up to 2 μL/mg of substrate), slurrying (ca. 2–12 μL/mg of substrate) or solution-phase reactions (>12 μL/mg of substrate). For LAG, it is considered that the reactant solubility does not affect the reaction outcome. There are examples where common solvents are replaced by polymer, ionic liquid, etc. as the grinding auxiliary and the corresponding methods are termed as POLAG (polymer assisted

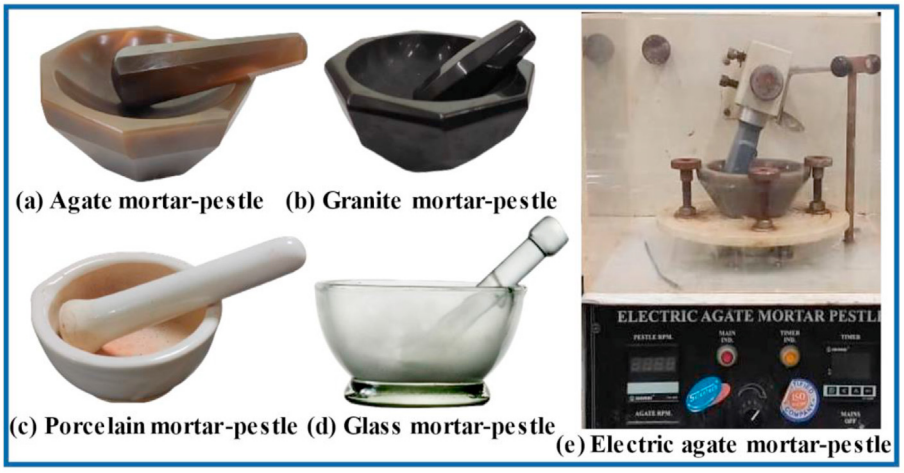


Fig. 1. Different types of grinding tools.

grinding) [68], IL-AG (ionic liquid assisted grinding) [69], ILAG (ion and liquid assisted grinding) [70], etc. A common component of POLAG is the use of polyethylene glycol (e.g. PEG-400), which offered excellent outcomes where other grinding auxiliary failed to deliver [68]. Besides, a variety of solid matrices were used as the grinding auxiliaries to facilitate a reaction such as Su and coworkers used silica for the synthesis of propargyl amines [71], alumina was used by Wu and coworkers for the synthesis of quinoxalines [72], KCl was used by Bhutia et al. for the synthesis of 7-oxa-4-thia-1-aza-bicyclo[3.2.1]-octane 4,4-dioxides [73].

Among other features, it aids in easy separation and purification of products; often the work-up step is avoided and sufficiently pure solid product is directly collected [74]. In several cases, easy recovery of heterogeneous catalysts by simple extraction of products by organic solvent and recycling is a common feature of grindstone chemistry. Patel et al. employed ionic liquid [DBU][Ac] as the catalyst for the synthesis of 3,4-dihydropyrano[*c*]chromenes, which was subsequently recovered and reused for five more runs with no drop in the catalytic activity [75]. These methods are environmentally benign than the corresponding solution-based protocols. For instance, the grindstone synthesis of zolimidine carried out by Das et al. using LAG with EtOH was found to have an E-factor of 1.77 [34], while an analogous method by Bagdi et al. employing solution-phase synthesis, with 1,2-dichlorobenzene as solvent generated an E-factor of 14.22 [76], although both garnered similar yields.

Grindstone reactions occasionally display exceptional control over chemo-, regio- and stereo-selectivity during the course of product formation by manual grinding. The high concentration of reacting species under neat or solvent*less* conditions offers different selectivities than analogous solution-based reactions [26]. For example, Tanaka et al. carried out Reformatsky and Luche reactions more efficiently in the absence of solvent [77]. Satasia et al. demonstrated *N*-formylation of amines by employing a novel ionic liquid (HIL-[Ch-OSO_3H]$_3W_{12}PO_{40}$) as the catalyst, in which only the *N*-formylated products were chemoselectively furnished [78]. Bhutia et al. developed an efficient hand-grinding procedure for the stereoselective synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles via an intramolecular 1,3-dipolar nitrone cycloaddition affording high diastereoselectivity as observed in solution phase methods [65,79].

1.3. Grinding vs. ball-milling

Mechanochemical force can be employed by two prominent techniques, either by grinding in a mortar and pestle, termed as grindstone chemistry or by milling in mixer mill or a planetary mill by the grinding balls which is referred as ball-milling [17]. Although milling, with much higher grinding force, several instrumental advantages, variation in milling parameters is by far a superior technique, grindstone chemistry with simple instrumentation, easy experimental set-up, no or less energy consumption is a frequently used technique for a plethora of applications. If the grinding is conducted at a speed of 50–200 rpm, the milling is conducted at a frequency of 5–60 Hz or 600–850 rpm. The power of high-energy ball milling (HEBM) is even higher. Therefore, energy-intensive organic reactions, such as C–H bond activation can be efficiently carried out in a ball-mill [18], but hand-grinding is hardly employed for similar transformations. The recent advancements in milling techniques include cryo-milling, continuous mode milling (twin-screw extrusion, TSE), photo-mechanochemistry, which offer the employment of mechanochemistry in a wide variety of reactions. However, grindstone chemistry is mostly limited to room temperature reactions. Often, the sheer power of a ball-mill speed-up the reactions, which are otherwise sluggish by simple grindstone chemistry [73]. However, simple grinding is occasionally more efficient and economical than a similar method using milling technique, for example, quinazoline synthesis reported by Kuntikana et al. [80] took only a few min for completion under a solvent-free condition while a similar reaction in a ball-mill took several hours for completion [81].

1.4. The scope of grindstone chemistry: Other than organic transformations

There are growing numbers of successful use of grindstone chemistry in the synthesis or formation of valuable materials and intricate structures including co-crystals, composites, dyes, metal organic frameworks (MOFs), covalent organic frameworks (COFs), etc. [17,21,23]. For instance, Das et al. constructed a new crystalline hydrazone-linked COF [TpTh (LAG)], COFs containing the porphyrin building unit [DhaTph (LAG)] and COFs with chemically labile Schiff base centers such as [LZU-1] by utilizing a variety of aromatic amine/hydrazide and aldehydes under LAG method [82]. This protocol delivered highly pure products in good yields with moderate crystallinity and porosity and at a faster rate as compared to the conventional solvothermal methodology. With regard to co-crystal synthesis, Solaimalai and coworkers employed the grindstone technique to investigate the suitability of a mixture of menthol and camphor as a green eutectic solvent in the synthesis of cocrystals, for the enhancement of biopharmaceutical properties of poorly water-soluble drugs [83]. Piroxicam-benzoic acid (PRX-BA) cocrystals were synthesized by grinding equimolar quantities of PRX and BA in a mortar-pestle with dropwise addition of the green eutectic solvent. This simple, economical method is well scalable and eliminates the disadvantages posed by conventional methods of synthesis. In another experiment, the cocrystallization behavior of antiprotozoal tinidazole (TNZ) was investigated in order to identify the possibility of preparing new solid forms as an attempt to enhance its solubility and physical stability [84]. Fandiño et al. employed LAG for the synthesis of three cocrystals of TNZ with *p*-aminobenzoic acid (PABA), citric acid (CA), and salicylic acid (SA), and two eutectics with nicotinamide (NA) and succinic acid (SA). Although the prepared cocrystals and eutectics did not significantly enhance the aqueous solubility of this API, the cocrystals, however, improved the solid-state photostability of TNZ.

Along with its ability to aid known reactions, grindstone chemistry is also instrumental in accessing the reactions that are not easily attainable through conventional methods. A series of API-ILs incorporating lidocaine and medium chain dicarboxylic acids as counter ions were synthesized using grindstone chemistry by Zotova et al., aimed towards their discovery and development for pharmaceutical applications [85]. Simple neat grinding afforded the ILs lidocainium hemiadipate solid salt and lidocainium hemiglutarate, lidocainium hemipimelate, lidocainium hemsuberate in higher yields, with shorter reaction times and in the absence of solvents in contrary to conventional solution-based synthesis, which requires large volumes of solvents and purification steps. Lee and group developed a simple approach for the synthesis of a fullerene-nanodiamond composite by hand-grinding dry C_{60} powder with nanodiamond (ND) in a mortar and pestle [86]. This novel protocol does not require organic solvents and is highly scalable. The furnished C_{60}-ND composites were found to be easily dispersible in water and displayed enhanced activity for the removal of water contaminants and for the induction of cancer cell apoptosis. Prusti et al. reported the design of two positional isomeric AIEgens TMBπCBZ and CBZπTMB [π = anthracene-linked vinyl] by interchanging the two electron-rich CBZ and TMB cores [87]. These compounds were easily synthesized in high yields (~80%) at room temperature by grinding phosphonates and

aldehydes, thereby avoiding the need for expensive metal/ligand combinations for their synthesis. Although both isomers are strong solid-state emitters, it was interestingly found that after grinding in a mortar and pestle, TMBπCBZ displayed reversible spectacular piezo-fluorochromic features with a 62 nm redshift, whereas, CBZπTMB remained unchanged. This protocol was found to be easily scalable, making real-world access to these materials more feasible [87]. The literature is vast in this direction and the above section is a glimpse of the scope of grindstone chemistry in conducting transformations other than organic reactions.

2. Grindstone derived organic transformations: A brief account

Over the years, grindstone chemistry has established itself as being a simple and greener technology for various chemical transformations from traditional C–C bond formation to different name reactions to various multicomponent transformations. In this section, we intend to give a brief overview of the use of grindstone chemistry for these classical organic transformations with selected recent examples.

2.1. Traditional C–C bond formation

Carbon-carbon bond formation reactions are crucial for synthetic chemists for years in building up molecules and have enormous industrial implications [88]. In the last century, Toda's group explored various traditional C–C bond formation reactions employing grindstone chemistry that include aldol condensation [28], Dieckmann condensation [89], Reformatsky reaction [77], Luche reaction [77], Grignard reaction [25], etc. which are reflected in their excellent review article on solvent-free reactions [22]. In this section, a few more recent and important contributions on C–C bond forming reactions are included demonstrating the scope of grindstone technique.

Grindstone chemistry was successfully used towards aldol condensation/Claisen-Schmidt condensation by grinding in mortar-pestle [90,91]. Recently, Li et al. synthesized novel quinoline-based α-arylidene cycloketones, i.e., (*Z*)-3-arylidene/ferrocenylmethylene-5-methyl/phenyl-1*H*-pyrano[3,4-*b*]quinolin-4(3*H*)-ones (**3**) involving solvent-free aldol condensation reaction between pyrano[3,4-*b*]quinoline-4(3*H*)-ones (**1**) and various aromatic aldehydes (**2**) by grinding in a mortar and pestle using KOH as the base at room temperature (Fig. 2a) [90]. They first synthesized **1**, the cyclic ketones with active methylene moiety, and performed aldol condensation with various aromatic and heteroaromatic aldehydes to get α-arylidene cycloketones (**3**) with quinoline ring in high to excellent yields. Out of the various acids and bases employed as catalysts for the aldol condensation, KOH (1 equiv) was found to give the best results under solvent-free grinding at room temperature. Notably, the condensation product of **1** and benzaldehyde afforded only 61% yield after refluxing in ethanolic

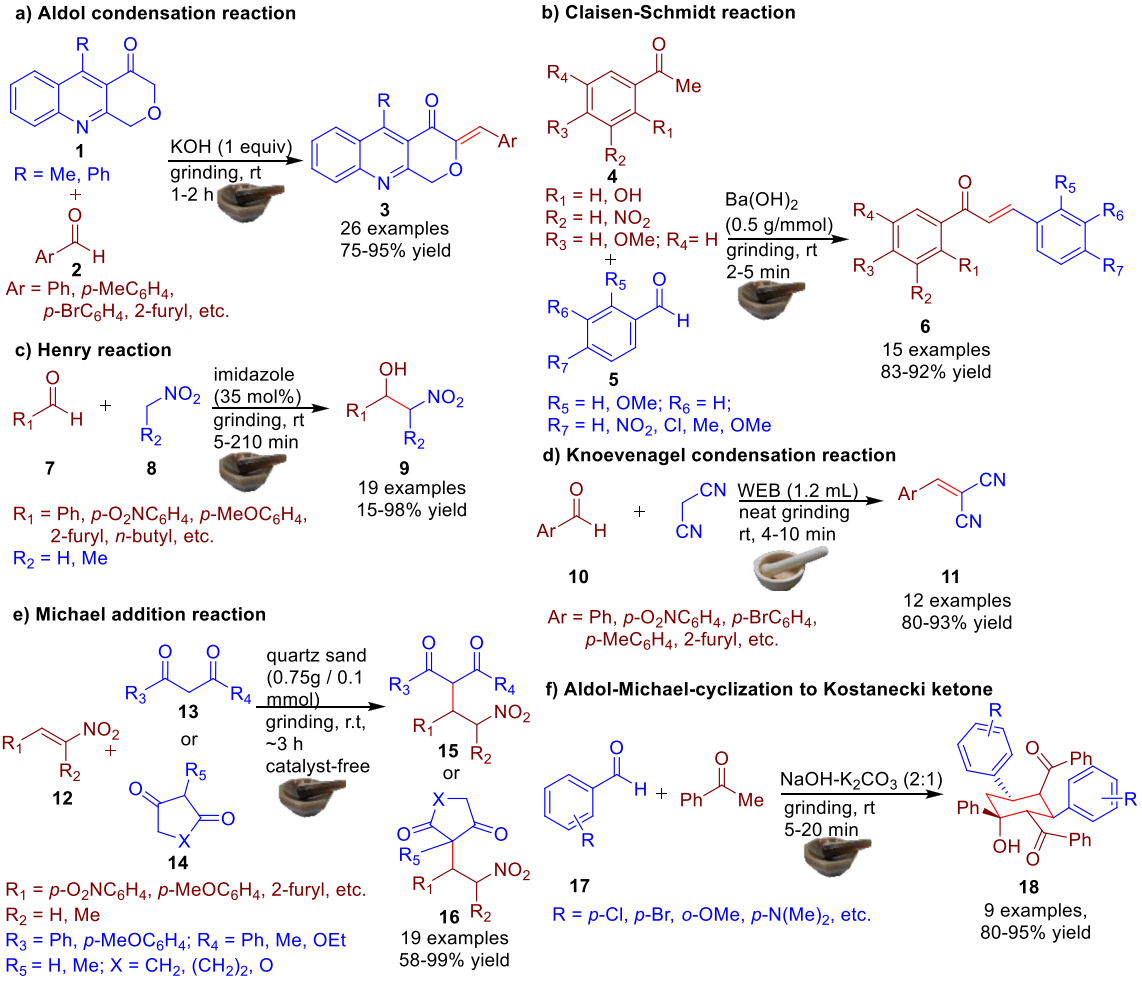


Fig. 2. Different condensation reactions carried out using grindstone technique.

solution for 5 h as compared to 89% yield in just 1 h by grinding, indicating hand-grinding a facile approach than solvent-based methods. Some of the compounds displayed anti-tumor activity when screened for the same. Kumar et al. demonstrated the Claisen-Schmidt condensation between acetophenones (**4**) and aryl aldehydes (**5**), and synthesized some interesting chalcones (**6**), useful intermediates of flavonoids, using anhydrous barium hydroxide (C-200) as solid support in a mortar-pestle in good to excellent yields within a short reaction time at room temperature (Fig. 2b) [91]. This method selectively furnished **6** without the formation of any cyclized products. In a different approach towards Claisen–Schmidt condensation, Rateb and Zohdi prepared several chalcones by grinding a mixture of appropriate methyl ketones with aldehydes in the presence of NaOH (solid) under solvent-free conditions [92]. The desired products were purified by simple filtration involving washing the product residue with cold water followed by recrystallization. Similar to aldol reaction, the first solid-state Lewis base-catalyzed Henry reaction for the synthesis of 2-nitroalkanols (**9**) by grinding technique was reported by Phukan et al. by employing cheap and readily available imidazole as the catalyst (Fig. 2c) [93]. In general, the grinding of aldehydes (**7**) with nitroalkanes (**8**) gave the desired products (**9**) generally in high yields. Furthermore, it was observed that the addition of sand (used as friction-enhancing solid) tremendously accelerated the reaction rate for solid/liquid and liquid/liquid substrates. The absence of side products and catalyst recyclability without much loss in the product formation are few important advantages of this method.

Knoevenagel condensation is one of the most widely applied reactions and studied well using grindstone chemistry. Various catalytic conditions have been successfully investigated for carrying out this reaction with various aldehydes and active methylene compounds as reactants using mechanochemical grinding [94–99]. To briefly illustrate them, a green and economic approach for the Knoevenagel condensation of substituted aromatic and heteroaromatic aldehydes (**10**) with malononitrile catalyzed by water extract of banana (WEB), a natural base, was described by Kantharaju et al. (Fig. 2d) [94]. The solvent-free procedure furnished the desired products (**11**) within just 10 min of grinding and sufficiently pure products were obtained by simple filtration. In another study, Ren et al. demonstrated an “improved” Knoevenagel condensation reaction by grinding aldehydes and malononitrile in glass mortar-pestle in the absence of solvents and catalysts [95]. Surprisingly no products were obtained when the same reaction conditions were employed using porcelain mortar and pestle. Pasha and coworkers used Na_2CO_3 to catalyze the Knoevenagel condensation of aromatic aldehydes with active methylene compounds to afford arylmethylidene products under grindstone chemistry [96]. Thirupathi and coworkers used L-tyrosine, an organocatalyst, in the Knoevenagel condensation between arylaldehydes with Meldrum's acid in a mortar-pestle at room temperature to produce substituted 5-benzylidene-2,2-dimethyl- [1,3]dioxane-4,6-diones [97]. Metwally and coworkers synthesized 5-arylidene-4-thiazolidinones from various aromatic aldehydes and 4-thiazolidinones by grinding in a mortar and pestle in the presence of anhydrous ammonium acetate [98]. Recently, in another interesting approach, Madan employed ZnO nanoparticles towards the synthesis of Knoevenagel condensation products of indole-3-carbaldehydes and 3-methyl-1-phenyl-5-pyrazolone with an active methylene group employing the same solvent-free grindstone protocol [99].

A Michael addition reaction was demonstrated by Xie et al. for the synthesis of various nitro diketone derivatives (**15** and **16**) employing grindstone chemistry (Fig. 2e) [100]. The optimization study of Michael addition between β-nitroalkenes (**12**) and 1,3-dicarbonyl compounds (**13**) or other active methylene compounds (**14**) revealed that quartz sand (0.75 g per 0.1 mmol of substrates) works better as the grinding auxiliary furnishing good to excellent yields of the desired products (**15** or **16**). In another interesting study, Luo and Shan synthesized highly substituted cyclohexanols (**18**), one of the Kostanecki ketones, by a tandem aldol condensation, Michael reaction and cyclization of acetophenone with various aromatic aldehydes (**17**) in 2:3 ratio (Fig. 2f) [101]. The two-component tandem cyclization was catalyzed by a mixture of NaOH and K_2CO_3 (2:1 M ratio) in mortar-pestle for 5–20 min at room temperature and the product formation was indicated by the disappearance of the liquid component and the insoluble solid product was collected after water-wash of inorganic bases making the protocol an efficient one for the synthesis of 1,2,3,4,5-pentasubstituted cyclohexanols. The products (**18**) showed identical stereochemistry with the adjacent groups bearing a trans relationship (Fig. 2f).

Among other important C–C bond formation reactions, Agarwal et al. demonstrated a rapid mechanochemical Diels-Alder reaction to access bi-, tri-, and tetra-cyclic systems (**23**–**26**) via LAG with EtOAc in mortar and pestle (Fig. 3a) [102]. Optimization studies revealed that the dienes (1,3-diphenyl-2-benzofuran, **19** and cyclopentadiene, **20**) and diverse electron-deficient dienophiles (**21** and **22**) under neat grinding afforded the product in only 75% yield after rigorous grinding for 15 min, whereas, the LAG protocol using EtOAc (2–3 drops) resulted in complete conversion of the reactants in just 5 min, giving the products in quantitative yields. Various dienes and diverse electron-deficient dienophiles were ground together under catalyst-free and solvent-free conditions in a mortar-pestle to afford the corresponding Diels-Alder adducts in quantitative yields. The high yields ensured no formal purification is required.

A Wittig reaction was explored by Leung and coworkers adopting hand-grinding protocol in synthesizing (*E*)- and (*Z*)-1-(4-bromophenyl)-2-phenylethene (**28**) by grinding a mixture of benzyltriphenylphosphonium chloride (**27**) and 4-bromobenzaldehyde in the presence of potassium phosphate under the solvent-free condition at room temperature in just 20 min (Scheme 3b) [30] The reaction produced both (*E*) and (*Z*) isomers of **28** in about 70% yield, but only the *E* isomer could be isolated by crystallization. A Horner-Wadsworth-Emmons reaction was demonstrated by Marroquín and coworkers for the synthesis of piperlotines A, C, and derivatives (**31**) via mechanochemical activation of different aldehydes (**29**) and β-amidophosphonate (**30**) in the presence of K_2CO_3 (1.2 equiv) in mortar-pestle (Fig. 3c) [31]. The gentle grinding of the substrates in open-air afforded thermodynamically controlled *E*-isomers as the sole products in moderate to good yields. This method tolerated both the presence of EDGs, EWGs and unsaturation in the aldehydes (**29**).

In another study, a solid-state Corey-Chaykovsky reaction was demonstrated by Yin et al. for the cyclopropanation of 4-ferrocenylacetophenones (**32**) via grinding of the substrates in mortar-pestle followed by microwave irradiation (Fig. 3d) [103]. Few novel (4-ferrocenyl)benzoylcyclopropanes (**34**) were prepared by grinding **32** with substituted aldehydes (**33**) using NaOH and Al_2O_3 as the grinding matrix followed by microwave irradiation of the reaction mixture. This was followed by the addition of another ground mixture of trimethylsulfoxonium iodide, NaOH, and Al_2O_3 to the previous mixture and the resultant mixture was further kept under microwave irradiation. The final cyclopropyl ketone derivatives (**34**) were obtained in 85–99% yields.

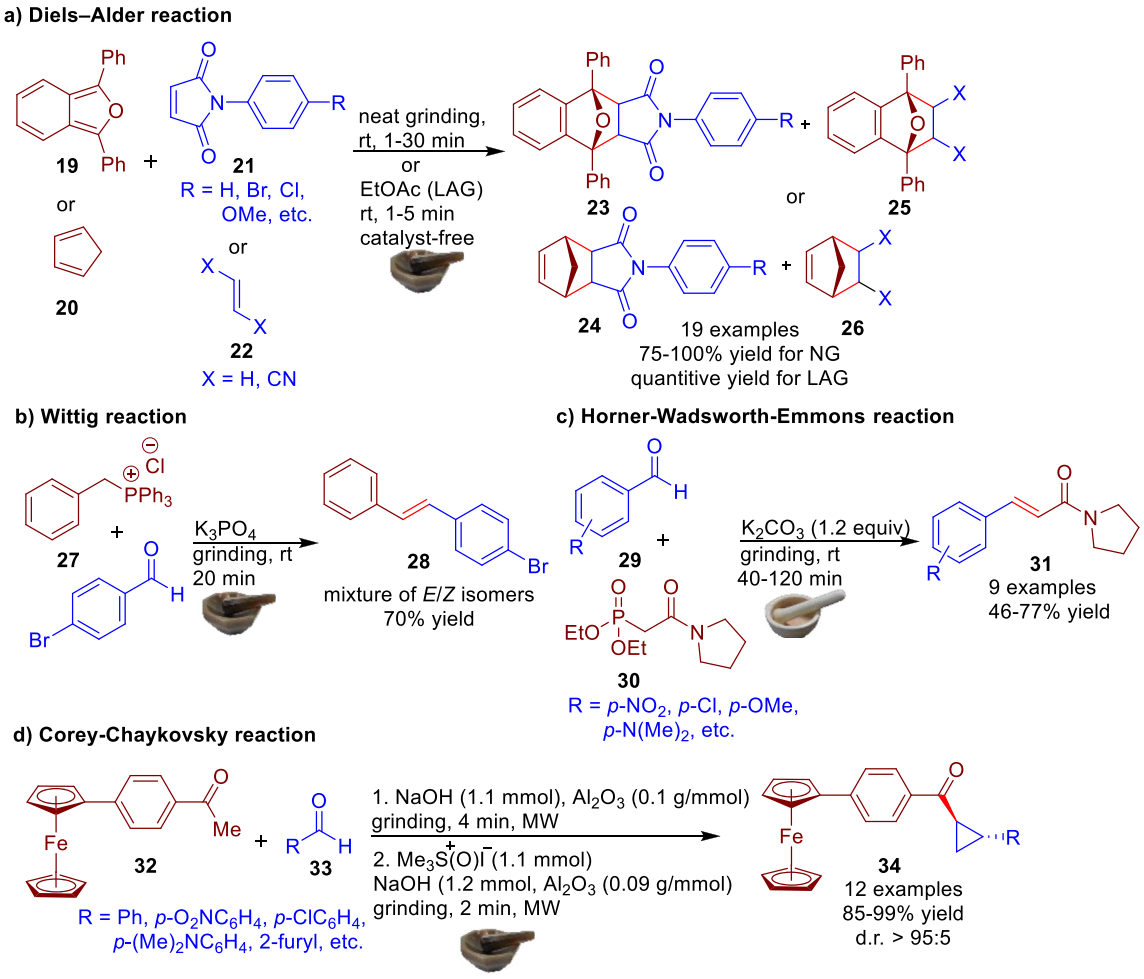


Fig. 3. Selected name reactions involving C–C bond formation by grindstone technique.

2.2. Formation of Schiff base and related derivatives

Schiff bases are organic compounds with a broad spectrum of biological activities, including anti-inflammatory [104], antimicrobial [105], antitubercular [106], anticancer [107], etc. and several of them are used in the medicinal and pharmaceutical fields. In addition, Schiff bases are useful intermediates in the synthesis of dyes, pigments, as polymer stabilizers, and so on [108].

Grindstone chemistry has been vastly employed for Schiff base formation reactions. In the past, solid-state condensation reactions afforded Schiff bases upon grinding a mixture of carbonyl compounds and amine derivatives in mortar and pestle under neat or solvent-less conditions, such as using water as an LAG agent [109–111]. For example, Sachdeva and co-workers demonstrated a protocol for the synthesis of racemic mixture of Schiff bases (**37**), as potential antimicrobial agents, by the condensation of substituted aromatic or heteroaromatic aldehydes (**35**) with DL-alanine (**36**) (Fig. 4a) [109]. Some of these Schiff bases derived from aromatic aldehydes with trimethoxy, dimethoxy, hydroxyl, nitro, and chloro groups or furfural showed good antibacterial and antifungal activities. The hydrazone formation by hand-grinding was explored by Filho and coworkers (Fig. 4b) [112]. The grinding of various carbonyl compounds **38** (including cyclic ketones, **39**) with *N*-acyl hydrazides (**40**) in the presence of catalytic amount of AcOH and a few drops of water as LAG agent only for a few minutes afforded a large number of *N*-acylhydrazones (**41**) in over 90% yields in each case. Notably, *N*-acylhydrazone (NAH) moiety is a privileged structural scaffold in medicinal chemistry. They validated the method with aromatic, heteroaromatic, aliphatic aldehydes and ketones as well as sugars (Fig. 4b). On the other hand, hydrazides derived from several benzoic acids, heteroaromatic acids or even ferrocene carboxylic acid participated equally well in the condensation reaction to prepare a library of 51 compounds. In most of the cases, the essentially pure hydrazones were obtained avoiding workup and purification steps. However, the same method failed to afford hydrazones (or imines) from *N*-Boc-amine or a sulfinamide (-$SONH_2$) or sulfonamide (-SO_2NH_2) derivatives. In another study, Barbazán et al. reported grindstone mediated hydrazone synthesis by condensation of ferrocene carboxaldehyde and benzoyl hydrazide [113]. Yang et al. developed another grindstone method to prepare *N*-arylsulfonylhydrazones by condensation of benzensulfonyl hydrazides with various arylaldehydes/ketones using L-tyrosine as the organocatalyst [114]. On the other hand, Aakeröy et al. reported the synthesis of ketoximes (**44**) via a mechanochemical synthetic pathway involving the grinding of different ketones (**43**) with hydroxylamine hydrochloride and NaOH in the presence of methanol (0.1–0.2 mL) as LAG agent in a porcelain mortar-pestle (Fig. 4c) [115]. Aromatic ketones with both EDG and EWG, heteroaryl ketones as well as aliphatic ketones participated in the reaction and several of them afforded stoichiometric yields of the corresponding ketoximes. In a similar approach, Saikia et al. prepared a series of aldo/ketoximes by solid-phase grinding of a mixture of

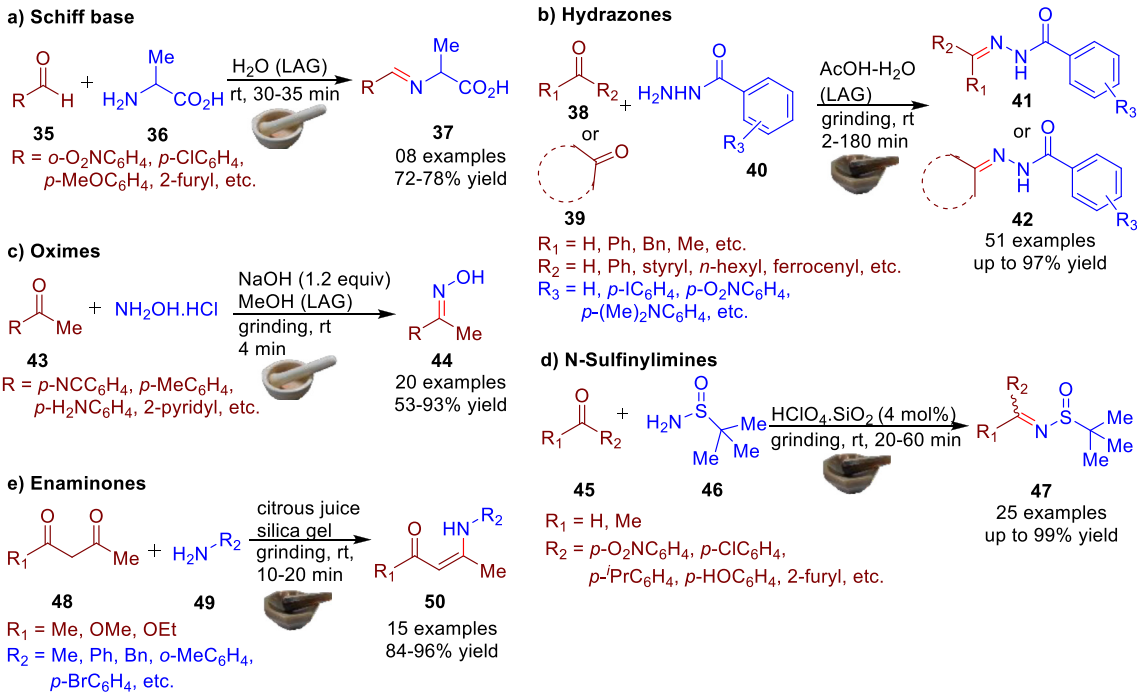


Fig. 4. Formation of Schiff bases and related reactions employing the grindstone technique.

carbonyl compounds (aliphatic, heterocyclic, and aromatic) and hydroxylamine hydrochloride in the presence of cheap Lewis acid, Bi_2O_3 as the catalyst [116]. Venkateswarlu and coworkers synthesized *N*-(*tert*-butylsulfinyl)imines (**47**) from chiral *tert*-butylsulfinamides (**46**) employing grindstone chemistry involving a solid acid, perchloric acid-silica ($HClO_4$·SiO_2) catalyzed reaction of various aldehydes (**45**) with *N*-*tert*-butylsulfinamides (**46**) (Fig. 4d) [117]. The use of simple silica gel or other solid acid catalysts (e.g. H_2SO_4·SiO_2, *p*-TSA.SiO_2) offered lower yields and took longer time. The grinding of substrates in an Agate mortar with a catalyst load of 80 mg/mol in the absence of solvent furnished the desired products in short reaction times, restoring the chirality of initial *tert*-butylsulfinamide derivatives. This method was validated by using both electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) in the aromatic aldehydes. No significant substituent effect was observed in terms of yield or reaction time. In another study, the acidic nature of aqueous citrus juices was explored in utilizing them as natural and green catalysts for the synthesis of β-enaminone derivatives (**50**) via enamination of 1,3-dicarbonyls (**48**) with various aromatic/aliphatic primary amines (**49**) in a mortar-pestle by Marvi et al. (Fig. 4e) [118]. Citrus juices of four different fruits i.e. lime, lemon, orange and grapefruit along with SiO_2 as a solid matrix were screened and the former delivered the best results. The catalytic system of lime/SiO_2 (5 drops/1 g) furnished about 15 derivatives of **50** in good to excellent yields under ambient conditions.

2.3. Aromatic substitution reactions

Aromatic substitution often ends up with the products which serve as the intermediates or precursors of important organic compounds, polymers, dyes, pharmaceuticals, agrochemicals, etc. [119]. In this direction, Suresh et al. used a grindstone protocol for the nitration of aromatic and heteroaromatic compounds (**51**) by a combination of $NaNO_2$/$KHSO_4$ under mild conditions avoiding the use of any mineral acid (Fig. 5a) [120]. The mono-nitration of aromatic substrates (**51**) with $NaNO_2$ (20 mol%), $KHSO_4$ (10 mol%) and peroxides (10 mol%) was smoothly carried out in a mortar-pestle and the products (**52**) were obtained in 65–85% yields. A total of five different peroxides (H_2O_2, TBHP, PDS, PMS or SPB) were tested and all gave similar results. The comparison between the conventional method and grindstone technique revealed that the reaction time can be shortened from hours to a few min by simple grinding in a mortar-pestle. They examined *in situ* generation of active nitronium ion as the nitrating species. Thus, the group commented that the method does not produce any radical species which are usually produced *in situ* when a peroxy species is used for several other reactions.

Karade and coworkers carried out halogenation of various arenes (**53**) by mortar pestle grinding with NaCl, NaBr or I_2 by using (diacetoxyiodo)benzene as an oxidant (Fig. 5b) [121]. As expected, the reaction offered high regioselectivity with *p*-position being more favoured. For example, halogenation of anisole, *N,N*-dimethylaniline and acetanilide exclusively furnished para-products. The yields of bromination and iodination products (**54**) were found to be relatively higher compared to the yields of chlorination. The alternative route of halogenation from diazonium salts, i.e. Sandmeyer reaction was also carried out by simple hand-grinding by Bamoniri et al. to synthesize various aryl iodides (**56**) in good to excellent yields via diazotization of electron-rich and electron-deficient aromatic amines (**55**) with $NaNO_2$ in the presence of a reusable solid-acid catalyst, nano silica periodic acid (nano SiO_2–HIO_4) followed by iodination with KI (Fig. 5c) [122]. The amount of catalyst used was fixed as 50 mg/mmol of the substrate which gave yields above 90%, whereas, with a decrease in the amount of catalyst, the yields reduced below 50%. The nanocatalyst was prepared by the group and its reusability study showed that it could be used up to 5 cycles without much decrease in its catalytic activity (83% effective). In another study, Vibhute and coworkers developed a hand-grinding protocol for the iodination of phenols with aldehyde and ketone functionalities by a combination of iodine and iodic acid [123].

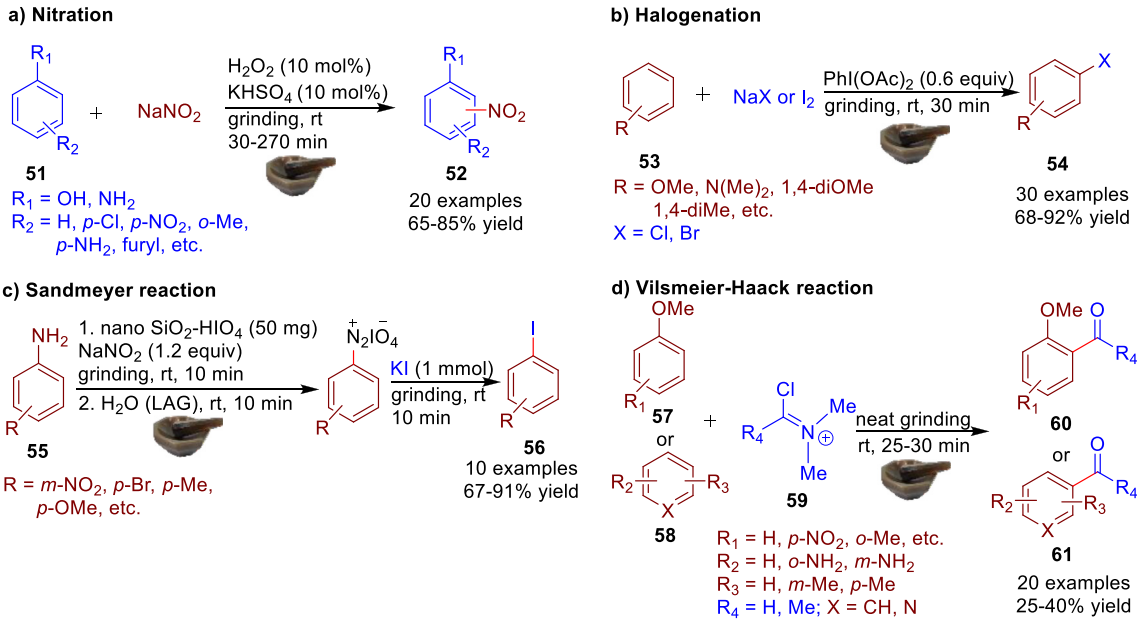


Fig. 5. Grindstone mediated aromatic substitution reactions.

The mechanochemical Vilsmeier-Haack reaction was reported by Mohammed et al. for formylation and acylation of various anisoles (**57**) and pyridines (**58**) by grinding them vigorously with Vilsmeier-Haack reagent, **59** to give the desired products (**60** and **61**) using a mortar and pestle (Fig. 5d) [124]. The protocol was found to be more advantageous over solution-phase reaction both in terms of reaction rate and environment friendliness. The method was validated using different EWGs and EDGs derivatives and it was found that the yields are almost comparable in both cases and not much substituent effect is observed. Balali et al. reported a regioselective *o*-formylation of phenols by grinding various phenols with paraformaldehyde and $Mg(OMe)_2$ [125]. This grinding protocol using mortar pestle gave exclusively the ortho-substituted products. A high yielding mechanochemical method for the synthesis of fluorescein-phenylalaninol (FPA) receptor was reported by Rathod et al., exploiting the Reimer-Tiemann reaction under the grindstone chemistry [126]. The manual grinding of fluorescein and solid NaOH in a mortar-pestle under LAG (few drops of MeOH) produced the desired fluorescein monoaldehyde in good yields. The synthesized fluorescein Schiff base was utilized as the colorimetric and fluorimetric sensor for the simultaneous detection and removal of toxic mercury ions in the aqueous solution.

2.4. Miscellaneous other reactions

The versatility of grindstone chemistry was demonstrated by several other name reactions as well. In this regard, Rahman and coworkers established a non-hazardous hand-grinding protocol for Cannizzaro reaction in which they ground various aryl aldehydes (**62**) with solid sodium hydroxide to get corresponding Cannizzaro products (**63** and **64**) in 94–99% yields in just 10 min of grinding (Fig. 6a) [127]. The reactions proceeded exothermically wherein the rise in temperature was recorded ranging between 25 and 100 °C. The purification was done by acidifying the reaction mixture, which leads to precipitation of the acid (**63**) and upon filtration pure alcohols (**64**) were obtained in the filtrate, thereby, avoiding the tedious purification steps. In another study, the Hunsdiecker-like conversion of α,β-unsaturated acids (**65**) to nitroalkenes (**66**) was accomplished by Ramesh et al. by grinding them along with PEG supported metal nitrates under acid-free conditions (Fig. 6b) [128]. The method involves the use of inexpensive and readily available 3d block nitrates of Fe(III) and Mn(II) which had been screened along with different PEGs such as PEG-200, 300, 400, 600, 3000 and 6000 as additives. The use of PEG-400 with the two nitrates was found to be the best among PEGs for cinnamic acid which resulted in better conversion within 30 min. The cinnamic acid derivatives with EDGs reacted faster (30 min) than those with EWGs (60 min). The aliphatic acid (such as crotonic acid) took more time for completion affording nitroalkenes in relatively lower yields.

The rearrangement reaction is also possible by simple grinding. Sharma et al. successfully demonstrated Baker-Venkataraman rearrangement of 2-cinnamoyloxyacetophenones (**67**) by solid-phase grinding with potassium hydroxide in a porcelain mortar-pestle (Fig. 6c) [129]. The desired products 2-hydroxybenzoylcinnamoylmethanes (**68**), which are the key intermediates in the synthesis of flavones and 2-styrylchromones, were formed by Baker-Venkataraman rearrangement within just 3–5 min. A short library of 2-hydroxydibenzoylmethanes were prepared from 2-aryloxyacetophenones by this rearrangement reaction. The reaction mixtures were filtered after acidification and pure products were obtained by recrystallization from aqueous ethanol in good to excellent yields.

The hand-grinding tool can be used for regio-/chemo-selective synthesis. Bharate and coworkers performed a regioselective *O*-benzylation or benzoylation on rohitukine (**69**), an alkaloid with anticancer activity, in mortar-pestle in the presence of catalytic amount of potassium fluoride impregnated alumina (Fig. 6d) [130]. Rohitukine (**69**) has two phenolic –OH groups at C5 and C7 and one is alcoholic –OH (at C2′). As C5–OH is H-bonded with 4-carbonyl oxygen, regioselective benzylation (or benzoylation) was possible at phenolic-OH group of C7. As no strong base was used in the reaction media, the method showed chemoselectivity towards phenolic –OH over an alcoholic functionality. Grinding of rohitukine (**69**) with different benzyl and benzoyl halides (**70**, X = Cl or Br) in the presence of 5 mol% of KF-alumina afforded the desired products (**71**) in high yields. The alkylation was found sluggish in the solution phase (e.g. acetone or DMF) or neat grinding in model reactions with 4-methoxy benzyl bromide. The solid catalyst could be recycled for several cycles without a loss in reactivity.

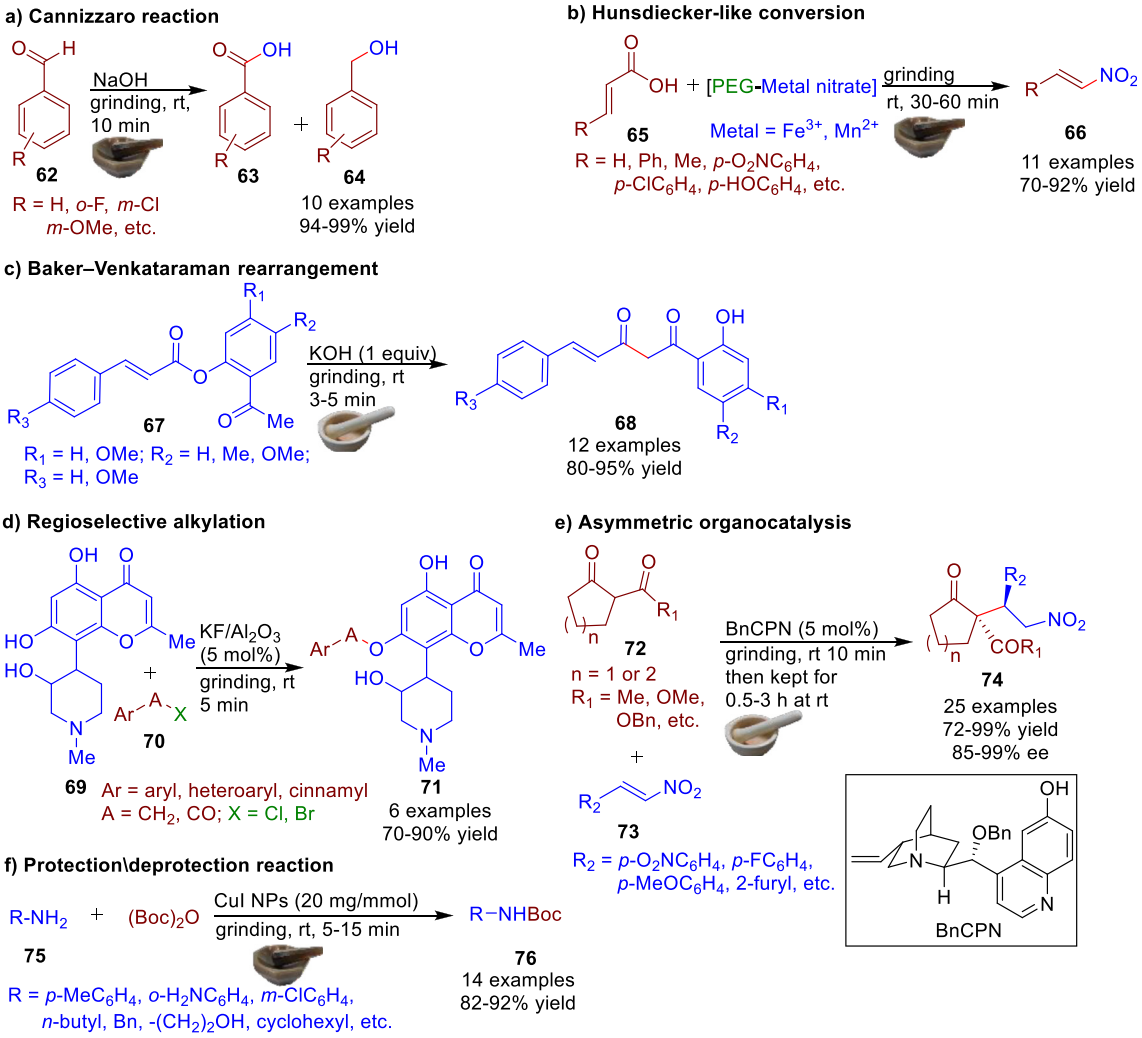


Fig. 6. Application of grindstone chemistry for miscellaneous other reactions.

Asymmetric transformation is recognized as one of the most important chemical transformations, particularly for the synthesis of chiral drugs. The hand-grinding method is occasionally employed for asymmetric catalysis [131]. Chauhan et al. developed a mechanochemical route for a highly stereoselective Michael addition of trisubstituted β-ketoesters (or 1,3-diketones, **72**) and nitroalkene derivatives (**73**) via simple grinding with pestle and mortar (Fig. 6e) [132]. Grinding an equimolar quantity of 1,3-diketone (**72**) and nitroalkene (**73**), in the presence of cupreine derived organocatalyst (BnCPN, 5 mol%) delivered the Michael adducts (**74**) with vicinal tertiary and quaternary stereocenters in high yields with excellent stereoselectivity (up to 99% *ee* and up to 99:1 d.r). The grinding-assisted organocatalysis protocol proceeded at a much faster rate in comparison to the reactions performed under traditional stirring in toluene or under neat conditions. The grinding enabled the appropriate mixing of the catalyst and substrates and frictional force pushed the reaction to the forward direction. The presence of EWGs in the substrate, **73** expedites the product formation with better yields as compared to EDGs.

Although protection-deprotection chemistry is highly useful in synthetic organic chemistry, only limited attempts are made in this direction employing grindstone technique. Recently, Kantharaju et al. described a mechanochemical protocol for the Boc-protection of primary amines (**75**) employing copper iodide nanoparticles as the catalyst (Fig. 6f) [133]. Various aliphatic, aromatic, and heterocyclic amines were successfully protected with Boc-group by grinding with $(Boc)_2O$ in the presence of CuI NPs (20 mg/mmol) in a mortar and pestle delivering 14 compounds (**76**). This method afforded the products in high yields (82–92%) within shorter reaction times (5–15 min). The CuI catalyst was recycled after centrifugation with EtOAc and water, and was used for three cycles with a slight drop in catalytic activity in the third cycle.

2.5. Multicomponent reactions

Over the years, multicomponent reactions (MCRs) gained immense importance as useful tools for the synthesis of value-added molecules in the fields like medicinal chemistry, drug discovery research, agrochemistry and so on. Mortar-pestle grinding is used in several types of MCRs leading to heterocycles, which will be discussed in the next section. In this section, we intend to discuss selected examples of MCRs leading to acyclic compounds. In this direction, Mani et al. synthesized several Mannich bases (**79**) involving the reactions of dopamine (**77**), vanillin and substituted ketones (**78**), utilizing the grindstone technique (Fig. 7a) [134]. A total of 12 compounds were prepared using the protocol under catalyst-free conditions with 87–96% of yields. These dopamine-derived Mannich bases (**79**) displayed significant antioxidant and anti-tyrosinase activities. In a similar approach, Mohan et al. developed a grindstone protocol for Betti reaction between aryl

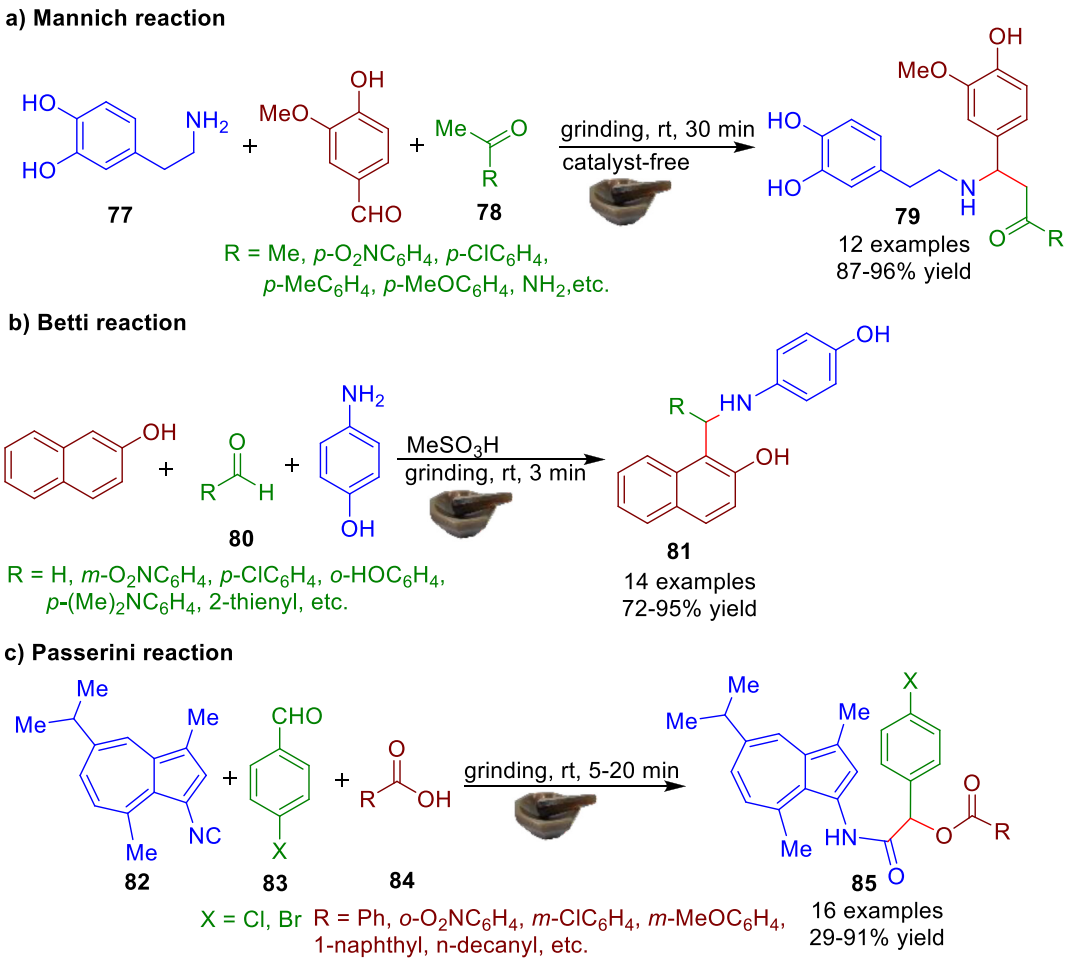
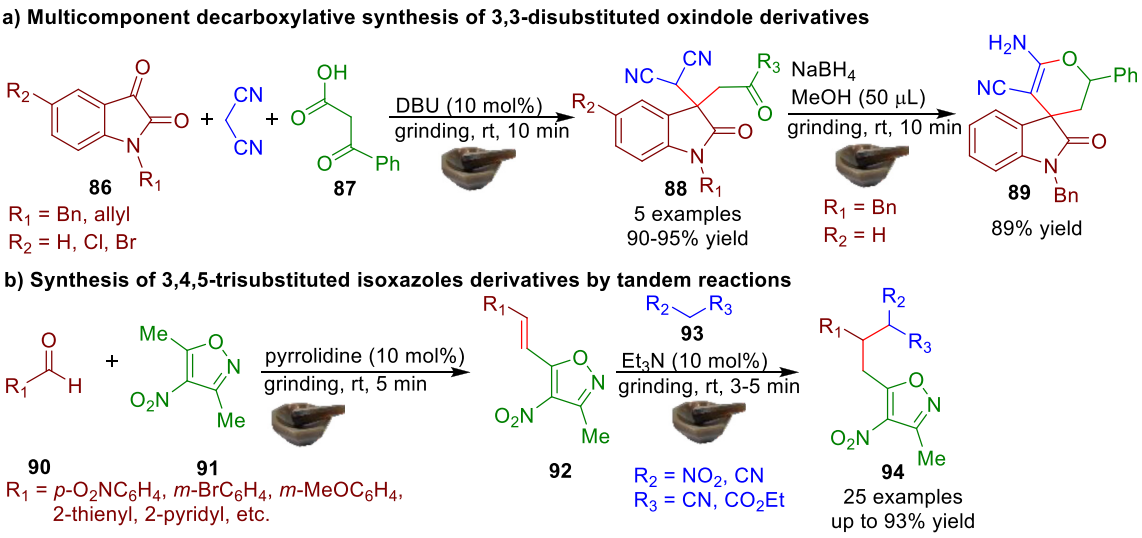


Fig. 7. Multicomponent name reactions aided by mortar-pestle grinding.

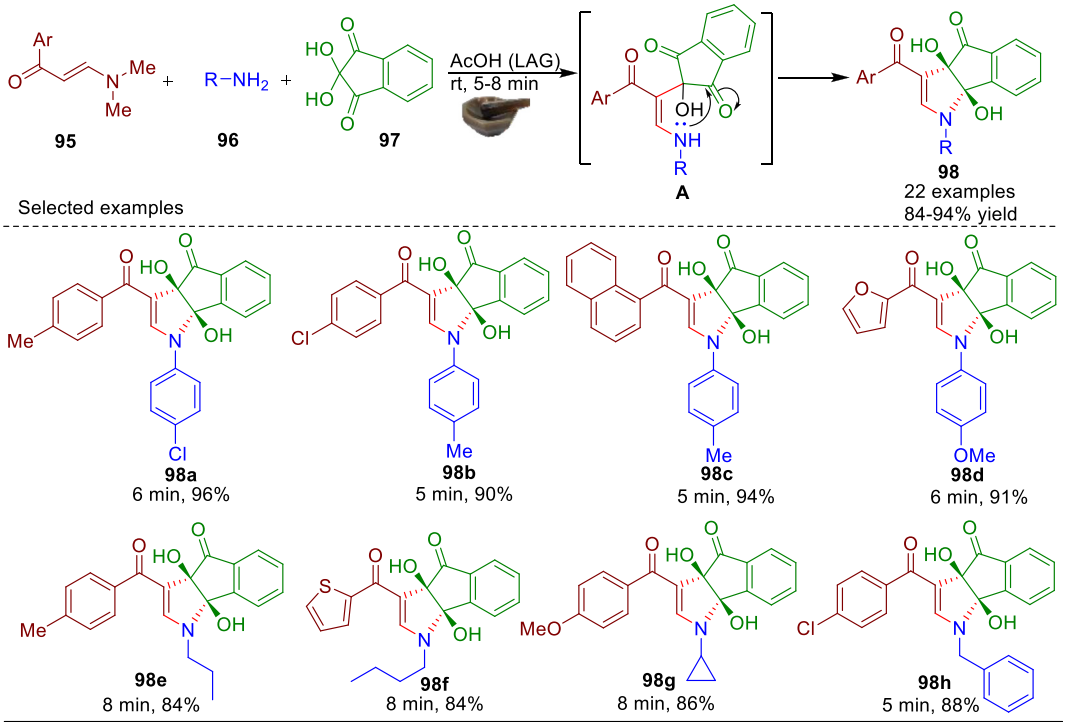
aldehydes (**80**), 2-naphthol, and aromatic amines (Fig. 7b) [135]. The grinding of these three components in a mortar-pestle in the presence of catalytic amount of $MeSO_3H$ gave 1-aminoalkyl-2-naphthol derivatives (**81**) in good to excellent yields. A syrupy reaction mixture was washed with water and once the acid was removed, the desired products (**81**) were obtained as solids making product separation easy. However, a couple of attempts with aliphatic aldehydes resulted in very poor yields of Betti products. The scope of the method was demonstrated by the synthesis of 1-aminoalkyl-2-naphthols (**81**) in large-scale (0.25 M batches). For these reactions, various components and the catalyst were taken in a large porcelain bowl and ground with the help of a hand-held electric food mixer with stainless steel rotors. The large-scale reactions were also completed within 5 min and the desired products were obtained in 83–95% yield.

A Passerini reaction was exploited by Sato et al. for the synthesis of 3-*N*-acylamino azulenes (**85**) via manual grinding of a mixture of 3-isocyano-7-isopropyl-1,4-dimethylazulene (**82**), benzaldehydes (**83**), and various carboxylic acids (**84**) in an Agate mortar-pestle (Fig. 7c) [136]. The grindstone protocol was found superior than the solution phase Passerini reaction. They demonstrated with model substrates, isonitrile (**82**, 1.0 equiv), *p*-chlorobenzaldehyde (2.0 equiv) and decanoic acid (2.0 equiv) that the reaction proceeds smoothly to completion within 20 min to furnish the corresponding Passerini product in 81% yield, while the same reaction in THF afforded 45% yield after 18 h, or in CTAB derived micellar media in 72% yield even after 24 h. They postulated that the solvent-free reaction based on the grinding of different solids involved the formation of a liquid phase with a uniformly distributed eutectic melt that brings the reacting components in close proximity to react efficiently. The scope of the method was explored with 16 examples.

Among various other multicomponent reactions, Chimni and coworkers reported decarboxylative reactions of isatin derivatives (**86**), malononitrile and β-ketoacids (**87**), carried out in a mortar and pestle with DBU as the catalyst to afford 3,3-disubstituted-2-indolinone derivatives (**88**) (Scheme 1a) [137]. Different organocatalysts, such as DMAP, DABCO, DBU, pyridine, pyrrolidine, were tested during the optimization studies and the best results were obtained with 10 mol% DBU. The protocol smoothly gave oxindole derivatives (**88**) in up to 98% yields in a short time. Water wash of the resultant reaction mixture and simple filtration offered column chromatography free purification of the products. They also demonstrated the reductive cyclization of suitable 2-indolinone derivatives to biologically important spirooxindoles (**89**) in high yield (89%) employing the grindstone technique (Scheme 1a). In another recent study, a one-pot, base-catalyzed tandem reaction involving sequential aldol condensation and Michael addition was developed by Hu et al. for the synthesis of 3,4,5-trisubstituted isoxazoles (**94**) by hand grinding (Scheme 1b) [138]. The grinding of aromatic aldehydes (**90**) and 3,5-dimethyl-4-nitroisoxazole (**91**) in the presence of pyrrolidine provided 5-styryl-3-methyl-4-nitroisoxazoles (**92**) via aldol condensation within just 3–10 min. The Michael addition between the aldol product (**92**) and active



Scheme 1. Other multicomponent reactions aided by grindstone chemistry.



Scheme 2. Regio- and stereo-selective synthesis of dihydroindeno[1,2-*b*]pyrrole derivatives (**98**) by hand-grinding [142].

methylene compounds (**93**) in the presence of Et_3N furnished (**94**) in up to 93% yields by grinding for another 3–5 min in the same mortar. It was observed that the protocol works only for malononitrile derivatives or nitroacetates but failed to give any product with ethyl acetoacetate or acetylacetone even after prolonged grinding.

3. Heterocycle synthesis by grindstone chemistry

Heterocyclic scaffolds are widely abundant among a variety of natural products including alkaloids, natural dyes, drugs, proteins, enzymes, etc. A large variety of heterocycles were prepared by simple grinding in a mortar-pestle by various two-component and multicomponent cyclocondensation reactions. The vast literature in this direction is presented below based on their core structures. The subsections are made based on the ring size and the number of heteroatoms present.

3.1. Five-membered heterocycles with a single heteroatom

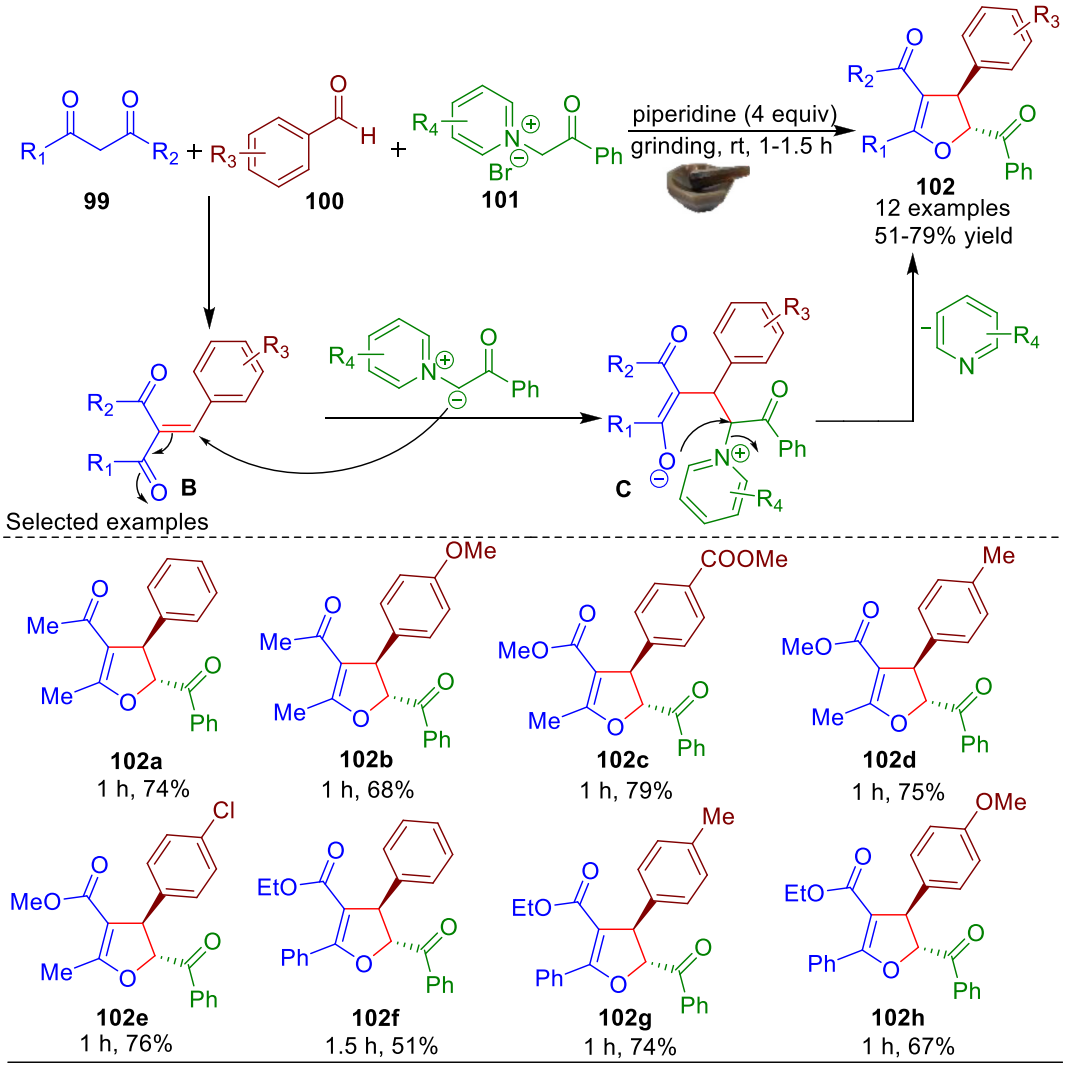
3.1.1. Pyrroles

Pyrrole or pyrrolidine is a common structural scaffold of several natural products and is one of the most explored heterocycles in drug discovery research [139,140]. Their profound bioactivities have motivated the development of various strategies for their synthesis [140,141]. Perumal and coworkers synthesized highly

functionalized indenone-fused dihydropyrroles (**98**) in a regio- and stereo-selective manner using a hand-grinding protocol (Scheme 2) [142]. The grinding of equimolar amounts of (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones (**95**) with anilines (**96**) and ninhydrin (**97**) in the presence of a few drops of acetic acid for a period of 5–8 min led to the construction of 3-aroyl-3a,8b-dihydroxy-1-aryl-1,8*b*-dihydroindeno[1,2-*b*]pyrrol-4(3*aH*)-ones (**98**) with *cis*-ring junction stereochemistry. A model reaction to prepare dihydroindeno[1,2-*b*]pyrroles, **98a** in the solution phase (DMF, TFA or water) afforded poor yields of the desired product even after employing a variety of catalysts such as CAN, *p*-TSA, $InCl_3$, or AcOH, and high temperature. Whereas, the reaction afforded 96% yield of **98a** in just 6 min of grinding the substrates with 0.1 mL of acetic acid per mmol of **95** (η = 0.2 μL/mg of solid substrates). Thus, liquid-assisted grinding expedited the reaction by several folds. As it can be seen in the selected examples, the protocol could be successfully extended to several aromatic, aliphatic (viz. n-propyl, *n*-butyl, cyclopropyl), or benzylamines in **96** and a variety of aryl and heteroaryl in enaminoketones (**95**) to generate a broad library of 22 dihydropyrrole heterocycles (**98**) in 84–94% of yields. The domino transformation follows an initial Michael addition of aniline (**96**) to enaminoketones (**95**) followed byelimination of dimethylamine and attack of the corresponding enaminoketones to ninhydrin (**97**) leading to the formation of intermediate **A**, which undergoes intramolecular cyclization to afford the title compound, **98**. No significant substituent effect was seen in terms of yield or reaction time. After completion, the reaction mixture was triturated with crushed ice, the resulting solid filtered off to afford sufficiently pure 3-aroyl-3a,8b-dihydroxy-1-aryl-1,8b-dihydroindeno[1,2-*b*]pyrrol-4(3*aH*)-ones (**98**) offering a simple way of product isolation without column chromatography. The low E-factor (0.44) makes the protocol an efficient one for the synthesis of dihydroindeno[1,2-*b*]pyrroles.

3.1.2. Furans

Furan, an oxygen-containing five-membered heterocycle, features in several pharmaceutically important molecules [143,144]. This instigates the development of environmentally benign synthetic methods for a variety of compounds containing this heterocyclic scaffold [145]. Among available grinding protocols, Chuang and Chen developed a one-pot three-component route for the synthesis of highly functionalized 2,3-dihydrofurans (**102**) from 1,3-dicarbonyl compounds (**99**), aromatic aldehydes (**100**), and *N*-phenacylpyridinium bromides (**101**) in a diastereoselective manner (Scheme 3) [146]. Initially, they developed a solution-phase method by heating the reaction mixture in acetonitrile at 60 °C for 14 h to

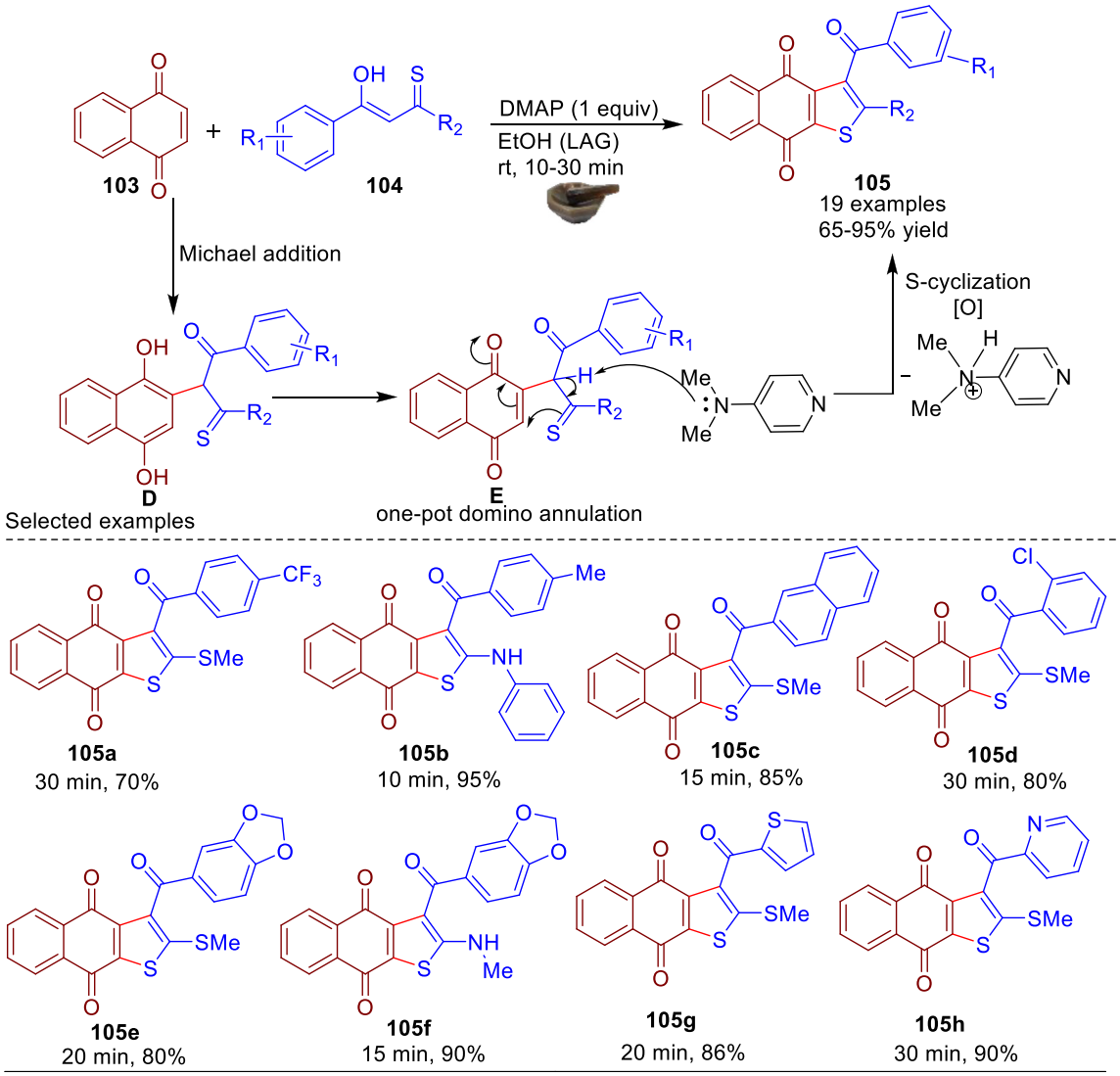


Scheme 3. The diastereoselective synthesis of 2,3-dihydrofurans (**102**) via a one-pot three-component route [146].

afford 2,3-dihydrofurans (**102**) in high yields, however, the reaction time was shortened to just 1 h when the substrates (**99**–**101**) were manually ground in a mortar-pestle. The presence of a Lewis base was required to catalyze the reaction and a short screening revealed that 2.5 equiv of piperidine gave the best results among the options tried (e.g. DABCO, DBU, etc.). The authors proposed that benzylidene-1,3-dicarbonyl compounds (**B**) were generated *in situ* by grinding **99** and **100**, which is followed by a Michael addition of pyridinium ylide, formed by the action of piperidine on **101**, to form Michael adduct **C** and its subsequent intramolecular cyclization of afforded 2,3-dihydrofurans (**102**) with *trans*-stereoselectivity. The method worked equally well with both EDGs and EWGs in the aromatic aldehydes and different 1,3-dicarbonyl compounds delivering the products in moderate to good yields (Scheme 3). The E-factor of this protocol was 3.74.

3.1.3. Thiophenes

Thiophene moiety is common in many therapeutically active agents and fused thiophenes are an important class of heterocycles due to the broad spectrum of biological activities [147,148]. Singh and coworkers developed the DMAP promoted mechanochemical route using solvent-drop grinding for the synthesis of highly regioselective naphtho[2,3-*b*]thiophenes (**105**) [149], a class of compounds which is known for significant cytotoxicity against several human solid tumors [150]. The thiophene fused naphthoquinone derivatives (**105**) were synthesized by grinding 1,4-naphthoquinone (**103**) with α-enolicdithioesters and β-oxothioamides (**104**) via a [3 + 2] oxidative heteroannulation process (Scheme 4) [149]. Notably, no additional co-catalyst or activator was necessary for the reaction. On screening with various bases including DABCO, TEA, TBU, pyridine, it was observed that 1 equiv DMAP afforded better yields. The reaction mechanism was proposed to proceed through the formation of Michael adduct **D**. The intermediate **D** upon *in-situ* oxidation forms **E** that undergoes regioselective [3 + 2] S-cyclization to exclusively furnish the desired 2,3-disubstituted naphtho[2,3-*b*]thiophene-4,9-diones (**105**). It was observed that α-enolicdithioesters (**104**) bearing electron-donating groups reacted faster and furnished the desired products (**105b,c, 105e,f**) in better yields than those (**105a**,**105d**) derived from **104** with electron-withdrawing groups. Even electron-rich heteroaromatic α-enolicdithioesters were tolerated well, offering similar yields of the corresponding products (**105g**,**h**).



Scheme 4. DMAP promoted regioselective mechanochemical synthesis of 2,3-disubstituted naphtho[2,3-*b*]thiophene-4,9-diones (**105**) in mortar-pestle [149].

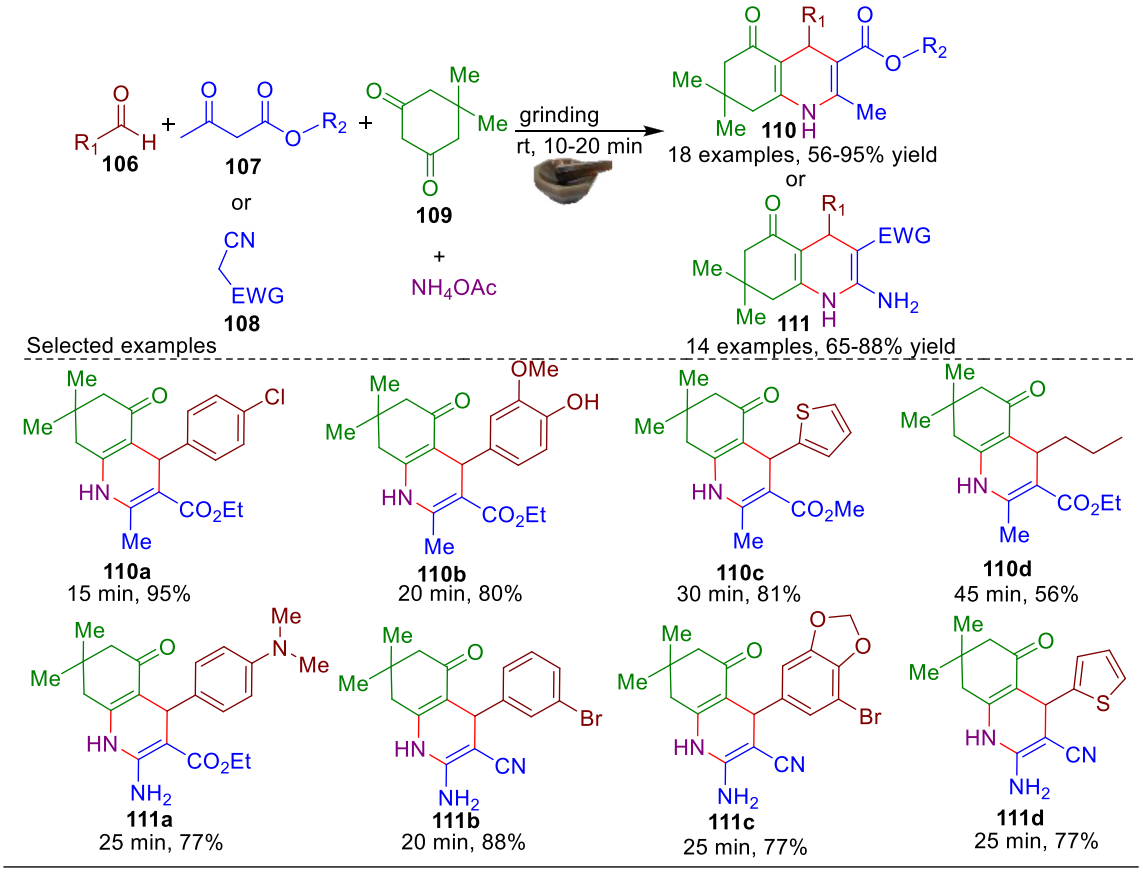
3.2. Six-membered heterocycles with a single heteroatom

3.2.1. Pyridines

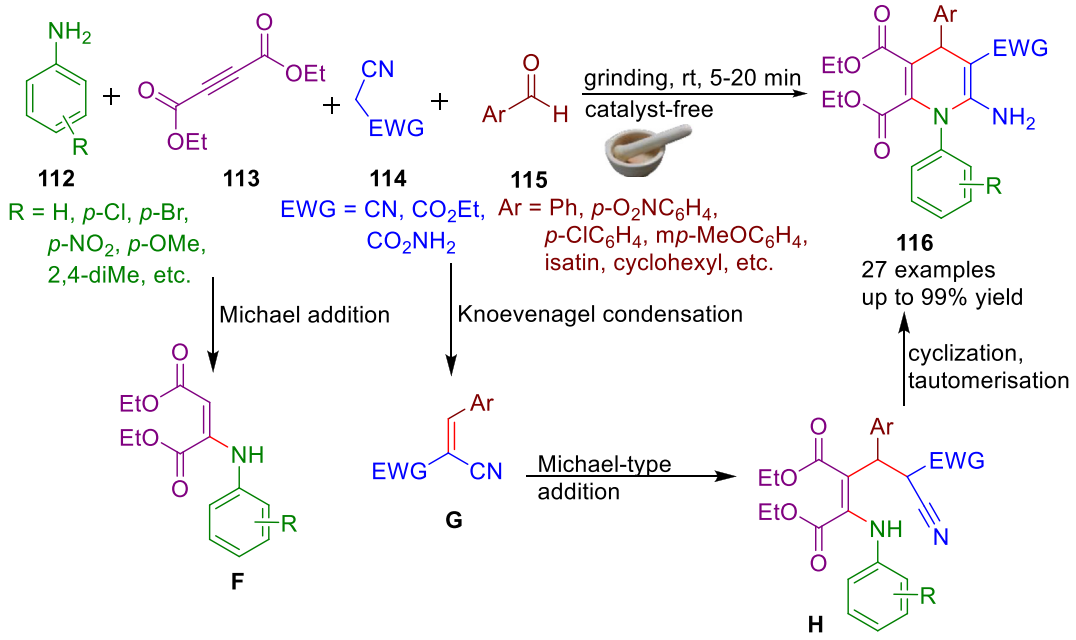
Pyridines and their derivatives are among the most prevalent heterocyclic scaffolds found in natural products, pharmaceuticals and specific functional materials and are known to possess significant biological activities such as antimicrobial, anticonvulsant, antiviral, antiHIV, anticancer, anti-inflammatory activities [151]. There are several methods for the synthesis of this important scaffold in conventional media violating several greener aspects [152–154]. In 2008, a mechanochemical version of Hantzsch synthesis of dihydropyrans was reported by Kapoor and coworkers (Scheme 5) [155]. The synthesis of 18 examples of hexahydroquinolines derivatives (**110**) involved the grinding of four components of aldehydes (**106**), β-ketoesters (**107**), dimedone (**109**), and ammonium acetate together in an Agate mortar-pestle for 10–20 min. The group reported that the optimization studies resulted in mediocre yield (55%) of product **110a** from benzaldehyde when the reaction was carried out in refluxing ethanol for 4 h, however, the solvent-free grindstone protocol furnished the same compound (**110a**) in 95% yield in 15 min. In a similar manner, 14 examples of 2-amino-hexahydroquinoline derivatives (**111**) were synthesized by taking a malononitrile/cyanoesters derivative (**108**) instead of β-ketoesters (**107**) in up to 88% yields. The versatility of the method was demonstrated with both electron-rich and electron-deficient aromatic aldehydes (selected entries **110a**,**b** and **111a**-**c**) as well as heteroaromatic aldehydes (selected entries **110c**, **111d**). However, the percent yield of the product dropped significantly for aliphatic aldehydes (entry **110d**).

Kumar and Sharma developed a grindstone method for the synthesis of another series of highly functionalized 1,4-dihydropyridines (**116**), a class of compounds which show cardiovascular and antihypertensive activity [156]. The reaction proceeds via a domino multicomponent reaction involving the grinding of amines (**112**), diethyl acetylenedicarboxylate (**113**), active methylene compounds (**114**) and aldehydes (**115**) in an Agate mortar-pestle for just 5–20 min in the absence of any catalyst (Scheme 6). A variety of aromatic amines (**112**) and aromatic aldehydes (**115**) were ground with **113** and **114** to afford 27 examples of the desired products (**116**) in 79–99% yields. However, isatin or aliphatic aldehydes did not afford any product. The reaction is proposed to proceed via an aza-Michael addition between **112** and **113** to form intermediate **F**, and a Knoevenagel condensation of **114** with **115** to form intermediate **G**. Another Michael type addition between donor **F** and acceptor **G** resulted in the formation of the adduct **H**, which on subsequent cyclization and tautomerization afforded the products (**116**).

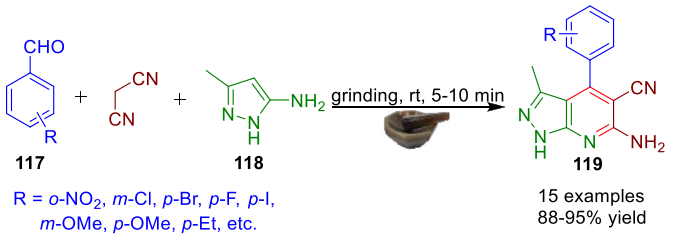
One of the earlier reports on the cyclocondensation of chalcone, malononitrile and NH_4OAc to pyridine derivatives using grindstone technique was reported by Gupta et al., in 2010 [157]. In recent times, Nikpassand and coworkers demonstrated a one-pot, catalyst-free grinding procedure for the synthesis of [6-amino-3-methyl-4-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**119**) having potential antiherpetic, antimicrobial and antitumor activ-



Scheme 5. One-pot, four-component synthesis of polyhydroquinolines (**110** or **111**) [155].



Scheme 6. Synthesis of highly functionalized 1,4-dihydropyridines (**116**) via a domino multicomponent synthesis [156].



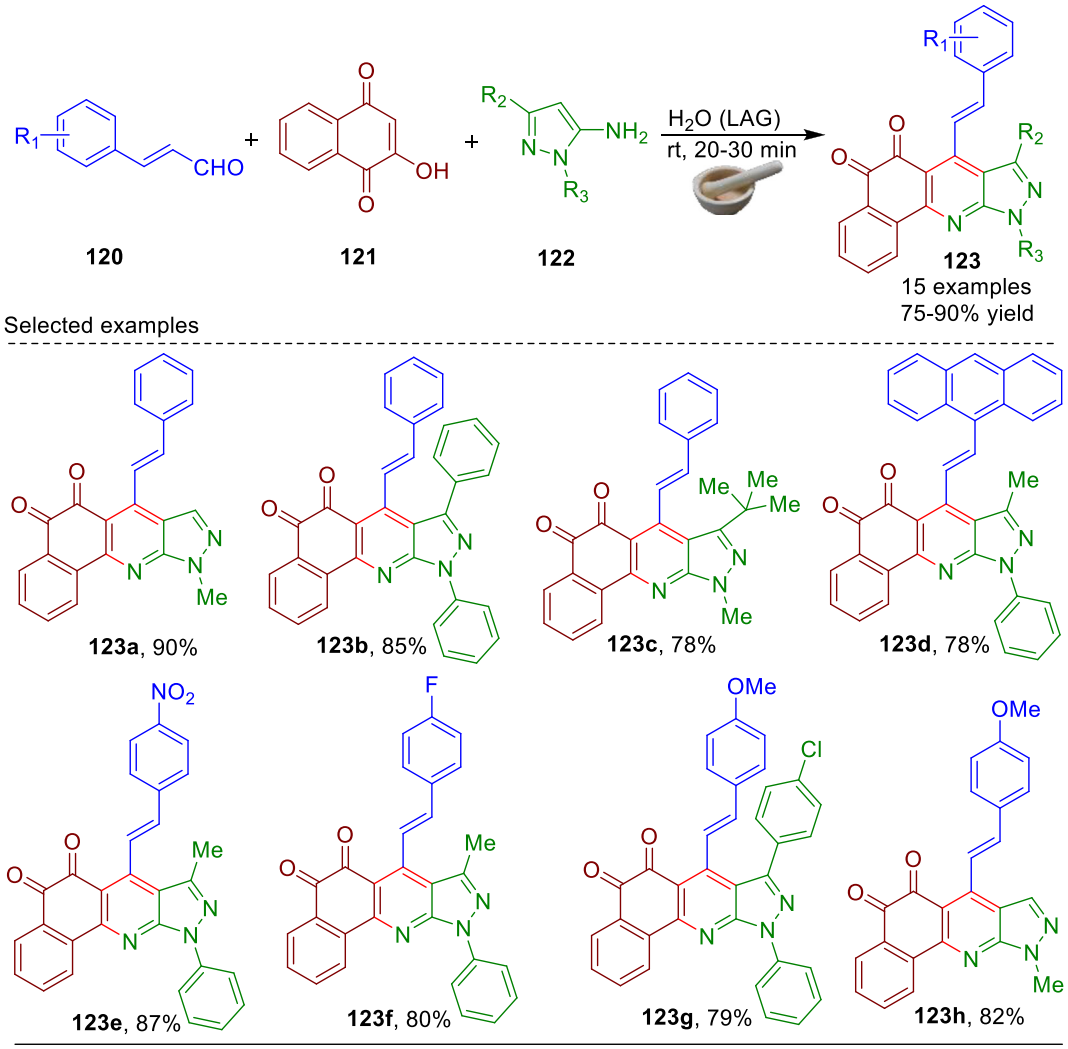
Scheme 7. Synthesis of 6-amino-3-methyl-4-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**119**) [158].

ities (Scheme 7) [158]. The cyclo-condensation of substituted benzaldehydes (**117**), 3-amino-5-methylpyrazole (**118**), and malononitrile afforded the pyridine derivatives (**119**) in excess of 90% yields in most of the cases. The optimization studies on model substrates employing Lewis acids (e.g. $ZnCl_2$, K10, and nano-Fe_3O_4) or Lewis bases (L-proline) as catalyst in refluxing EtOH hardly affected complete conversion to the desired product. Even the use of other green media, the ionic liquids (e.g. [bmim]BF_4) at elevated temperature (80 °C) could offer products in much lower yields. The protocol was validated with various substituents in the aromatic ring of the aldehydes (**117**) and no substituent effect was observed both in terms of yields or the rate of the reaction.

Yadav and Parvin reported a protocol for the construction of pyrazole-fused pyridine ring by liquid assisted grinding of α,β-unsaturated aldehydes (**120**), 2-hydroxy-1,4-naphthoquinone (**121**) and 5-aminopyrazoles (**122**) in the presence of water as LAG agent (η = 0.25 μL/mg of substrate) (Scheme 8) [159]. This three-component reaction yielded styryl-linked benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-diones (**123**) by grinding the reactants in a porcelain mortar for 20–30 min in the presence of 0.25 μL of H_2O per mg of substrate. The optimization studies revealed that the reaction under neat conditions was sluggish producing **123a** in 68% yield after 80 min of rigorous grinding, whereas, the same reaction got completed within 25 min with 86% yield of **123a** upon the addition of water as an additive. Notably, the reaction in refluxing ethanol could afford 40% yield of **123a** and the addition of *p*-TSA (10 mol%) as the catalyst could not show much improvement (45% yield after 1.5 h). It was considered that the reactions proceed via an initial Knoevenagel condensation between **120** and **121** followed by Michael addition of 1,3-disubstituted-5-amino-pyrazole (**122**), cyclization and subsequent aerial oxidation to produce pyrazolo[3,4-*b*]quinolone derivatives (**123**). Different cinnamaldehyde derivatives (**120**) as well as a variety of 5-amino-pyrazoles with aromatic and aliphatic ssubstituents at 1- and 3-positions (**122**) participated equally to afford yields of corresponding products (**123**) in a range of 75–90% and so, no significant substituent effect was observed (Scheme 8).

3.2.2. Pyrans

The pyran ring is the core part of various classes of biologically and pharmaceutically important heterocycles like benzopyrans, chromones, coumarins, flavonoids, xanthones, and naphthoquinones [160,161]. Recently, a one-pot multicomponent reaction was reported by Awasthi and coworkers for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans (**125**), a class of heterocycle with a range of bioactivities including anticoagulant, antitumor, anticancer, antiallergic, diuretic, antibacterial activities [162]. A mixture of aromatic aldehydes (**124**), dimedone (**109**) and malononitrile were ground in a mortar-pestle for just 2–10 min to afford 2-amino-4*H*-benzo[*b*]pyran derivatives (**125**) in high to excellent yields (Scheme 9) [162]. The reactions were catalyzed by a specially designed amine functionalized magnetic nano-particle, NH_2@SiO_2@Fe_3O_4, as the heterogenous catalytic system. An amount of 10 mg of catalyst per mmol of **124** was found optimum for faster reactions and better yields. The amine functionality in NH_2@SiO_2@Fe_3O_4 has a definite role to play in catalyzing Knoevenagel condensation followed by Michael addition steps as a Lewis and subsequent intramolecular cyclization, protonation leads to tetrahydrobenzo[*b*]pyrans (**125**). As seen in Scheme 9, aromatic aldehydes containing electron-

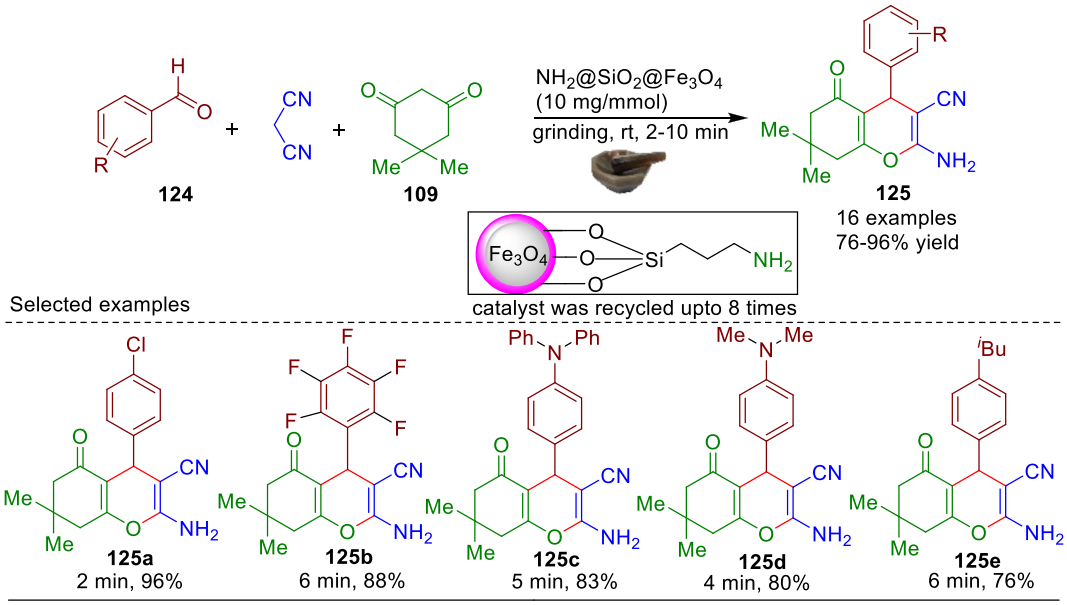


Scheme 8. Liquid assisted synthesis of styryl linked benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-diones (**123**) [159].

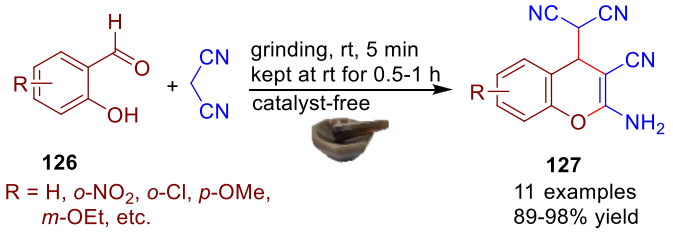
withdrawing groups provided the expected products (**125a**,**b**) in relatively higher yields than those with electron-donating groups (see entries **125c**-**e**). They demonstrated that the catalyst (NH_2@SiO_2@Fe_3O_4) could be recycled up to eight times with a nominal drop in %conversion. The estimated E-factor was as low as 0.08 and a high atom economy (95.4%) ensured the grinding protocol a more viable alternative than several other existing methods for tetrahydrobenzo[*b*]pyrans [162]. In an earlier work, Thangamani employed the grindstone technique to synthesize biologically active 2-amino-4*H*-benzo[*b*]pyran derivatives by grinding various substituted aromatic aldehydes, dimedone, and malononitrile in the presence of solid sodium ethoxide (10 mol%) as catalyst [163].

Chromene or 1-benzopyran are ubiquitous among several natural products and display a spectrum of biological activities [164]. Trivedi and coworkers investigated the condensation of malononitrile with salicylaldehyde (**126**) towards the synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl)malononitriles (**127**) using three different strategies i.e. mechanochemical grinding, thermal heating and direct crystallization (Scheme 10) [165]. The strategy involving catalyst-free grinding delivered the best results affording the products (**127**) in up to 98% yields when the ratio of **126** and malononitrile was kept as 1:2. After grinding was complete, reaction mixtures were kept at room temperature for 0.5–1 h for complete conversion. As compared to mechanochemical grinding, thermal heating and direct crystallization yielded the desired product (**127**) in lower yields (<50%) in an equimolar ratio of the substrates. The generality of the protocol was established by reacting various salicylaldehyde derivatives (**126**) with malononitrile to prepare a short library of 11 examples of **127**. The strategy was further extended towards the synthesis of quinoline derivatives via grinding of malononitrile with *o*-aminobenzaldehydes under neat conditions.

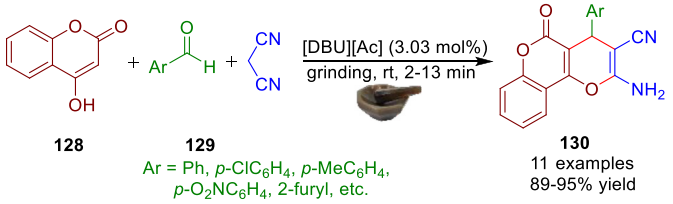
In a similar line, Raval and coworkers described a grindstone assisted multicomponent synthetic route to 3,4-dihydropyrano[*c*] chromene derivatives [**130**] by ionic liquid assisted grinding of a mixture of 4-hydroxycoumarin (**128**), aromatic aldehydes (**129**) and malononitrile at ambient temperature (Scheme 11) [75]. The reaction was catalyzed by the ionic liquid, [DBU][Ac], which was separately prepared from DBU and acetic acid by ultrasound irradiation [166]. The model reaction, carried out by them, did not proceed in the absence of the ionic liquid but smoothly resulted the product (**130a**) in the presence of just 3.03 mol% of [DBU][Ac] in 5 min. They prepared 11 examples of **130** taking both EDGs or EWGs in the aldehyde (**129**) with >90% yields in most of the cases. The catalyst, [DBU][Ac], could be successfully recycled up to 5 cycles without much depreciation in the yields.



Scheme 9. Synthesis of 2-amino-4*H*-benzo[*b*]pyran derivatives (**125**) by amine functionalized nano-catalyst, NH_2@ SiO_2@Fe_3O_4 [162].



Scheme 10. Mechanochemical synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl) malononitrile (**127**) [165].

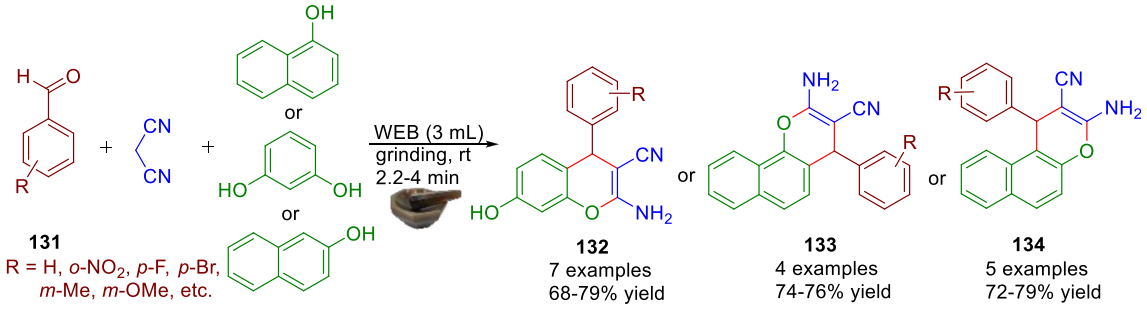


Scheme 11. Synthetic route to access 3,4-dihydropyrano[*c*]chromene derivatives (**130**) using grindstone chemistry [75].

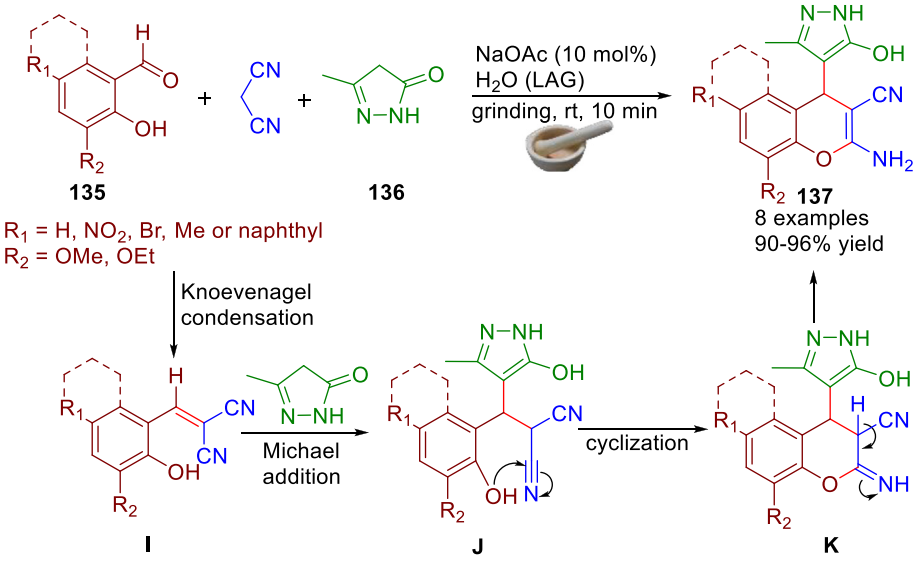
In order to use a green catalyst in a green protocol, Kantharaju and Khatavi used water extract of banana (WEB) to catalyze the synthesis of 2-amino-4*H*-chromene derivatives (**132**–**134**) from several benzaldehydes (**131**), malononitrile and α/β-naphthol (or resorcinol) in a mortar-pestle (Scheme 12) [167]. WEB from the agro-waste of banana-peels ash has a basic character and the extract also provides a media for liquid-assisted grinding of the substrates.

They observed that 3 mL per mmol of the substrate was the ideal volume of WEB required for the above conversion. The employment of resorcinol, α-naphthol and β-naphthol furnished the corresponding products (**132**) in 68–79% (7 examples), **133** in 74–79% (4 examples) and **134** in 72–76% (5 examples), respectively. The bioassay of some of these chromene derivatives showed good antimicrobial activities.

In another solvent-free approach to chromene synthesis, Elinson et al. demonstrated the condensation of salicylaldehydes (**135**), malononitrile and 3-methyl-2-pyrazolin-5-one (**136**) in a porcelain mortar-pestle [168]. The three-component reactions were catalyzed by sodium acetate in the presence of small quantities of water as a LAG agent to furnish 2-amino-4-(1*H*-pyrazol-4-yl)-4*H*-chromenes (**137**) in excellent yields (Scheme 13) [168]. In



Scheme 12. Use of water extract of banana (WEB) for the synthesis of 2-amino-4*H*-chromene derivatives (**132**–**134**) [167].

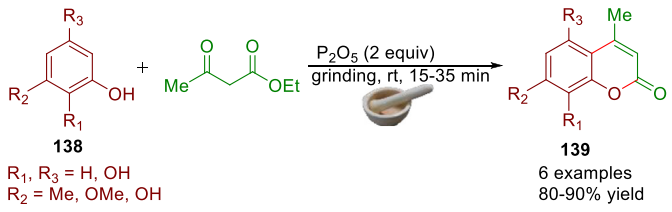


Scheme 13. Multicomponent synthesis of substituted 2-amino-4-(1*H*-pyrazol-4-yl)-4*H*-chromenes (**137**) by LAG with water [168].

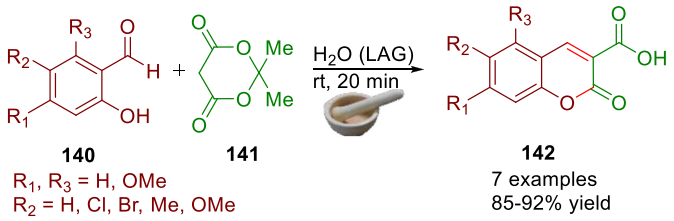
model reactions it was observed that 10 mol% of NaOAc and 0.5 mL of water per mmol of the substrate was ideal for LAG to achieve 95% yield of the desired product after 10 min of grinding while the reaction was sluggish in the absence or lower mol% of the catalyst. According to the proposed mechanism, sodium acetate catalyzes a Knoevenagel condensation between **135** and malononitrile and the corresponding adduct **I** reacts with **136** via a Michael addition to form **J,** which subsequently cyclizes to **K** and tautomerizes to form **137**. The easy product separation by water wash of the catalyst is a merit of this grindstone protocol.

Coumarins are ubiquitous among many natural products and are important intermediates in industries like pharmaceuticals, perfumes, cosmetics, etc. [169]. This has fascinated chemists towards developing various methods for their synthesis [170]. One of the common routes for coumarin synthesis is Pechmann condensation [171], which was adopted by Narwal et al. employing a hand-grinding technique to synthesize various coumarin derivatives (**139**) from activated phenols (**138**) and ethyl acetoacetate in the solid phase (Scheme 14) [172]. Both phenols (**138**) and ethylacetoacetate were ground in the presence of P_2O_5 in a porcelain mortar-pestle to furnish a small library of coumarin derivatives within a short period of time in excellent yields. Employment of two equivalents of anhydrous P_2O_5 produced the maximum yield of the products. In a similar study, Jain et al. demonstrated a two-component approach to access coumarins via Pechmann condensation involving substituted phenols and α-keto esters in the presence of catalytic amount of *p*-TSA [173].

Kumar et al. developed a grindstone protocol for the synthesis of 3-carboxycoumarins, which are key synthetic intermediates of cephalosporins, penicillins, isoureas and oxygen-bridged



Scheme 14. Grindstone assisted Pechmann condensation for the synthesis of coumarin derivatives (**139**) [172].



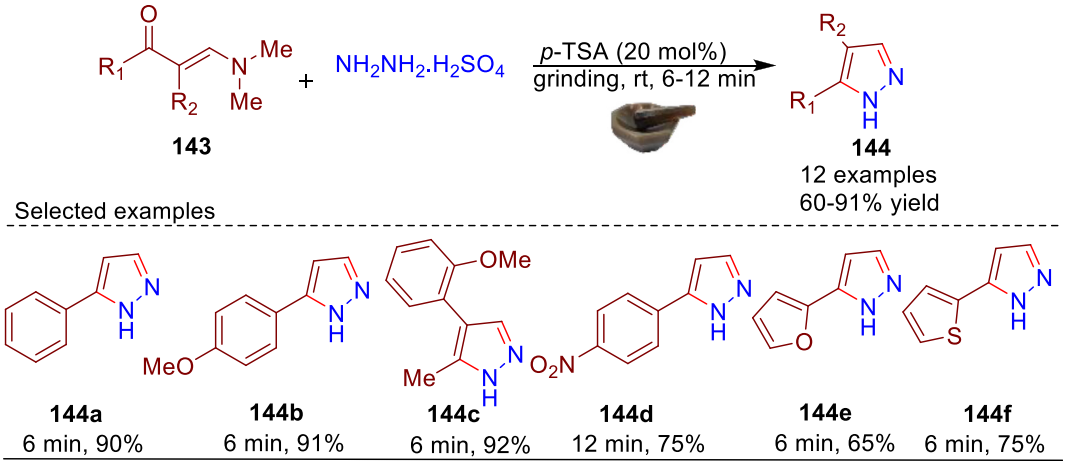
Scheme 15. Synthesis of 3-carboxycoumarin derivatives (**142**) by water-assisted grinding [174].

tetrahydropyridones compounds [174]. Grinding of various 2-hydroxybenzaldehydes (**140**) with Meldrum's acid (**141**) in a catalyst-free condition gave high to excellent yields of 3-carboxycoumarin derivatives (**142**) (Scheme 15). The reaction mixture was moistened with a few drops of water to assist grinding of mostly a solid mass of substrates at room temperature. After 20 min of grinding, the reaction mixture was left at room temperature for another 40 min for complete conversion (yield: 85–92%). The grinding protocol offers a facile synthetic route to these biologically important coumarin derivatives in a non-hazardous way devoid of organic solvents and costly catalysts, which are usually required for their synthesis in the conventional ways [175].

3.3. *Five-membered with two heteroatoms*

3.3.1. *Pyrazoles*

Pyrazoles and their derivatives display a plethora of biological activities such as antimicrobial, anticancer, antidepressant, etc. [176,177]. There are several reports on the synthesis of these compounds in conventional media having drawbacks like the use of organic solvents, strong base and long reaction times [178]. In 2010, Martins and coworkers described a solvent-free mechanochemical protocol for the synthesis of pyrazoles (**144**) by condensation of β-dimethylaminovinylketones (**143**) and hydrazine (as H_2SO_4 salt) in the presence of *p*-TSA (20 mol%) as catalyst (Scheme 16) [179]. The optimization studies revealed that the reaction does not proceed in neat conditions, however, the use of 50% *p*-TSA as catalyst resulted in the formation of the desired product, **144a**, with a decent yield of



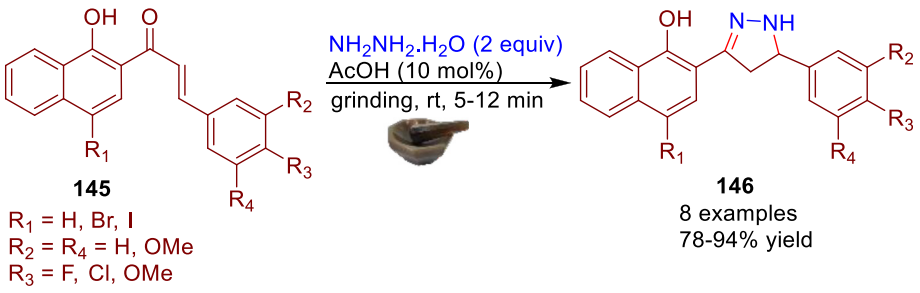
Scheme 16. Mechanochemical protocol for the synthesis of substituted pyrazoles (**144**) [179].

64% after 6 min. Upon reduction of the catalyst concentration to 20%, the yield of **144a** improved to 90%. The screening of catalysts and grinding matrices such as SiO_2, $KHSO_4$, and $NaHSO_4$ could not afford a better yield. Notably, under classical reaction conditions, heating in ethanol in the presence of *p*-TSA afforded 79% of **144a** only after 2 h. Thus, the grinding condition was a much facile approach for the synthesis of pyrazoles (**144**). It was proposed that the grinding generates heat leading to melting of the substrates in the reaction mixture to provide a uniformly distributed liquid phase with a high density of reactants in close contacts to propel the reaction to completion in just a few minutes. The validation study with different β-enaminones derivatives (**143**) including heteroaromatic substrates, afforded the respective products (**144**) with yield in the range of 60–91%. It was observed that the products bearing electron-donating groups (**144b**,**c**) formed at a faster rate, whereas, the presence of strong electron-withdrawing groups in the substrates slows down the product formation (e.g. **144d** took 12 min). This protocol was successfully employed towards the large-scale synthesis of pyrazoles following the same reaction kinetics with no drop in the yield (e.g. **144a** was obtained in 90 and 92% yields for 25 mmol and 50 mmol batches, respectively in 6 min).

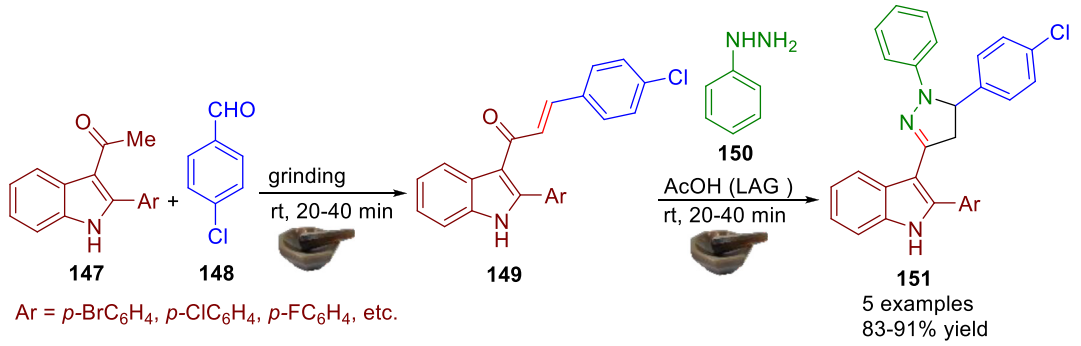
In a similar approach, Vibhute and coworkers developed a grindstone strategy towards the synthesis of 2-pyrazolines (**146**) by reacting different substituted 2′-hydroxychalcones (**145**) with hydrazine hydrate under LAG conditions (Scheme 17) [180]. The group synthesized 8 pyrazoline compounds (**146**) using acetic acid (10 mol%) ($\eta = 0.19$ μL/mg of substrates) as the catalyst to afford the products with a yield of 78–94% within a short span of 5–12 min of grinding. AcOH played the dual role of a catalyst and an LAG agent.

Pathak and coworkers adopted the grinding technique to bring about the cyclization of indolylchalcone (**149**) with phenylhydrazine (**150**) to afford 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-*N*1-phenylpyrazoles (**151**) (Scheme 18) [181]. The synthesis of **149** by grinding 3-acetyl-2-aryl-1*H*-indoles (**147**) with *p*-chlorobenzaldehyde (**148**) in a mortar-pestle was previously reported by the same group [182]. The reaction progressed well in the presence of a few drops of acetic acid as the catalyst as well as the LAG agent and complete conversion was observed after grinding the substrates for 20–40 min in the mortar to afford the products (**151**) in 78–91% yield. In contrast, the same reaction under conventional conditions by refluxing in ethanol gave lower yields of **151** (yield of 71–79% after 6 h of reflux). The E-factor of the grinding method was much lower (0.152) than the solution-phase synthesis of **151** using EtOH (E-factor 103.93). The newly synthesized phenylpyrazoles (**151**) showed good antibacterial activities against *E. coli* and *S. aureus*, and also found potent antifungal agents against *C. albicans* and *A. niger*.

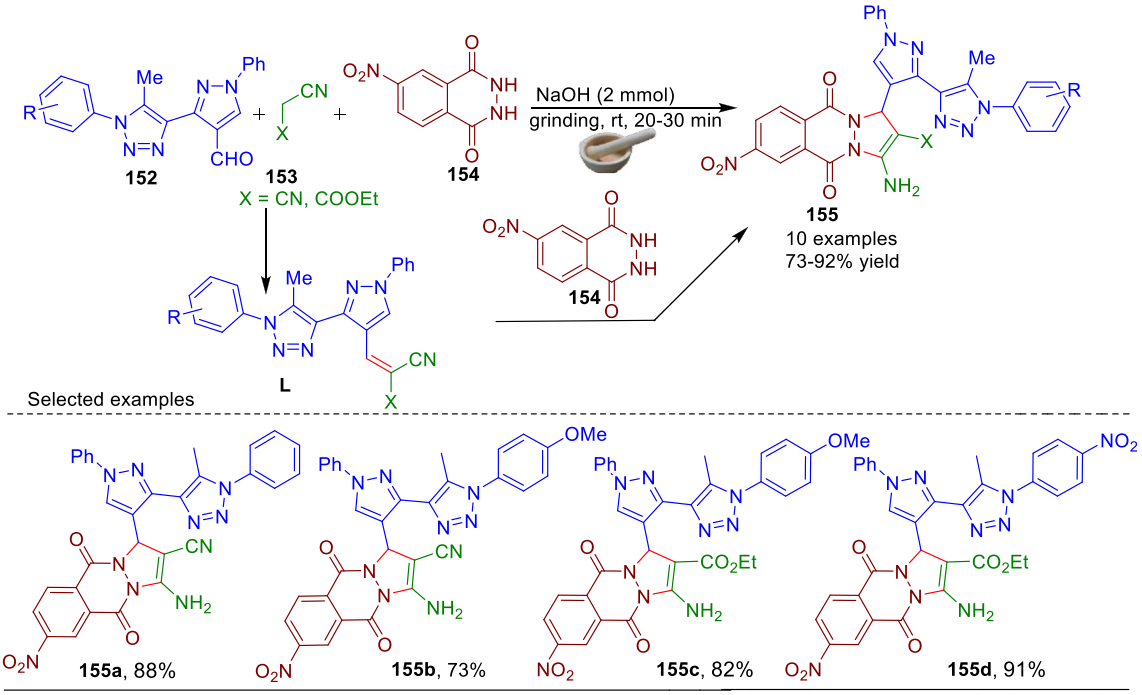
On the other hand, Rashdan et al. reported a one-pot three-component condensation reaction for the synthesis of novel pyrazolo[1,2-*b*]phthalazinedione derivatives (**155**) by employing grindstone chemistry (Scheme 19) [183]. The method involved the solvent-free grinding of 1,2,3-triazolyl-pyrazolecarbaldehydes (**152**), active methylene compounds (such as malononitriles or ethyl cyanoacetate) (**153**) and 6-nitrophthalhydrazide (**154**) in the presence of sodium hydroxide at room temperature for 20–30 min to afford products in 73–92% yields. The group first synthesized a series of hydrazones containing the 1,2,3-triazole moiety by grinding acetyl triazole derivatives with phenylhydrazine in the presence of a drop of glacial acetic acid, which were then subjected to Vilsmeier reaction conditions to deliver the 1,2,3-triazolyl-pyrazole-carbaldehyde (**152**) derivatives. The group reported that the



Scheme 17. Solvent-free synthesis of 2-pyrazolines (**146**) using grinding technique [180].



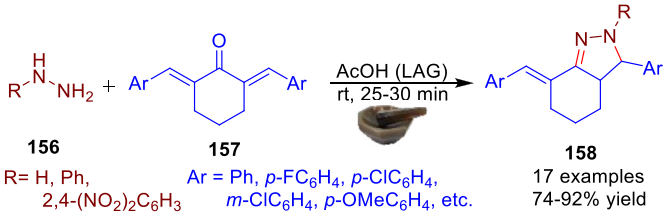
Scheme 18. Synthesis of 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-*N*1-phenylpyrazoles (**151**) using grindstone technique [181].



Scheme 19. Synthesis of novel pyrazolo[1,2-*b*]phthalazinedione derivatives (**155**) by employing grindstone chemistry [183].

formation of **155a** took 2 h time in refluxing ethanol, indicating the superiority of the grindstone technique over the solution-phase method. The reaction proceeds via Knoevenagel condensation to form heterylidenenitrile intermediate, **L** which upon Michael addition of the NH group of **154** to the olefinic bond of **L**, followed by cyclization affords the corresponding products in a facile way. Some of these pyrazolo[1,2-*b*]phthalazinedione derivatives (**155**) showed good antiproliferative activity toward hepatic cancer cells in *in-vitro* studies with IC_{50} values as low as 3.01 ± 0.21 μg/mL.

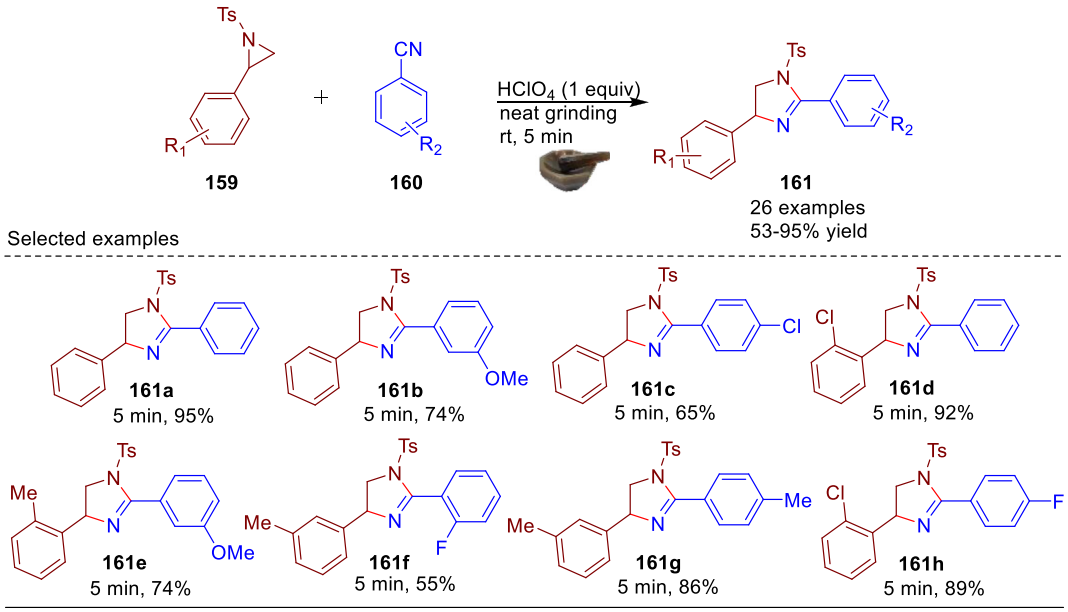
Very recently, Raut et al. explored the use of grindstone technique for the synthesis of 7-benzylidene-substituted phenyl-3,3*a*,4,5,6,7-hexahydro-2*H*-indazoles (**158**) involving the reaction between differently substituted hydrazines (**156**) and various 2,6-bis-(substituted-benzylidene)-cyclohexanones (**157**) in the presence of acetic acid (Scheme 20) [184]. The method was validated by synthesizing 17 examples in good to excellent yields.



Scheme 20. AcOH catalyzed synthesis of 7-benzylidene-substituted phenyl-3,3*a*,4,5,6,7-hexahydro-2*H*-indazoles (**158**) [184].

3.3.2. Imidazolines

2-Imidazolines are prevalent in natural products and are valuable intermediates for designing molecules with pharmacological activities and also applied in asymmetric catalysis [185]. Majee and coworkers described a mechanochemical protocol for the synthesis of 2-imidazoline derivatives [186]. This strategy involved solid-state co-grinding of *N*-tosylaziridines (**159**) and aromatic nitriles (**160**) in the presence of perchloric acid as the catalyst to deliver 2-imidazolines (**161**) in moderate to excellent yields (Scheme 21) [186]. The optimization studies carried out with different acid catalysts such as AcOH, TsOH, TFA, H_3PO_3 did not show any product formation (**161a**), whereas, HCl and H_2SO_4 resulted in poor yields of **161a**. Perchloric acid was found the most efficient catalyst for this

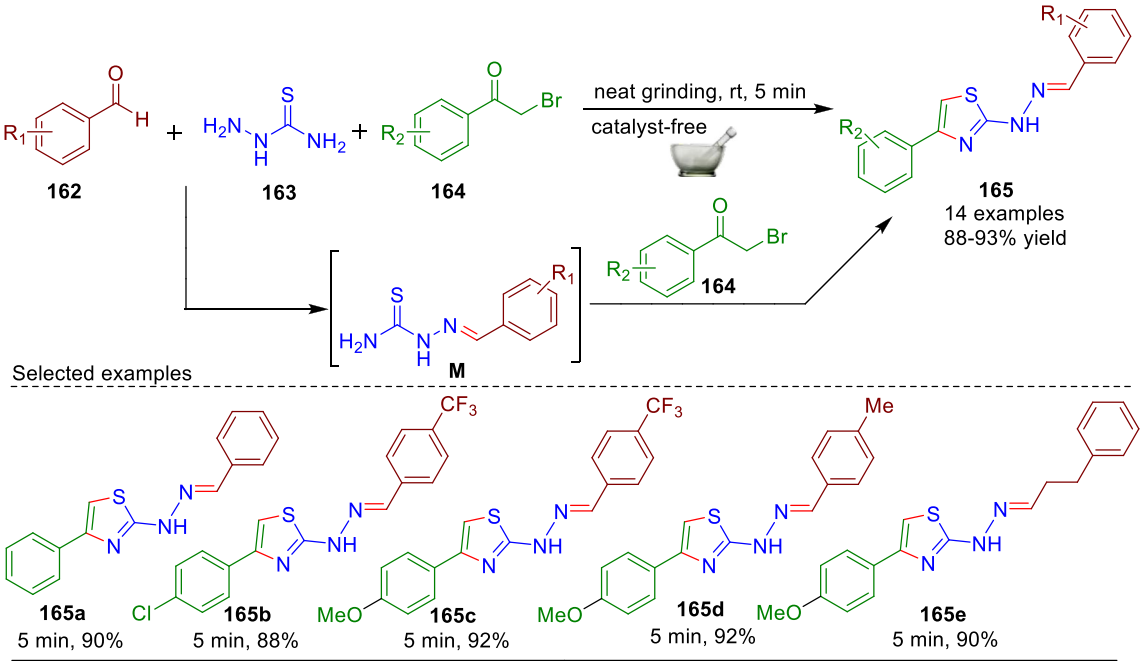


Scheme 21. $HClO_4$ catalyzed mechanochemical synthesis of 2-imidazoline derivatives (**161**) [186].

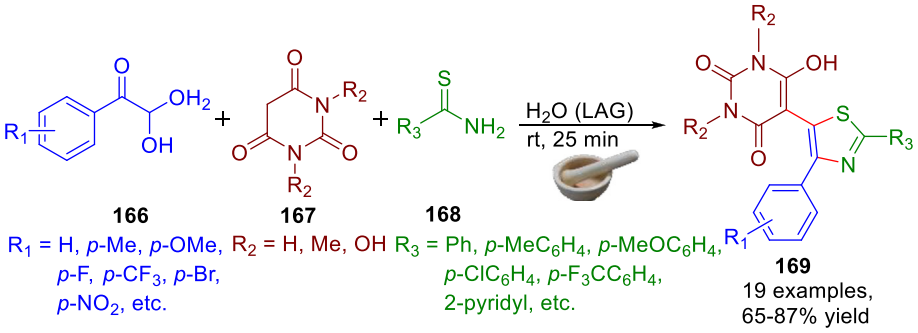
transformation affording 95% yield of **161a** within 5 min. As many as 26 substituted 2-imidazoline derivatives (**161**) were prepared by Majee's protocol. The method did not show strong substituent effects, however, in some cases with EWG in aromatic nitriles (**160**), a significant drop in the yield of the corresponding product was seen (entry **161f**, yield: 55%).

3.3.3. *Thiazoles*

Thiazoles and their benzo-fused derivatives are important and find growing applications as APIs [187]. Chen and coworkers described a grindstone-mediated one-pot multicomponent protocol for the synthesis of 2,4-disubstituted thiazole derivatives (**165**) by manually grinding of aromatic aldehydes (**162**), thiosemicarbazide (**163**) and α-bromoketones (**164**) under catalyst-free conditions in a glass mortar-pestle (Scheme 22) [188]. Interestingly, the optimization study revealed that the liquid-assisted grinding of α-bromoacetophenone, benzaldehyde and thiosemicarbazide in water and EtOH afforded the product, **165a** in 38% and 46% yields, respectively, whereas, the neat-grinding gave 90% yield of the same product within 5 min. The authors, based on the mechanistic studies, proposed that the condensation of **162** with **163** takes place at first, leading to the formation of 2-benzylidenehydrazine carbothioamide (**M**). The nucleophilic attack of *N*-atom of the thiourea unit to the α-carbon of α-bromoketones (**164**) followed by



Scheme 22. Synthesis of 2,4-disubstituted thiazole derivatives (**165**) under catalyst- and solvent-free grinding conditions [188].



Scheme 23. Synthesis of novel diphenyl-1,3-thiazole linked barbituric acid hybrids (**169**) by liquid-assisted grinding [189].

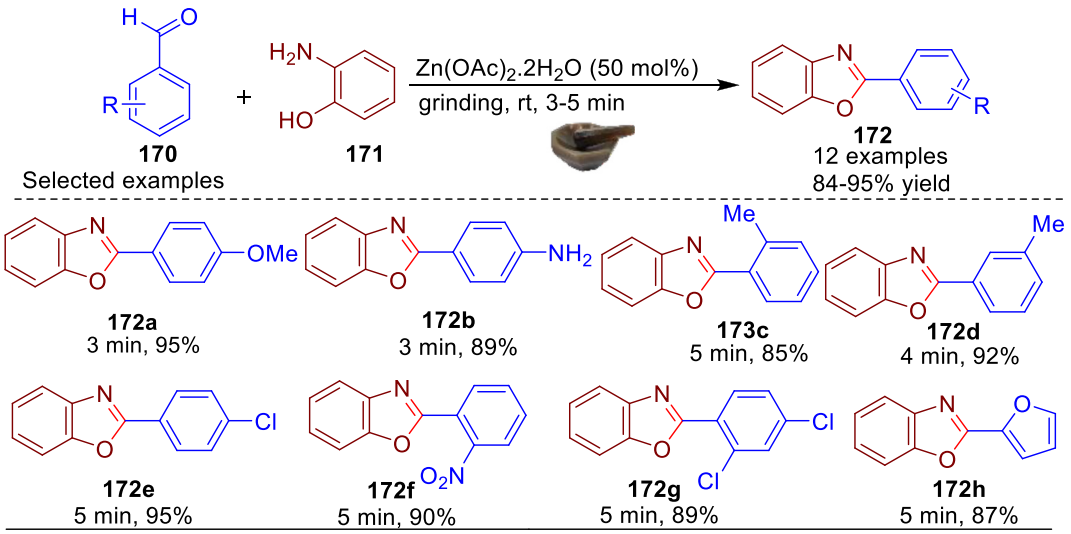
cyclo-condensation leads to the desired products (**165**). Various derivatives of **162** and **164** containing electron-withdrawing or electron-donating groups underwent smooth transformations to give the corresponding products (**165a-c**) in 88–93% yields. Likewise, the reactions of aliphatic aldehydes too progressed smoothly delivering the desired products in similar yields (entry **165e**).

In another approach, developed by Choudhury and coworkers, novel diphenyl-1,3-thiazole linked barbituric acid hybrids (**169**) were obtained by liquid assisted grinding of arylglyoxal (**166**), barbituric acid (**167**) and aryl thioamides (**168**) in the presence of a small amount of water (Scheme 23) [189]. They checked that the neat grinding of the substrates (**166**–**168**) delivers the product (**169**) only in moderate yield (55%) after 45 min. Interestingly, however, LAG in the presence of 2–3 drops of water afforded the same product in 83% at a shorter time (25 min). Notably, the same reaction by stirring in different solvents at room temperature took 12–24 h for completion. The method was validated by synthesizing 19 derivatives of **169**. Some of these thiazole derivatives showed blue emissions with good quantum yields in DMSO medium.

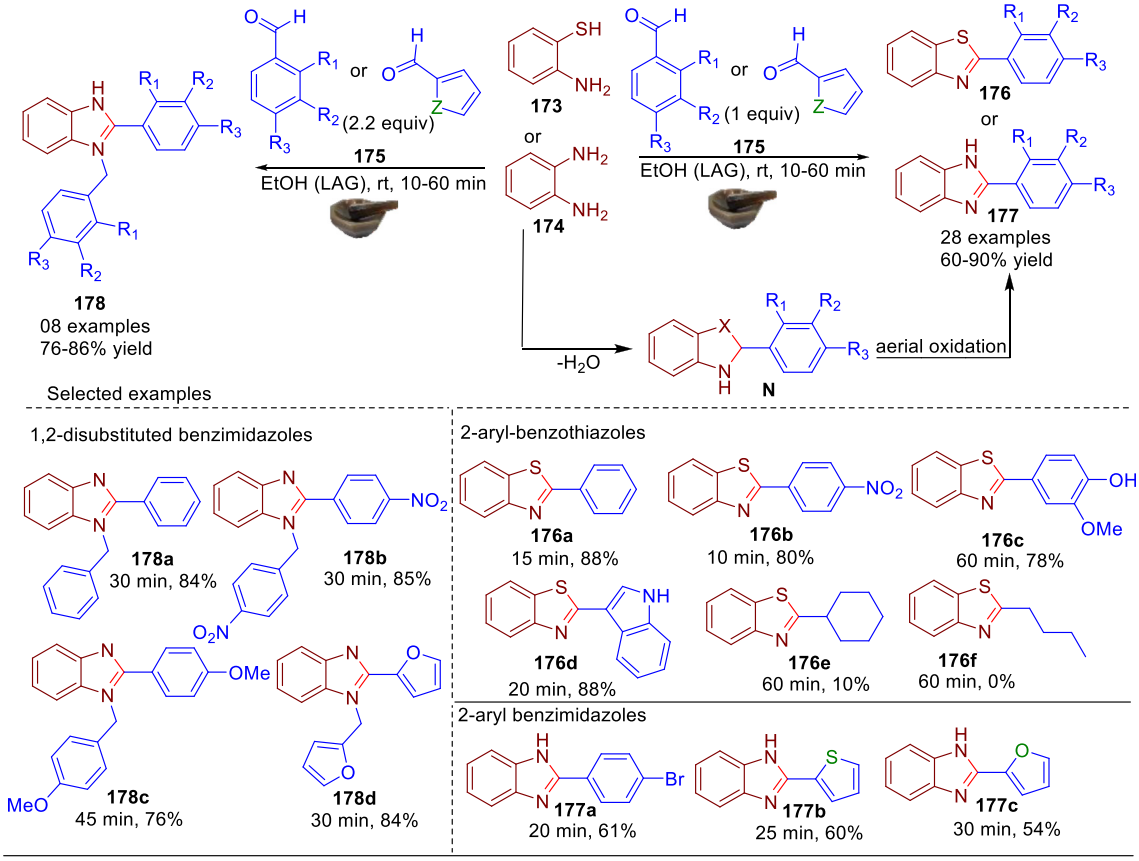
3.3.4. 1,3-Benzazoles: Benzimidazoles, benzoxazoles, benzothiazoles

1,3-Benzazoles, namely benzimidazoles, benzoxazoles and benzothiazoles display a wide range of bioactivities and form the core units of various marketed drugs [190–192]. Pasha and coworkers reported a simple grindstone strategy towards the synthesis of 2-substituted benzoxazoles (**172**), a scaffold of many biologically active compounds [193]. The synthesis involved the condensation of various aromatic aldehydes (**170**) with 2-aminophenol (**171**) catalyzed by $Zn(OAc)_2.2H_2O$ (50 mol%) in a mortar-pestle (Scheme 24). The optimization study using anisaldehyde as the model substrate, indicated no product (**172a**) formation in the absence of $Zn(OAc)_2.2H_2O$. However, a loading of 50 mol% of $Zn(OAc)_2.2H_2O$ was sufficient to form the benzoxazole derivatives (**172**) in 84–95% yields within just 3–5 min. The proposed mechanism involves an initial imine formation by condensation of **170** and **171**, and cyclization by the nucleophilic attack of the phenolic –OH group to the imine bond of the intermediate to form 2-substituted-2,3-dihydro-benzoxazole, which upon aerial oxidation produce benzoxazoles. The protocol was successfully employed to aldehydes containing both EDGs and EWGs with equal ease and hardly any substituent effect was observed in terms of reaction times and yields, although the number of examples was rather limited.

Banerjee and coworkers developed a versatile mechanochemical route to access 2-aryl benzothiazoles (**176**) as well as 1,2-disubstituted benzimidazole derivatives (**178**) (Scheme 25) [66]. The 1,3-benzazole synthesis was achieved in the absence of any catalyst by grinding a mixture of *o*-aminothiophenol/*o*-phenylenediamine (**173/174**) and the corresponding aldehydes (**175**) in an Agate mortar-pestle. The optimization studies involving the synthesis of **176a** pointed out that grinding under neat condition is not suitable as intermediate imines get trapped inside the unreacted solid substrates. However, the addition of a small amount of solvents like $CHCl_3$, EtOAc, ACN, MeOH, EtOH or H_2O as LAG agents



Scheme 24. The synthesis of 2-substituted benzoxazoles (**172**) catalyzed by $Zn(OAc)_2.2H_2O$ [193].

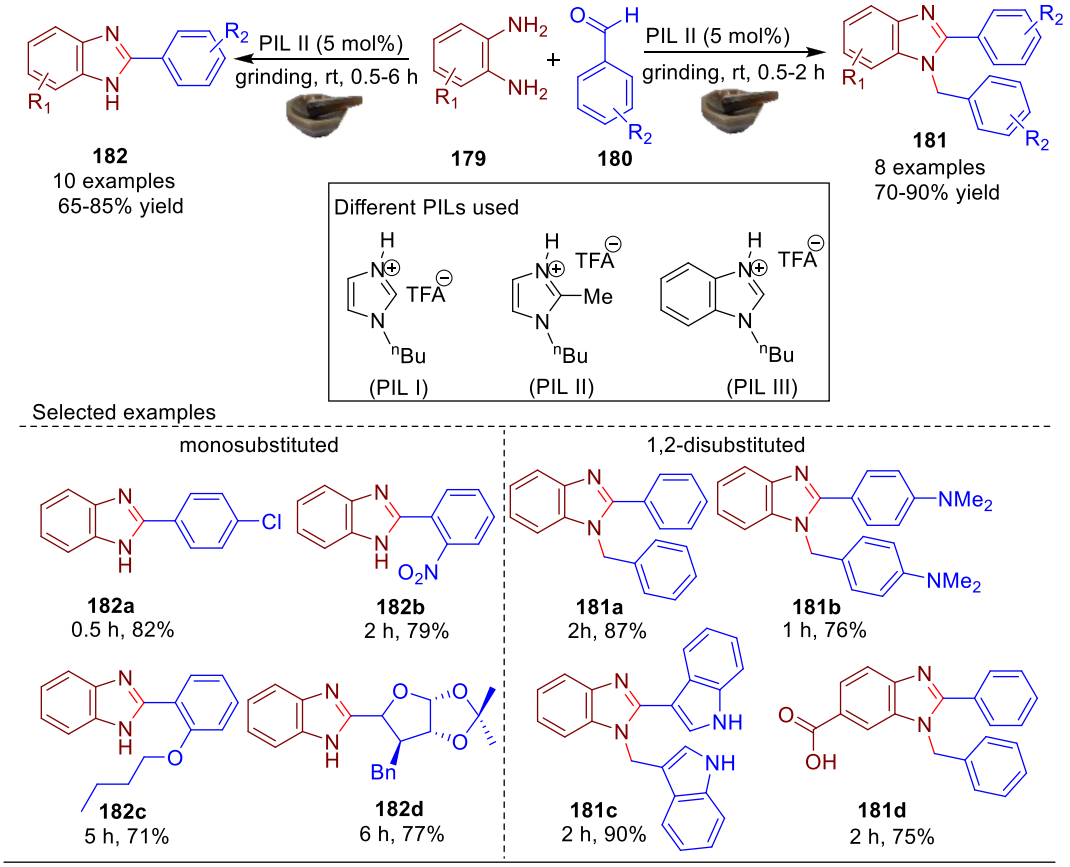


Scheme 25. Mechanochemical synthesis of 2-aryl benzothiazoles (**176**) and both 2-substituted (**177**) and 1,2-disubstituted benzimidazole (**178**) derivatives [66].

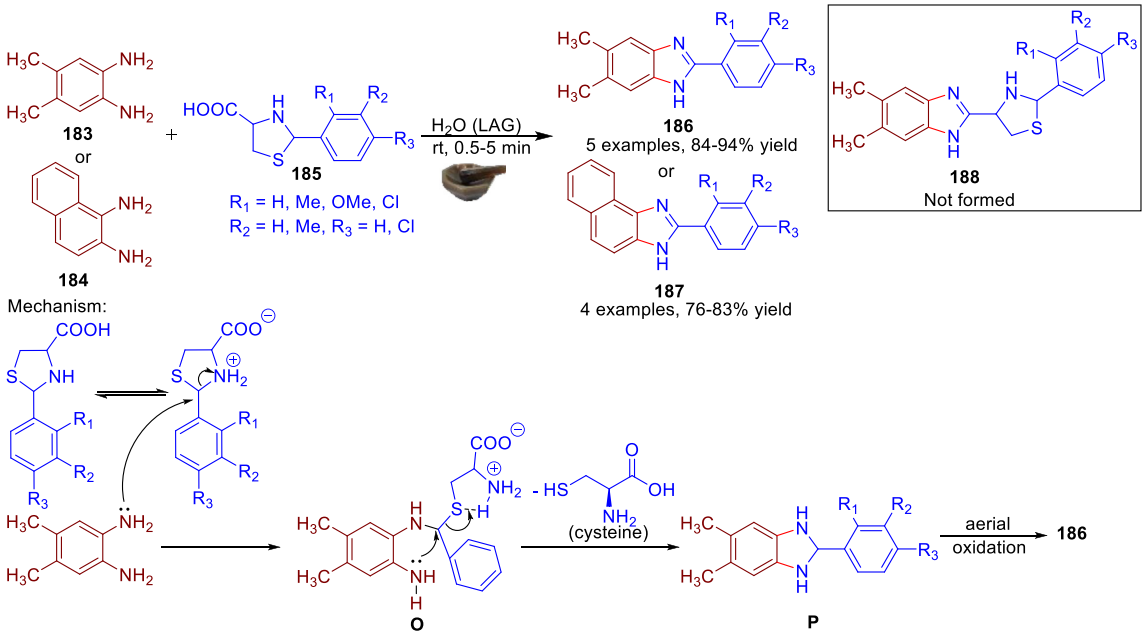
could afford higher yields of **176a**. Among them, EtOH was found the best LAG agent affording **176a** in 90% yields within 15 min. Banerjee's group also proposed that the reaction proceeded by the formation of a Schiff's base by condensation of **173** with **174** followed by intramolecular cyclization by the attack of thiol group to the imine bond to form dihydro-benzothiazole, **N** which undergoes a spontaneous aerial oxidation delivering the corresponding products (**176**). Notably, the addition of oxidants such as H_2O_2, iodine or $(NH_4)_2S_2O_8$ did not offer much changes in the yield of **176a** indicating there is no role of any oxidant in the conversion of **N** to the final product, **176**. A series of aromatic aldehydes with EDG (entry **176c**) and EWGs (entry **176b**) as well as heteroaromatic aldehydes with 2-aminothiophenols (entry **176d**) underwent smooth transformations delivering the desired products in good to high yields. The rates of the reactions were affected as aldehydes with strong electron-donating groups reacted (entry **176c**) slowly than that with EWGs (entry **176b**). However, the method showed limitations when aliphatic aldehydes were used for the formation of benzothiazole (entry **176e**,**f**). When *o*-phenylenediamine (**174**) was used in place of aminothiophenol (**173**), both 2-aryl benzimidazoles (**177**) and 1,2-disubstituted benzimidazoles (**178**) can be obtained using the simple mortar-pestle grinding by taking appropriate amount of *o*-phenylenediamine (**174**) in the reaction media. The condensation of equimolar mixture of aldehydes and *o*-phenylenediamine (**174**) resulted the corresponding 2-arylbenzimidazoles in relatively lower yields (54–66%); also, a small amount of 1,2-disubstituted benzimidazoles were formed. However, the formation of 1,2-disubstituted benzimidazole derivatives (**178**) were rather facile when 2.2 equiv of **174** was used (entry **178a-d**, 76–86% yields). Thus, a single method could afford benzothiazoles (**176**), 2-arylbenzimidazoles (**177**) and 1,2-disubstituted benzimidazoles (**178**) within short reaction times, avoiding a tedious work-up step.

Afterward, Majumdar and coworkers developed a similar grinding protocol for the synthesis of benzimidazoles derivatives (**181**, **182**) using imidazolium trifluoroacetate protic ionic liquid (PIL) as the catalyst (Scheme 26) [194]. Out of three PILs tested for catalysis, PIL II (1-butyl-2-methyl imidazolium tri-fluoroacetate) provided better results for both 1,2-disubstituted (**181**) and 2-substituted benzimidazoles (**182**). The grinding of *o*-phenylenediamine with 2.2 equiv of benzaldehyde with different PILs revealed that the use of 5 mol% of PIL II afforded **181a** in 87% yield after 2 h, whereas, 10 mol% of PIL I and III afforded **181a** with 83% and 80% yields, respectively. Out of the limited numbers of substrates used to validate the method, 70–90% yields were observed for **181** and 65–80% yields for **182**. However, the grinding of long 6 h were required in some cases (entries **182c**,**d**). As such, the studies suggested that the ionic liquid assisted method of Majumdar's group was inferior to the catalyst-free grindstone protocol of Banerjee's group.

In an interesting approach, Almansour et al. demonstrated a highly selective construction of 2-aryl substituted benz-/naphthimidazoles (**186** or **187**) involving the reaction of aromatic 1,2-diamines (**183** or **184**) with a series of substituted arylthioprolines (**185**) in the presence of 3–5 drops of water as the LAG agent (Scheme 27) [195]. The cyclocondensation of 1,2-diamines (**183** or **184**) with arylthioprolines (**185**) was expected to furnish the thiazole grafted benzimidazole (**188**) instead benz-/naphtha-imidazoles (**186** or **187**) were formed by the removal of cysteine residue



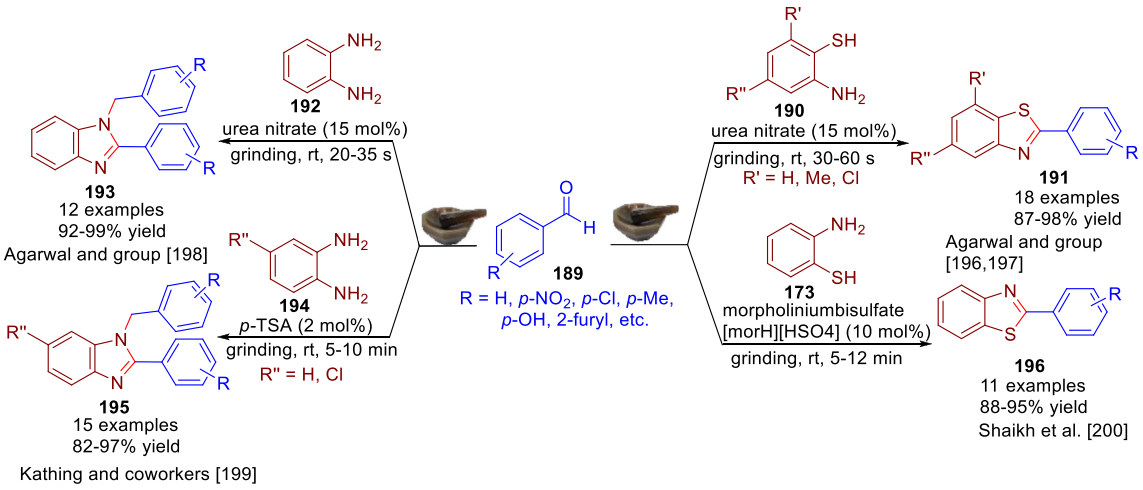
Scheme 26. Synthesis of substituted benzimidazoles (**181**, **182**) by ionic liquid assisted grinding [194].



Scheme 27. Selective construction of 2-aryl substituted benz-/naphtha-imidazoles (**186**, **187**) [195].

from **183**. As per their suggested mechanistic pathway, perhaps the arylthioprolines could be in the zwitterionic form, which could react with 1,2-diamine giving the intermediate **O**, which upon cyclization affords the dihyrobenzimidazole (**P**). Intermediate **P** undergoes aerial oxidation to furnish 2-aryl benzimidazoles (**186**). The products were obtained by simple filtration, avoiding typical work-up and chromatographic purification steps.

The vast bioactivities led to the development of several other



Scheme 28. Urea nitrate and Morpholinium bisulfate [morH][HSO_3] catalyzed synthesis of 2-arylbenzothiazole derivatives [196–200].

grinding protocols for 1,3-benzazoles by changing the type of catalysts in the subsequent years [196–200]. Agarwal and coworkers used urea nitrate as the catalyst for the synthesis of a series of 2-arylbenzothiazole derivatives (**191**) by grinding aromatic aldehydes (**189**) and *o*-aminothiophenol derivatives (**190**) (Scheme 28) [196]. The reactions proceeded at an unusually faster rate in the presence of 15 mol% of urea nitrate and complete conversion was seen within just 30 s of grinding. A short library of 6 arylbenzothiazole derivatives (**191**) were prepared in 95–98% yields (Scheme 28). However, they have not investigated the mechanistic background to explain the extraordinarily fast reaction kinetics. Subsequently, they employed the same protocol for the synthesis of 5-chloro substituted benzothiazoles [197]. The reusability of the catalyst was performed up to four cycles with no significant loss in its catalytic activity. At a similar time, the same group separately reported the synthesis of 1,2-disubstituted benzimidazoles (**193**) in excellent yields by a urea nitrate catalyzed grinding of aromatic aldehydes (**189**) and *o*-phenylenediamine (**192**) under solvent-free conditions (Scheme 28) [198]. The catalyst load was this time optimized as 15 mol% as lower loading of urea nitrate afforded lower yields of benzimidazoles at a slower rate (5% and 10% urea nitrate yielded 50% and 72% of **193** in 5 min and 1 min, respectively). Once again, the 1,2-disubstituted benzimidazole derivatives (**193**) were obtained in 92–99% yields by grinding the reaction mixture for a few seconds. At a similar time, Kathing et al. reported the use of *p*-TSA for the synthesis of 1,2-disubstituted benzimidazoles (**195**) via the same cyclo-condensation reaction [199]. Just a few milligrams of *p*-TSA (3.8 mg, 2 mol%) per mmol of *o*-phenylenediamine (**194**) was enough to catalyze the reactions with a series of aromatic aldehyde (2 equiv with respect to **194**) to afford the corresponding products (**195**) in excess of 90% yields within 5–10 min of grinding. In another study, Shaikh and Chaudhar reported the use of a cheap and reusable ionic liquid, morpholinium bisulfate[morH][HSO_3] as the catalyst for the synthesis of 2-arylbenzothiazoles (**196**). 10 mol% of morpholinium bisulfate [morH][HSO_3] was required to successfully convert 2-aminothiophenol (**173**) and aromatic aldehydes (**189**) to 2-arylbenzothiazoles (**196**) within 5–8 min of grinding in 88–95% of yields (Scheme 28) [200].

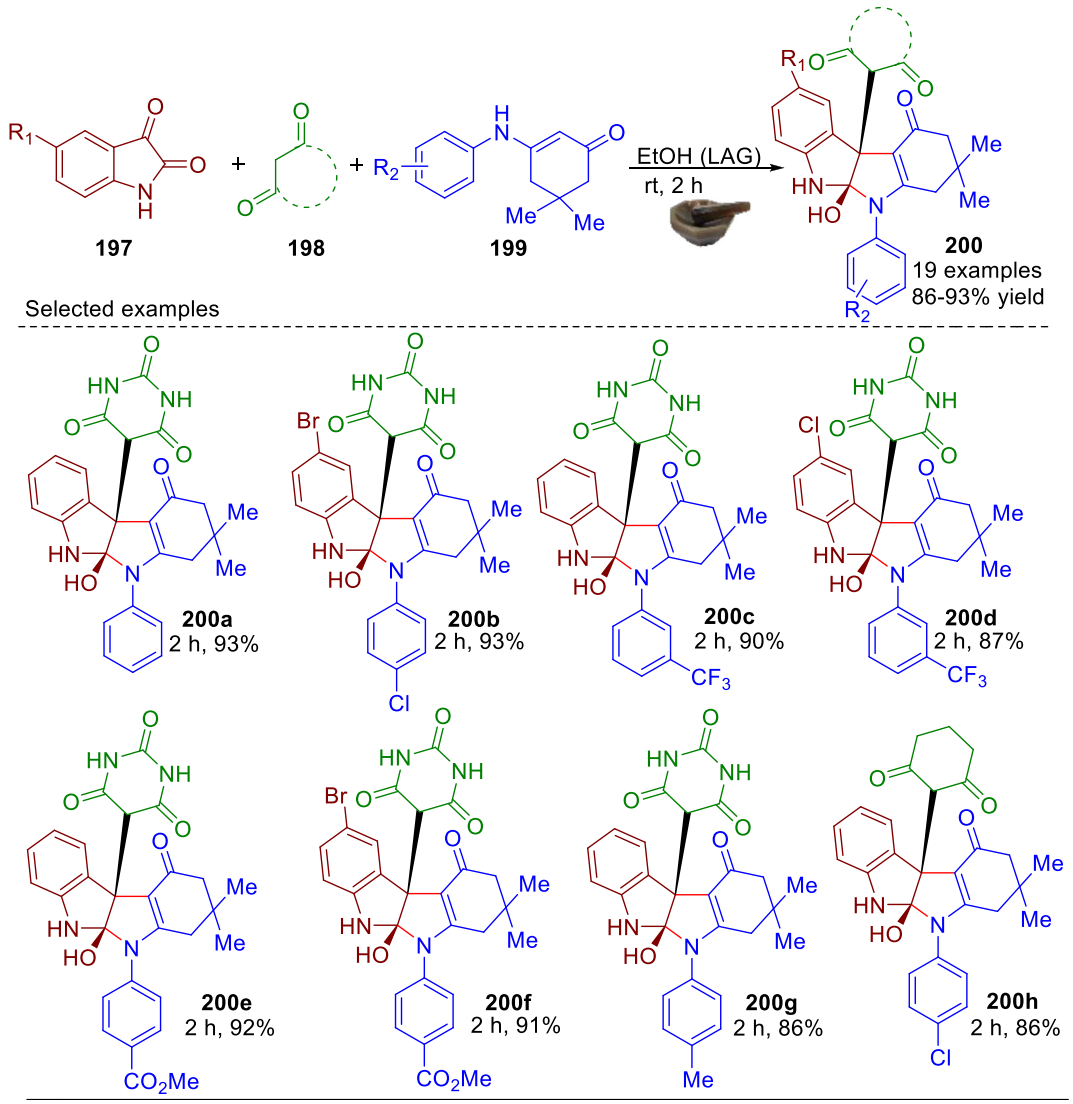
3.3.5. Indoloindoles

Indoles exhibit therapeutic properties over a wide range of targets including antiviral, antitumor, anticonvulsant, antiinflammatory, antibacterial, cardiovascular activities, etc. [201,202]. Due to these enthralling biological properties, various strategies have been established for the construction of indoloindolpyrimidine derivatives [203,204]. In an attempt to get a viable alternative route, Maury et al. reported a catalyst-free mechanochemical protocol for the synthesis of indoloindolpyrimidines (**200**) utilizing the mortar and pestle grinding method (Scheme 29) [205]. Liquid assisted grinding of a variety of isatin derivatives (**197**) with 1,3-diketones (**198**) and enaminones (**199**) with few drops of EtOH at room temperature over a period of 2 h delivered indoloindolpyrimidine derivatives (**200**) in excellent yields (86–93%). In a model reaction using barbituric acid as the 1,3-diketones it was observed that the reaction does not proceed in neat condition even after 6 h. However, in the presence of catalytic amount of a Lewis acid (e.g. *p*-TSA, sulfamic acid) or Lewis base (e.g. Et_3N), the progress was satisfactory affording **200a** in 78–82% of yields after 3–4 h of grinding. Interestingly, just the addition of a few drops of EtOH as the LAG agent in the reaction mixture, in the absence of any catalyst, could take the reaction to completion within 2 h to give **200a** in 93% yield. Notably, aprotic solvents like DMF, DMSO, toluene was found ineffective as LAG agent. According to the mechanistic considerations, initially, a Knoevenagel adduct is formed by the reaction of 1,3-diketones and isatin, followed by a Michael-type addition that takes place via enamine and gives an open-chain intermediate. This intermediate undergoes imine-enamine tautomerization and *N*-cyclization via the attack to the carbonyl group of amidic isatin, delivering the desired compounds. They extended the scope of their methodology by investigating a wide range of isatins, 1,3-diketones and enaminones under optimal conditions and found no significant substituent effect in terms of yields of **200**.

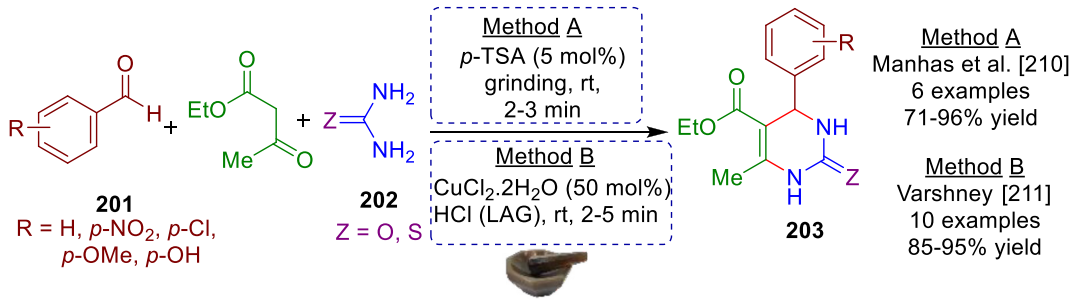
3.4. Six-membered with two heteroatoms

3.4.1. Pyrimidines and pyrimidones

Pyrimidines, pyrimidones and dihydropyrimidones (DHPM) are of immense interest to researchers due to the wide range of bioactivities and use in material science [206–208]. Several biomolecules (e.g. ribonucleotides) possess pyrimidine substructures and many marine alkaloids comprise of a dihydropyrimidone (DHPM) framework. Dihydropyrimidones are effortlessly synthesized by Biginelli reaction [209], which was adopted by Bose et al. for the synthesis of this important heterocycle by grindstone technique [210]. The strategy involved the grinding of different benzaldehyde derivatives (**201**), ethyl acetoacetate and urea/thiourea (**202**) in the presence of acid catalyst *p*-TSA (5 mol%) to afford



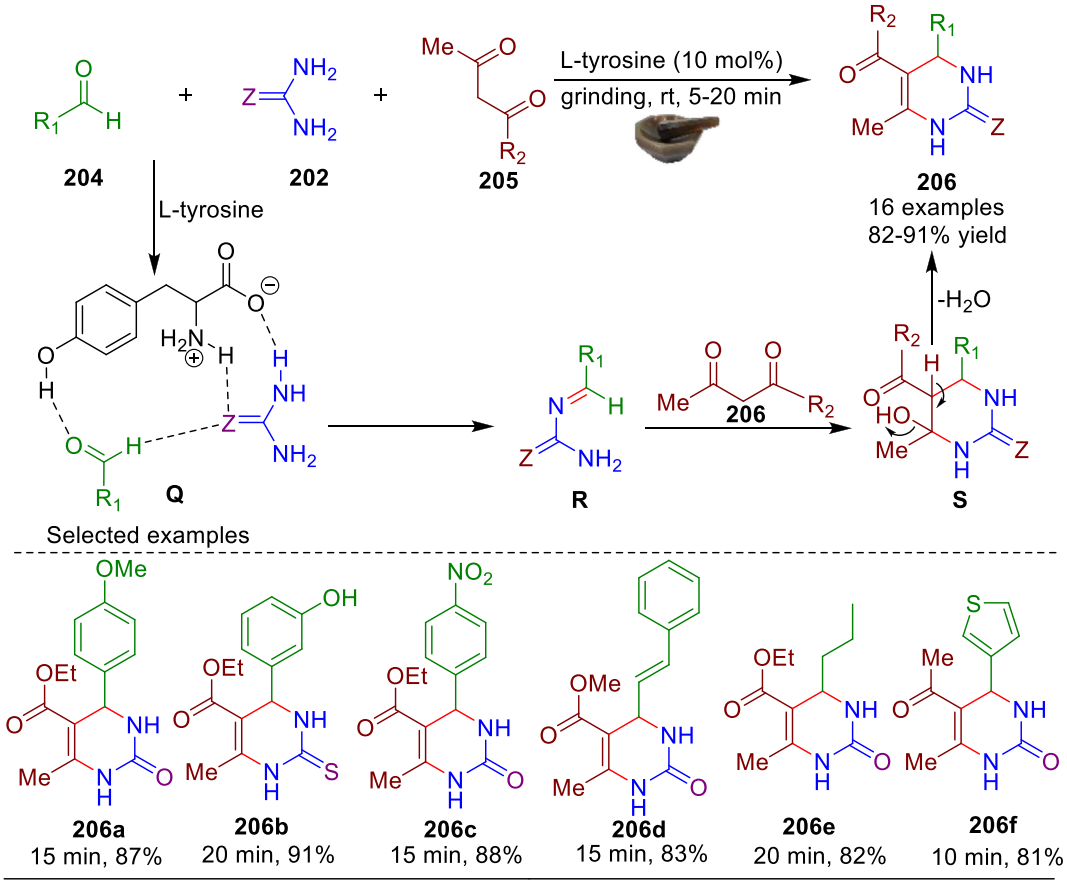
Scheme 29. Synthesis of indoloindolpyrimidine derivatives (**200**) using grindstone technique [205].



Scheme 30. Biginelli reaction in mortar-pestle for the synthesis of dihydropyrimidines (**203**) [210,211].

the corresponding dihydropyrimidines (**203**) in good to excellent yields (71–96%) (Scheme 30) [210]. They demonstrated a large-scale synthesis of dihydropyrimidines by taking benzaldehyde, ethylacetoacetate and urea as the model substrates and carried out the reaction at 0.5 M scale, placing the substrates and reagents in a large porcelain bowl and grinding conducted with the help of a hand-held electric food mixer with stainless steel rotors. The reaction was completed in less than 15 min with a yield of 94%. In a similar manner, Pathak and coworkers exploited Biginelli reaction with similar substrates but $CuCl_2 \cdot 2H_2O$ as the Lewis acid catalyst to furnish dihydropyrimidinones (**203**) under solvent-free conditions (Scheme 30) [211]. The aromatic aldehydes (**201**), ethyl acetoacetate and urea/thiourea (**202**) were ground in the presence of 0.5 equiv of $CuCl_2 \cdot 2H_2O$ and a few drops of conc. HCl for 2–5 min to afford **203** in up to 95% yield.

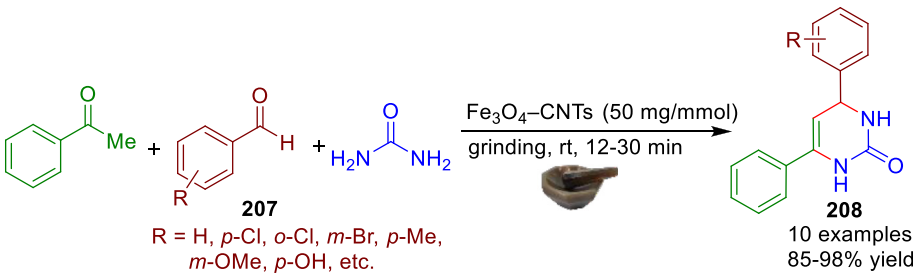
In another study, the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-



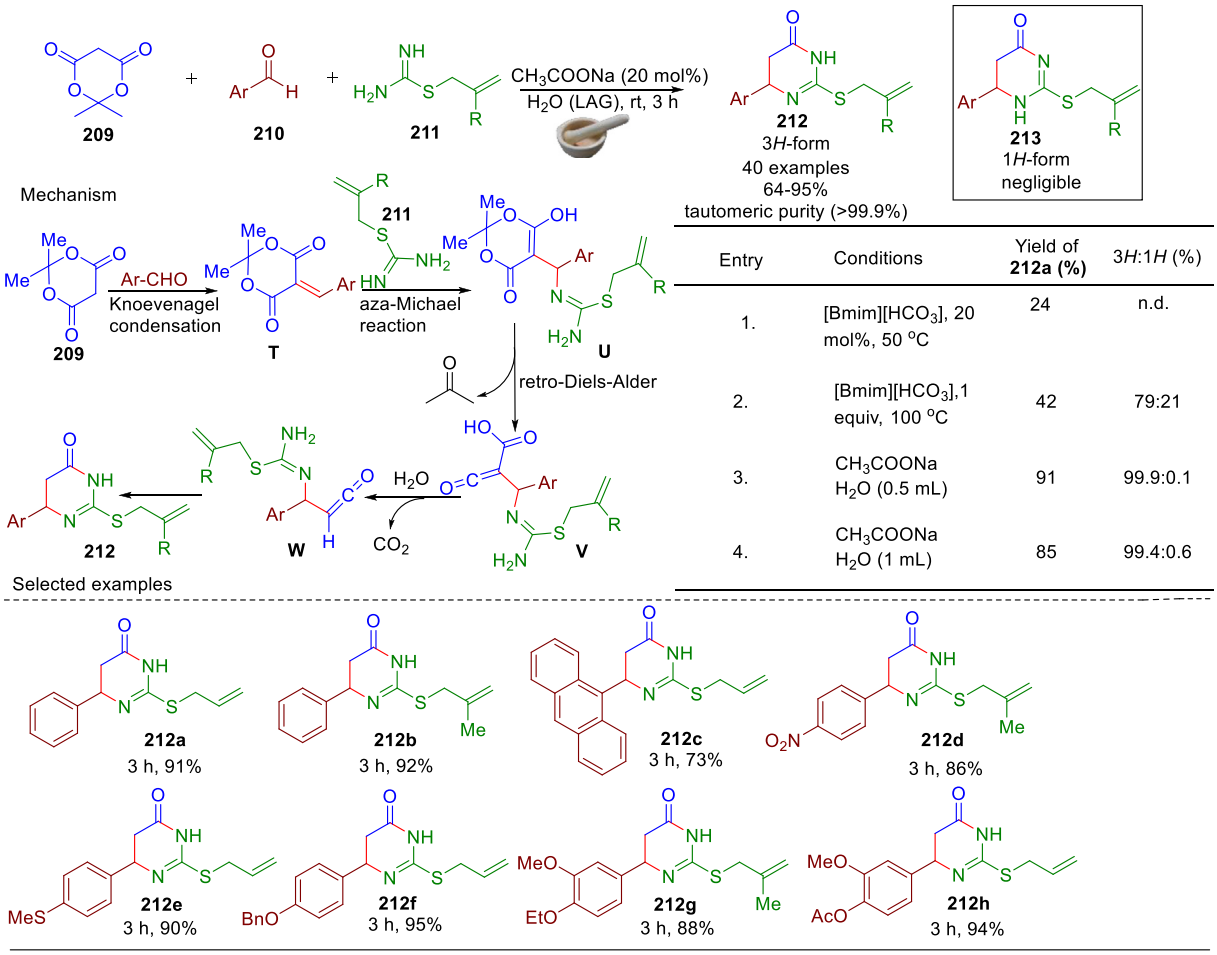
Scheme 31. L-tyrosine catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (**206**) [212].

ones (**206**) by hand-grinding was reported by Khaskel et al. (Scheme 31) [212]. They used L-tyrosine as the organocatalyst for Biginelli reaction of various aldehydes (**204**), urea/thiourea (**202**) and 1,3-diketones (**205**). The catalyst screening revealed that several amino acids like glycine, L-serine, L-proline, L-tyrosine and Brønsted acids like camphorsulphonic acid, oxalic acid, $HClO_4$ can catalyze the reaction but 10 mol% of L-tyrosine is ideal for faster conversion and higher yields. It was proposed that L-tyrosine form a three-prone H-bonded network (**Q**) with an aldehyde (**204**) and urea derivative (**202**) and subsequently form intermediate **R**, which undergoes intramolecular cyclization to **S** followed by dehydration to furnish 3,4-dihydropyrimidin-2-(1*H*)-ones (**206**). The aromatic aldehydes, irrespective of the presence of EDGs or EWGs, resulted in 3,4-dihydropyrimidones, **206** in high yields (entries **206a-c**). The aliphatic (entry **206e**) as well as heteroaromatic aldehydes (entry **206f**) participated equally efficiently in the reaction. There are other reports on Lewis acid-catalyzed Biginelli reaction as well [213].

In an interesting approach, Safari et al. reported a grinding protocol towards a one-pot three-component synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-ones (**208**) by Biginelli-like reaction employing carbon nanotubes (CNTs) derived magnetic nanoparticles as reusable heterogeneous catalyst (Scheme 32) [214]. The synthesis involved the condensation reaction between various benzaldehyde derivatives (**207**), urea and acetophenone in the presence of the heterogeneous catalyst, Fe_3O_4–CNTs, which was developed by them. The amount of Fe_3O_4–CNTs was optimized as 50 mg/mmol for better conversion. The protocol afforded dihydropyrimidine-2(1*H*)-ones (**208**) in high to excellent yields in the range of 85–98% within a short span of grinding (12–30 min). The recyclability of Fe_3O_4–CNTs showed no loss in catalytic activity up to 5th cycle; for a model reaction yield dropped to 93% from 98% on the 5th cycle. Similarly, Ramachandran et al. demonstrated the synthesis of dihydropyrimidinones (DHPM) using grindstone chemistry involving the grinding of aromatic aldehydes, *N*-phenylacetoacetamide and urea/thiourea in the presence of $CuCl_2 \cdot H_2O$



Scheme 32. Fe_3O_4–CNTs catalyzed synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-ones (**208**) [214].



Entry	Conditions	Yield of **212a** (%)	3*H*:1*H* (%)
1.	[Bmim][HCO_3], 20 mol%, 50 °C	24	n.d.
2.	[Bmim][HCO_3],1 equiv, 100 °C	42	79:21
3.	CH_3COONa H_2O (0.5 mL)	91	99.9:0.1
4.	CH_3COONa H_2O (1 mL)	85	99.4:0.6

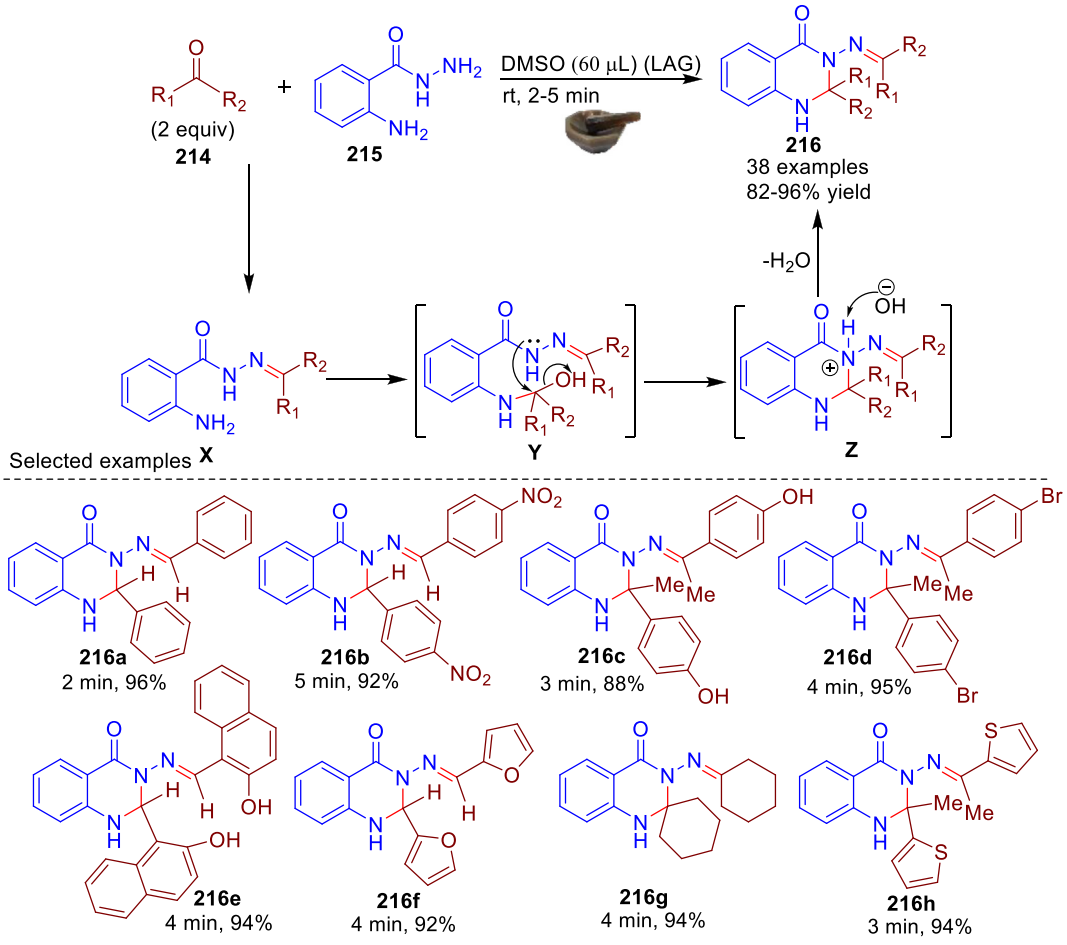
Scheme 33. Grindstone assisted tandem Knoevenagel, aza-Michael and retro-Diels-Alder for the synthesis of 5,6-dihydropyrimidin-4(3*H*)-one scaffold (**212**) [216].

(1 equiv) and a few drops of conc. HCl in a mortar and pestle under solvent-free conditions at room temperature to obtain good to excellent yields [215].

Bugarčić and coworkers introduced a grindstone method for the synthesis of structurally interesting 5,6-dihydropyrimidin-4(3*H*)-one scaffold (**212**) (Scheme 33) [216]. 5,6-dihydropyrimidin-4(3*H*)-one is the precursor of dihydrouracil and is a difficult target for one-pot synthesis. They showed that simple grinding can initiate a tandem Knoevenagel, aza-Michael and retro-Diels-Alder reactions to produce **212** in one-pot by condensation of Meldrum's acid (**209**), aldehydes (**210**) and isothioureas (**211**). During optimization of the reaction condition, they observed that the use of weak bases such as $NaHCO_3$, Na_2CO_3 in excess (5 equiv) at 50 °C could not afford the desired product (**212a**) even after a long time of grinding. On the other hand, the use of ionic liquid [Bmim][HCO_3] (20 mol%) as a soft base at 50 °C was effective in initiating the reaction with 24% yield of **212a**, which eventually increased to 42% with 1 equiv of the ionic liquid at 100 °C. However, the tautomeric purity between 3*H*/1*H* was low (79:21) (condition table, Scheme 33). Interestingly, grinding of the same reaction in the presence of CH_3COONa (20 mol%) as the catalyst and 0.5 mL of water as the LAG agent ($\eta = 0.26$ μL/mg with respect to solid substrates) for 3 h could afford the desired products (**212a**) in excellent yields with high tautomeric purity of 99.9:0.1 (condition table, Scheme 33). The grinding of the same reaction mixture at elevated temperature (100 °C) marginally lowered the yield and the tautomeric purity of **212a** (85%, 3*H*/1*H*:99.4:0.6) (condition table, Scheme 33). Different spectroscopic studies revealed that the reaction mechanism followed a three-step tandem process involving Knoevenagel, aza-Michael and retro-Diels-Alder reactions. Initially, aldehyde and Meldrum's acid furnish benzylidene adduct **T** via Knoevenagel condensation, which is then attacked by isothiourea via the aza-Michael step to furnish another intermediate **U**. This intermediate (**U**) undergoes a retro-Diels-Alder step to generate carboxyketene, **V** which in the presence of water undergoes decarboxylation to generate intermediate **W** followed by cyclization to give the product, **212**. The protocol was validated with a vast library of forty 5,6-dihydropyrimidin-4(3*H*)-one derivatives with the yields ranging from 64 to 95%.

3.4.2. *Quinazolines*

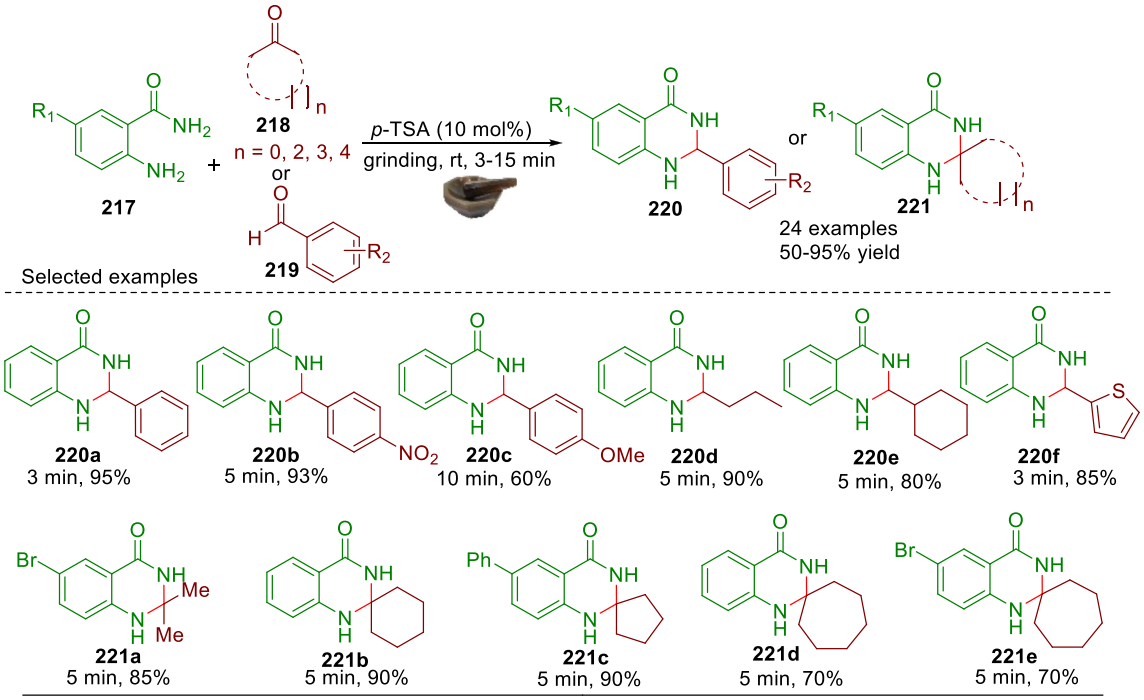
Quinazolines and their derivatives have been long studied as they exhibit therapeutic properties over a wide range of targets [217,218]. Quinazoline and quinazolinone rings are a part of many marketed drugs, for example, prazosin (used for blood pressure), gefitinib (anti-cancer drug) and albaconazole (antifungal agent) [219]. The available synthetic protocols require the use of metal catalysts (e.g. $Sc(OTf)_3$, SmI_2) [220–222]. As a catalyst-free, greener alternative, Rong and coworkers reported a grindstone protocol for synthesizing 3-benzylquinazolin-4(1*H*)-one derivatives involving a one-pot three-component reaction of isatoic anhydride, benzylamine and aromatic aldehydes [223]. In another recent approach, Kuntikana et al. developed a method for the synthesis of 3-arylideneaminoquinazolin- 4(1*H*)-ones (**216**) via a cascade



Scheme 34. Synthesis of 3-arylideneaminoquinazolin-4(1*H*)-one derivatives (**216**) using grindstone chemistry [80].

condensation-cyclization reaction at ambient temperature, a synthetic scaffold which were inaccessible by conventional methods (Scheme 34) [80]. This two-component synthesis involving 'liquid-assisted grinding' reactions of aldehydes/ketones (**214**) and *o*-aminobenzhydrazide (**215**) by DMSO afforded quinazolin-4(1H)-ones (**216**) in high yields, whereas, a similar solution-phase reaction only led to the Schiff base formation [80]. Although in a few cases, neat grinding was sufficient for complete conversion using liquid aldehyde (e.g. **216a**), in several other cases, the reactions did not proceed unless 2–3 drops of DMSO were added as LAG agent ($\eta \sim 0.15$ μL/mg of substrates) to the reaction mixture (e.g. **216b**). Notably, the reactions were completed very fast within 2–5 min via liquid-assisted grinding. They proposed an imine formation between carbonyl and the benzhydrazide group of **215** to form hydrazone (**X**), which interacts with another carbonyl group of **214** to form the intermediate **Y**. This undergoes intramolecular cyclization (**Z**) and subsequent water removal to form the desired quinoxalinones (**216**). The E-factor of this method is low (0.53), which is several folds lower than Su's method (12.85) [220]. Some selected products were screened for their antioxidant activity using 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging technique and compounds which displayed considerable antioxidant activity were later tested for their protective capacity against deoxyribonucleic acid (DNA) impairment. Among other similar methods, Pramanik et al. demonstrated a three-component cyclo-condensation reaction of dimedone, thiourea and aromatic aldehydes for the synthesis of octahydroquinazolinones by employing solvent- and catalyst-free grindstone technique [224].

Very recently, Saha and coworkers utilized the grindstone technique to efficiently synthesize the structurally interesting 2,3-dihydroquinazolin-4(1*H*)-one (**220** or **221**) by simple grinding in a mortar-pestle (Scheme 35) [225]. The synthesis involved the grinding of anthranilamide derivatives (**217**) with ketones (**218**) or benzaldehyde derivatives (**219**) in the presence of *p*-TSA (10 mol%) as the catalyst to afford the products in moderate to excellent yields. During catalyst screening, it was observed that Lewis acids such as $InCl_3$, $FeCl_3$ and I_2 could furnish the product (**220a**) of benzaldehyde and anthranilamide only in moderate yields, but swapping the catalyst from Lewis acids to Brønsted acids such as *p*-TSA or TFA afforded the product, **220a** in excess of 90% yield. The catalyst loading of 10 mol% of *p*-TSA was found optimum for complete conversion of **220a** within 3 min in 95% yield. The broad applicability of the process was tested with various aromatic and aliphatic aldehydes as well as ketones and a total of 15 differently substituted derivatives of **220** were obtained in moderate to excellent yields. Notably, the yields of the products drop in case of aldehydes with EDG (entry **220c**). A scale-up reaction produced **220b** in 90% yield within 10 min validating the workability of the process in bulk-scale. The low E-factor (0.243) makes the protocol an efficient one for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one.



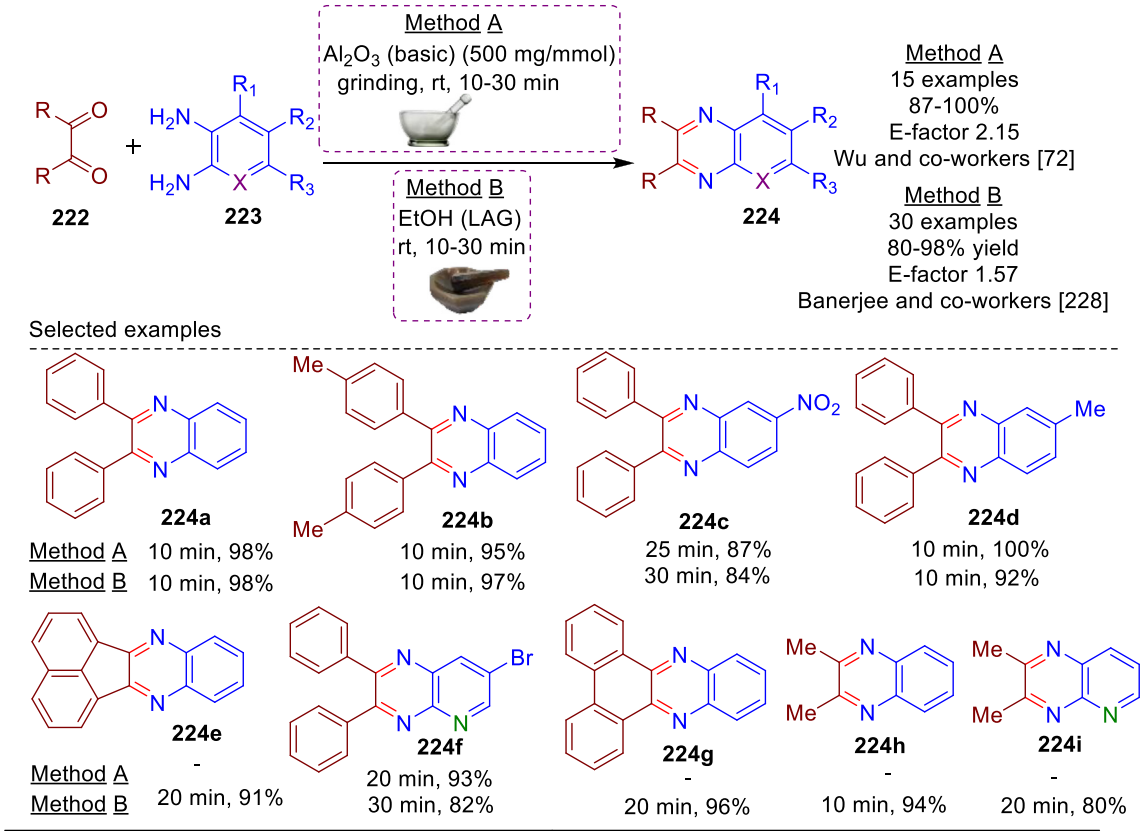
Scheme 35. Synthesis of 2,3- dihydroquinazolin-4(1*H*)-one (**220** or **221**) in the presence of *p*-TSA [225].

3.4.3. Quinoxalines

Another privileged class of nitrogen-containing heterocycle is quinoxaline and its derivatives due to their wide range of biological activities including antiviral, antibacterial, antiinflammatory and anticancer activities [226,227]. In an earlier approach, Wu and co-workers synthesized quinoxaline derivatives (**224**) by solid-phase grindstone chemistry using alumina as the grinding auxiliary (Scheme 36) [72]. The condensation of various 1,2-diketones (**222**) and 1,2-diamines (**223**) were carried out in basic alumina (500 mg/mmol). They reported that the reaction of *o*-phenylenediamine with benzil in neat condition afforded the desired product (**224a**) in only 32% yield, insisting the need for a grinding auxiliary. The use of SiO_2, acidic Al_2O_3, neutral Al_2O_3 enhanced the product formation, but the best result was obtained with basic Al_2O_3 to get **224a** in 98% within 10 min of grinding. However, one clear drawback associated with this protocol is the product isolation from the solid support by using organic solvent (EtOAc). Otherwise, the E-factor of the reaction is low (2.15). Subsequently, Banerjee and coworkers adopted a liquid-assisted grinding route for quinoxalines (**224**) in another catalyst-free approach (Scheme 36) [228]. The optimization studies revealed that the neat reaction of benzil with *o*-phenylenediamine as model reaction took 2 h for complete conversion with a yield of 92% of **224a**, whereas, the presence of a small amount of solvent such as ethanol, methanol, chloroform (0.5 mL per mmol of the substrate) accelerated the reaction to more than 10 folds and the reaction was completed within 10–20 min. The best LAG agent was ethanol ($\eta = 1.5$ μL/mg of solid substrates). They suggested water as not a viable solvent for LAG as partial hydrolysis of intermediate imine bond is possible. However, the condensation of aqueous glyoxal with diamine went to completion without the addition of EtOH and even if water was present in the system because of the high reactivity of glyoxal, which is able to suppress hydrolytic decomposition of intermediate imine. A total of 30 different derivatives of **224** were synthesized by taking different 1,3-carbonyl compounds and diamine compounds with an overall yield of 80–98%, indicating the substituent effect in this reaction is insignificant. The crude products were recrystallized from EtOH to get pure **224**. The E-factor of this method is 1.57, which is lower than Wu's method [72]. Moreover, they estimated the cost of Wu's method with their method and found the LAG method is about 33 folds cheaper than solid-phase grinding involving column chromatography for product purification. Banerjee and coworkers also examined the microbial activities of these quinoxaline derivatives and compounds like pyrido[2,3-*b*]pyrazines (**224i**) showed effective antibacterial properties against *M. smegmatis*. In the same line, Khalafy et al. demonstrated the use of clay as a catalyst to synthesize a series of arylquinoxalines from various aromatic 1,2-diamines with arylglyoxals in solvent-free grindstone chemistry [229].

3.4.4. Phthalazine

Phthalazine derivatives display important biological and pharmaceutical activities [230]. Selvaraj et al. explored the synthesis of naphtho[2,3-*g*]phthalazine derivatives (**227**) via grindstone chemistry employing heterogeneous catalyst, Tel-Cu-NPs (telmisartan-copper nanoparticles) (1 mg/mmol) (Scheme 37) [37]. Telmisartan is a benzimidazole-based drug used to treat high blood pressure and heart failure. The heteroaromatic-N can legate to Cu(II). The catalyst was synthesized by grinding $CuCl_2 \cdot 2H_2O$ with telmisartan in ethanol and then treating this mixture with NaOH. Subsequently, the catalyst was used in the Mannich reaction of 1,4-dihydroxyanthraquinone (**225**) and substituted aldehydes (**226**) in the presence of hydrazine hydrate and Tel-Cu-NPs in EtOH (1.5 mL/mmol) at room temperature yielding naphtho[2,3-*g*] phthalazine derivatives (**227**) in high yields. Furthermore, an in-flask extraction permitted for the recycling of the catalyst, which even after additional 10 cycles showed almost no loss in catalytic activity. They subsequently carried out molecular docking and



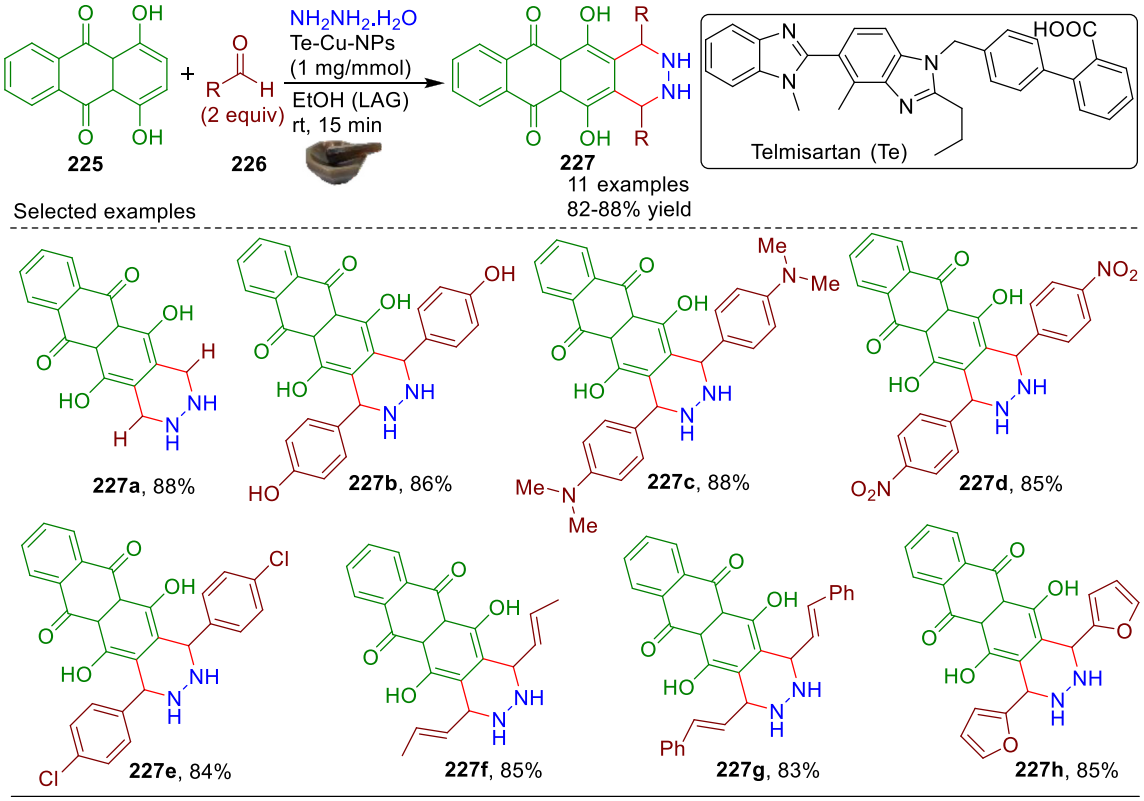
Scheme 36. Grindstone aided synthesis of quinoxaline derivatives (**224**) using alumina [72], or LAG using EtOH [228].

tyrosinase inhibitory activity studies with their synthesized compounds and a few of naphtho[2,3-*g*]phthalazines showed promises as potential antityrosinase agents.

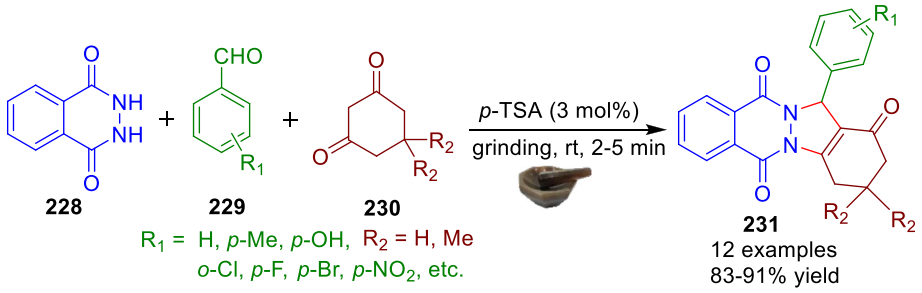
Wang and coworkers reported a solvent-free route for the three-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones (**231**) in the presence of a catalytic amount of *p*-TSA by hand-grinding (Scheme 38) [231]. The reaction involves the grinding of phthalhydrazide (**228**), aldehyde derivatives (**229**), and dimedone derivatives (**230**) in the presence of *p*-TSA (3 mol%) to afford the desired products with high yields in short times. The optimization studies with a model reaction of phthalhydrazide, benzaldehyde and dimedone revealed that the reaction progress is very slow in the absence of any catalyst with a yield of only 25% after grinding for 30 min. However, the use of 3 mol% of *p*-TSA increased the yield of the reaction significantly to 91% within 2 min (yield is 63% and 76% in the presence of 1 mol% and 2 mol% of *p*-TSA after 10 min of grinding). Furthermore, they also presented a comparative study with the earlier reports, which clearly showed the superiority of this protocol over the conventional methods. The scope of the method was validated by synthesizing 12 derivatives of **231** in excellent yields.

3.4.5. Perimidines

Perimidines are fused nitrogen-containing heterocyclic naphthalenes that possess significant biological properties [232]. Employing the grinding method, Anilkumar and coworkers very recently described the synthesis of perimidines (**234**) by grinding various aldehydes/ketones (**232**) with 1,8-diaminonaphthalene (**233**) (Scheme 39) [233]. Mortar-pestle grinding for 5 min under solvent-free and catalyst-free conditions afforded the desired 2,3-dihydro-1*H*-perimidines (**234**) in moderate to excellent yields within short reaction times. Their validation studies indicated that the electronic effects of aldehydes did not influence the yields of the products, but the steric effect did impact the yields as the products of ortho-substituted aldehydes (entries **234b**,**c**) were obtained in lower yields as compared to the corresponding para-substituted ones (entries **234d**,**e**). The reaction proceeded well with heterocyclic aldehydes (thiophene-2-carboxaldehyde and pyridine-2-carboxaldehyde) to furnish the corresponding products (entries **234f**,**g**) and also with aliphatic aldehydes to form the products (**234h**,**i**) in high yields. However, this protocol did not work in the case of ketones which was attributed to the less electrophilic nature of the carbonyl carbon as well as its steric hindrance and resulted in lower yields of the corresponding products (**234j**). At similar times, Agarwal and coworkers adopted an analogous strategy for the synthesis of perimidine derivatives (**234**) using a recyclable solid-acid catalyst under metal-free conditions (Scheme 39) [36]. Different substituted aldehydes (**232**) demonstrated cyclo-condensation reaction with 1,8-diaminonaphthalene (**233**) in the presence of carbon sulfonic acid (C–SO_3H, 15 mol%) as the catalyst and EtOH as LAG agent under ambient reaction conditions to deliver the desired products (**234**) in excellent yields (95–99%) with very fast kinetics of few seconds to a minute only. The optimization studies revealed that the reaction is sluggish in the absence of a solvent or catalyst. The reaction progress was slow, and only 60% of **234k** was obtained after 5 min of grinding, as observed by Anilkumar's group. However, when the reaction was carried in the presence of 15 mol % of C–SO_3H and EtOH as LAG agent, the reaction showed complete conversion within 1 min yielding 98% of **234k**. The scope of the reaction was examined with various aldehydes to afford the products with electron-donating (**234k**) or electron-withdrawing groups (**234b**,**d**,**e**) as well as



Scheme 37. Synthesis of naphtho[2,3-*g*]phthalazine derivatives (**227**) via grindstone chemistry [37].

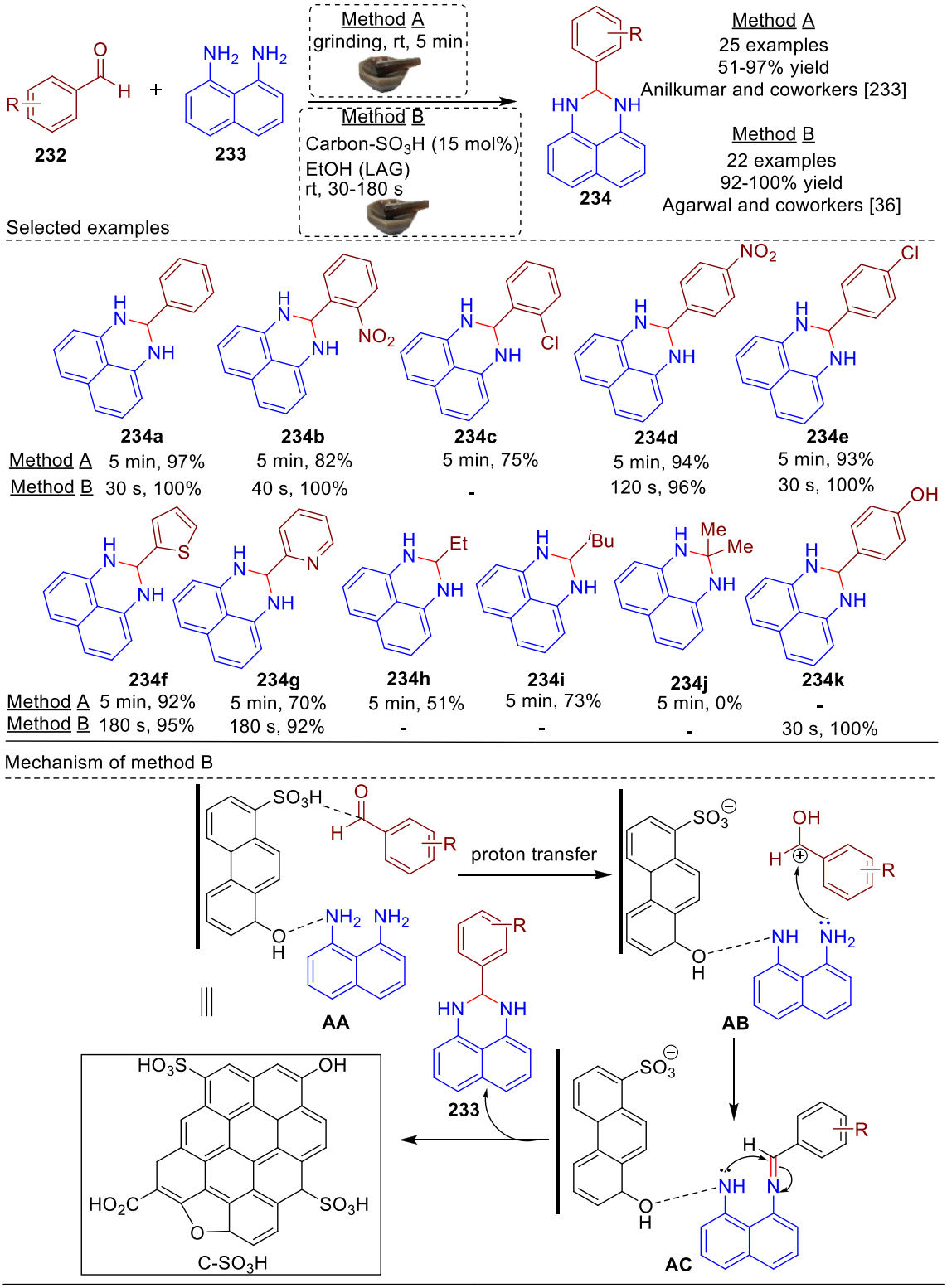


Scheme 38. Grindstone mediated three-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones (**231**) [231].

heteroaromatic aldehydes (**234f,g**). The authors proposed that carbon sulfonic acid quickly activates the carbonyl group of **232** and the −OH functionality present in C− SO_3H activates the amine groups of **233**. This facilitates the Schiff base formation and the subsequent attack of the other amine group of 1,8-diaminonaphthalene (**233**) to form the perimidine derivative (**234**) by cyclocondensation. Reusability studies of the solid catalyst revealed that it could be used up to 5 runs without any copious loss in its activity. The protocol worked well in gram-scale, giving the desired product in the same yield (**234e** was obtained in 98% yield). The estimated green matrices, E-factor 0.075, atom-economy 93.9% and reaction mass efficiency 93.04% indicate the efficiency of the protocol.

3.4.6. Naphthyridines

1,6-Naphthyridines are explored as antitumor agents for cancer chemotherapy [234] and show antibacterial properties as well [235]. Several reported methods use multi-step sequences [236] or expensive catalysts [237] for their synthesis. A few green protocols for 1,6-naphthyridine derivatives are also available [238]. In 2015, Hameed demonstrated a grinding protocol towards a one-pot, catalyst-free, pseudo-five-component synthesis of 1,2-dihydro [1,6]naphthyridines (**237**) involving substituted ketones (**235**) (2 equiv), malononitrile (2 equiv) and amines (**236**) (1 equiv) using a mortar-pestle at room temperature (Scheme 40) [239]. The reaction followed a fast reaction kinetics and the products were obtained in just about 5–7 min with 90–97% yields. Notably, the green protocol by Mukhopadhyay et al. requires refluxing the substrates in aqueous media for hours to achieve good yields of **237** [238]. The method was employed on different aliphatic primary amines and cyclic secondary amines to afford the desired products (**237g,h**) and (**237a-f**), respectively in excellent yields. The products were easily purified by filtering the resulting precipitate, then washing with EtOH and recrystallizing from absolute EtOH.

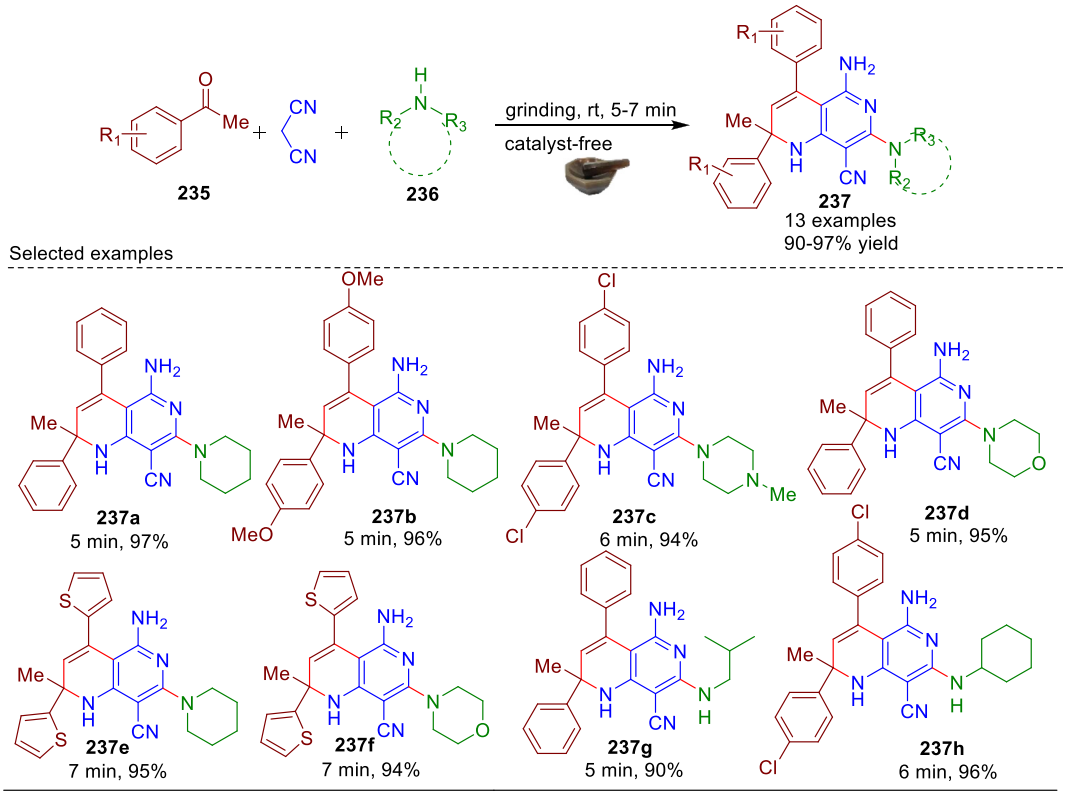


Scheme 39. Synthesis of perimidine derivatives (**234**) using a recyclable solid acid catalyst, carbon-SO_3H [36,233].

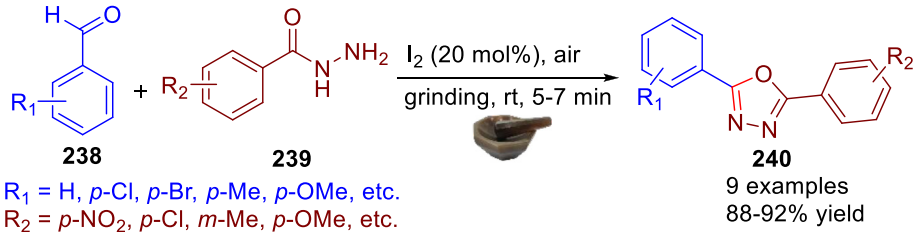
3.5. Heterocycles with three or more heteroatoms

3.5.1. Oxadiazoles

1,3,4-Oxadiazoles are known for anticancer, antiviral and antifungal properties [240,241]. Makrandi and coworkers developed a mechanochemical protocol for the synthesis of symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazole derivatives (**240**) using grindstone chemistry (Scheme 41) [242]. The solvent-free grinding of aryl aldehydes (**238**) with aromatic hydrazides (**239**) in the presence of a catalytic amount of molecular iodine (20 mol%) in a mortar-pestle afforded the desired 2,5-disubstituted oxadiazoles (**240**) in excellent yields within 5–7 min. The reaction



Scheme 40. Pseudo-five-component synthesis of 1,2-dihydro [1,6]naphthyridines (**237**) [239].



Scheme 41. I_2 catalyzed synthesis of 2,5-disubstitutedoxadiazoles (**240**) using grindstone chemistry [242].

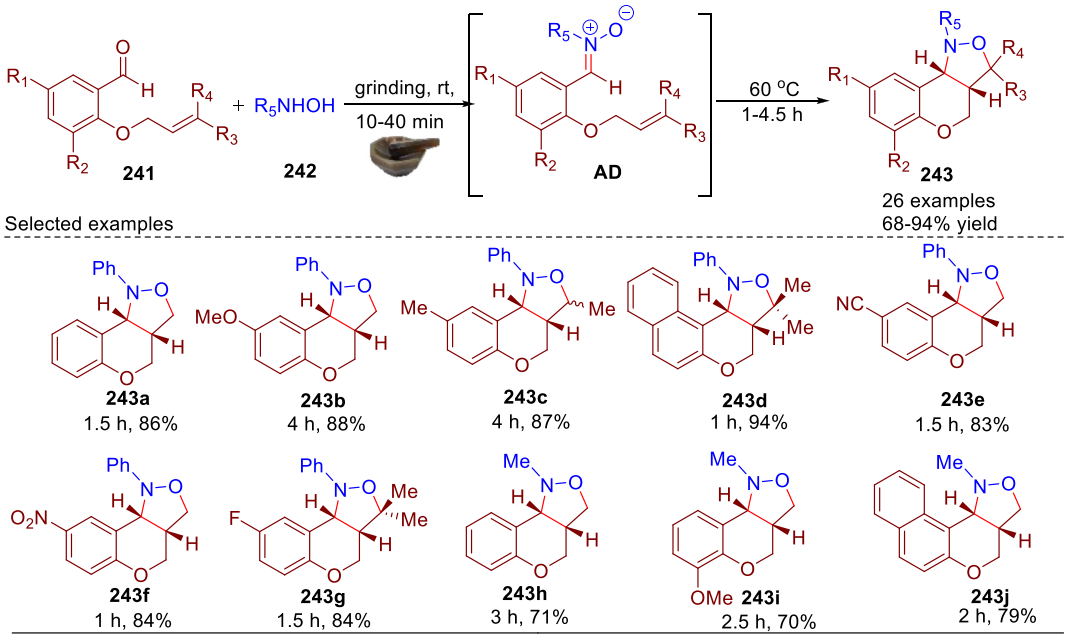
proceeds via the formation of acyl hydrazone followed by oxidative cyclization in the presence of aerial oxygen to give the desired 2,5-disubstituted 1,3,4-oxadiazoles (**240**). A short library of 9 oxadiazoles was prepared in 88–92% yields.

3.5.2. *Chromano[4,3-c]isoxazoles*

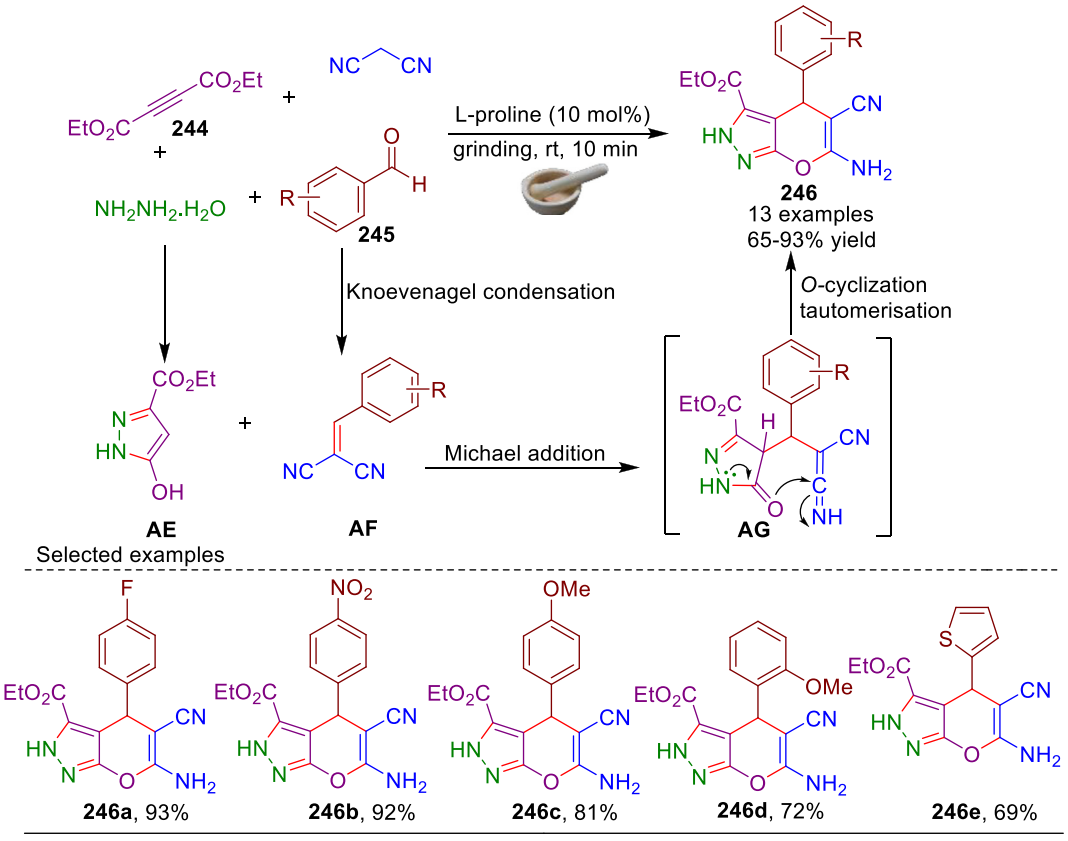
Chromanoisoxazoles are known to possess biomedical properties such as antidepressant, antipsychotic and antianxiolytic activities [243]. Banerjee and coworkers used the hand-grinding technique to access *cis*-fused chromano[4,3-*c*]isoxazoles (**243**) in a catalyst and solvent-free manner (Scheme 42) [65]. Grinding of *O*-allyl salicylaldehydes (**241**) and alkyl/aryl hydroxylamines (**242**) in an Agate mortar-pestle afforded the corresponding nitrone and the reaction mass was heated at 60 °C for 4 h to afford the desired products (**243**) in good to excellent yields via intramolecular 1,3-dipolar nitrone cycloaddition. The model reaction of *O*-allyl salicylaldehyde and hydroxylamine under neat grinding resulted in a pasty mass containing the nitrone (**AD**) within 15 min. Further grinding the reaction mixture to form chromanoisooxazole (**243a**) was slow and only 20% product was obtained after grinding for 2 h. Interestingly, for this reaction, LAG with EtOH, ACN or $CHCl_3$ did not afford any better results for grinding at room temperature. As the intramolecular cycloaddition was sluggish at room temperature, the reaction mass was heated at 60 °C for 1.5 h for complete conversion (yield of **243a** was 84%). The protocol worked well with aliphatic as well as aromatic hydroxylamines and was applied to different *O*-allyl salicylaldehydes with the same effectiveness. It was noticed that nitrones derived from *N*-phenylhydroxylamine afforded the intramolecular cycloaddition product (entries **243a-g**) at a faster rate compared to *N*-methylhydroxylamine nitrones desired products (entries **243h-j**). As the phenyl group is an electron pulling unit, the corresponding nitrones are more reactive, whereas the electron donation ability of the methyl group makes the 1,3-dipolarophile less reactive.

3.5.3. *Dihydropyrano[2,3-c]pyrazoles*

Ambethkar et al. synthesized an array of dihydropyrano[2,3-*c*] pyrazole derivatives (**246**) through a one-pot four-component reaction by grinding acetylene ester (**244**), hydrazine hydrate, aryl aldehydes (**245**) and malononitrile in the presence of L-proline as catalyst (Scheme 43) [74]. The model reaction by grinding 4-fluorobenzaldehyde, diethylacetylene dicarboxylate, hydrazine



Scheme 42. Synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles (**243**) via intramolecular 1,3-dipolar nitrone cycloaddition reaction involving hand-grinding in mortar-pestle [65].



Scheme 43. L-proline catalyzed one-pot protocol for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives (**246**) by hand-grinding under solvent-free conditions [74].

hydrate and malononitrile in neat conditions afforded only 40% yield of the desired product (**246a**) after 10 min. However, with the addition of 10 mol% L-proline the reaction proceeded to completion within 10 min providing **246a** in 93% yield. The Brønsted acid, *p*-TSA or Lewis acid, $SnCl_2$ can act as catalysts but the corresponding yields of **246a** are low (84% and 58%, respectively), L-proline was found to be the most efficient. The products derived from aldehydes bearing EWGs (entries **246a**,**b**; yields >90%) gave better yields than those with EDGs (entries **246c**,**d**; yields ~70%). The authors suggested the following probable mechanistic pathway involving the

formation of a cyclic intermediate **AE** from the interaction of diethylacetylenedicorboxylate (**244**) and hydrazine hydrate, and a Knoevenagel adduct of aldehyde (**245**) and malononitrile. These intermediates undergo Michael addition followed by intramolecular cyclization and tautomerization to furnish the desired products (**246**). They also tested the antimicrobial activities of these compounds and some of them exhibited activity against *Staphylococcus albus*, *Streptococcus pyogenes*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Candida albicans* fungal strains.

3.6. Fused heterocycles with N-atom at the ring junction

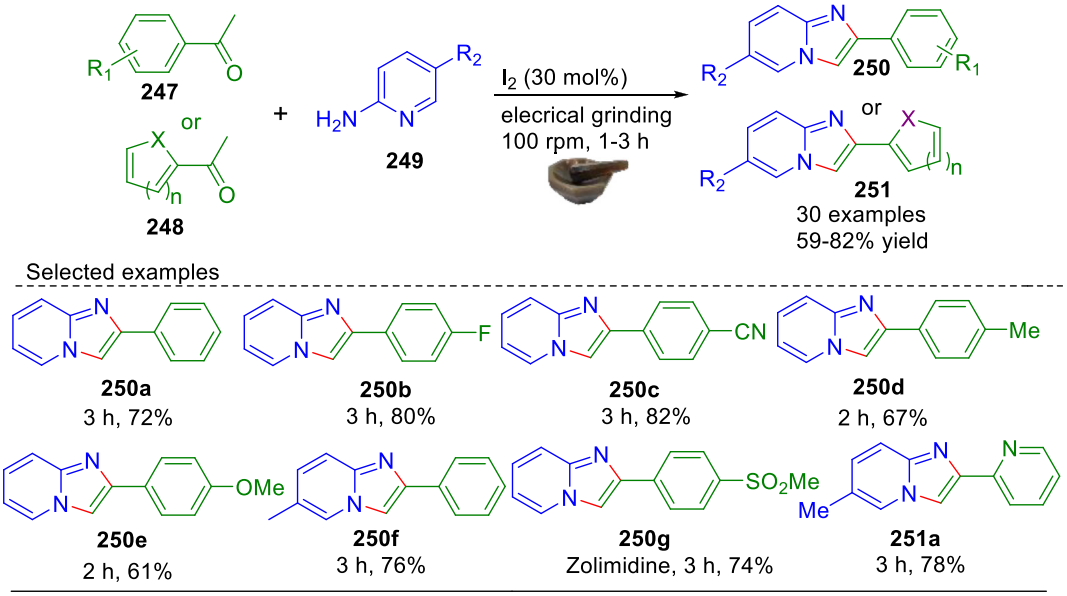
3.6.1. Imidazo[1,2-a]pyridines

The imidazo[1,2-*a*]pyridines, predominantly with substituents at 2- and 3-positions, are of significant pharmaceutical interest as they exhibit a huge spectrum of pharmacological activities [244,245]. Several imidazo[1,2-*a*]pyridines are marketed drugs, for example, the alpidem is anxiolytic agent, zolpidem is used for insomnia, zolimidine for peptic ulcer, and many more [62,245,246]. Most of the available two-component and multi-component strategies for their synthesis involve metal catalysts and hazardous organic solvents [62,245,246]. As a greener alternative, Banerjee and coworkers demonstrated a grindstone procedure for the iodine promoted synthesis of 2-arylimidazo[1,2-*a*]pyridines (**250** or **251**). They used an indigenous electrical grinder for the cyclocondensation reactions of aryl methyl ketones (**247** or **248**) and 2-aminopyridines (**249**) (Scheme 44) [34]. The automated grinding was found better over manual grinding and neat heating. The grinding speed of the electrical grinder was also varied and it was found that 100 rpm was the best. A model reaction of acetophenone and 2-aminopyridine by grinding for 6 h in the absence of any catalyst did not afford any product, **250a**. The addition of I_2 as the catalyst could take the reaction to the forward direction and 30 mol % of I_2 was found as the optimum concentration for a better yield of **250a** (72% in 3 h). The reactions were conducted under neat-grinding conditions if one of the substrates was liquid and LAG (0.2 mL per mmol of the substrate, $\eta = 1.08$ μL/mg) when both were solids to deliver an array of the desired products (**250** or **251**) in good to high yields at ambient temperature. Different acetophenone derivatives (**247** or **248**) and 2-aminopyridines (**249**) with both electron-withdrawing and electron-donating substituents were well tolerated in the cyclocondensation. The yields of the final products derived from acetophenones with electron-withdrawing groups (entries **250b**,**c**) were found to be a little higher than electron-rich derivatives (entries **250d**,**e**). The successful transformation with acetyl heteroaromatic compounds further added to the broad substrate scope of this mechanochemical protocol (entry **251a**). They demonstrated a gram scale synthesis of zolimidine showcasing the utility of the grinding protocol. The E-factor (1.77) and cost of this method was found to be significantly lower than the reported conventional methods for zolimidine synthesis [76].

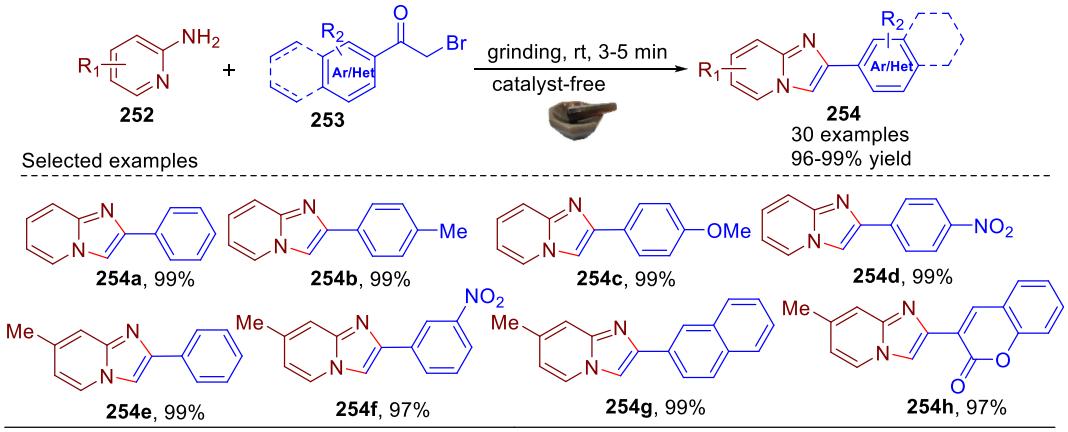
In a different strategy, the solvent-free and catalyst-free grinding of 2-aminopyridines (**252**) and a wide variety of ω-bromomethylketones (**253**), described by Nallagondu and coworkers, gave imidazo[1,2-*a*]pyridine derivatives (**254**) in excellent yields (Scheme 45) [247]. Interestingly, the model reaction of 2-aminopyridine and ω-bromoacetophenone under neat conditions afforded the product (**254a**) in 99% yield within 3 min, in contrast, LAG with different solvents like EtOH, water, IPA, PEG, glycerol gave poor results yielding **254a** in a range of 60–85% only after 7–10 min of grinding in Agate mortar-pestle. As seen in Scheme 45, the desired products (**254a-h**) from structurally varied ω–bromomethylketones and 2-aminopyridines were obtained in 99% yields within just 3–5 min, making it a very efficient protocol for C2-substituted imidazo[1,2-*a*]pyridines. Furthermore, they conducted the grinding reaction in the multi gram-scale without any drop in the yield of the corresponding product.

3.6.2. Benzo[d]imidazo[2,1-b]thiazole

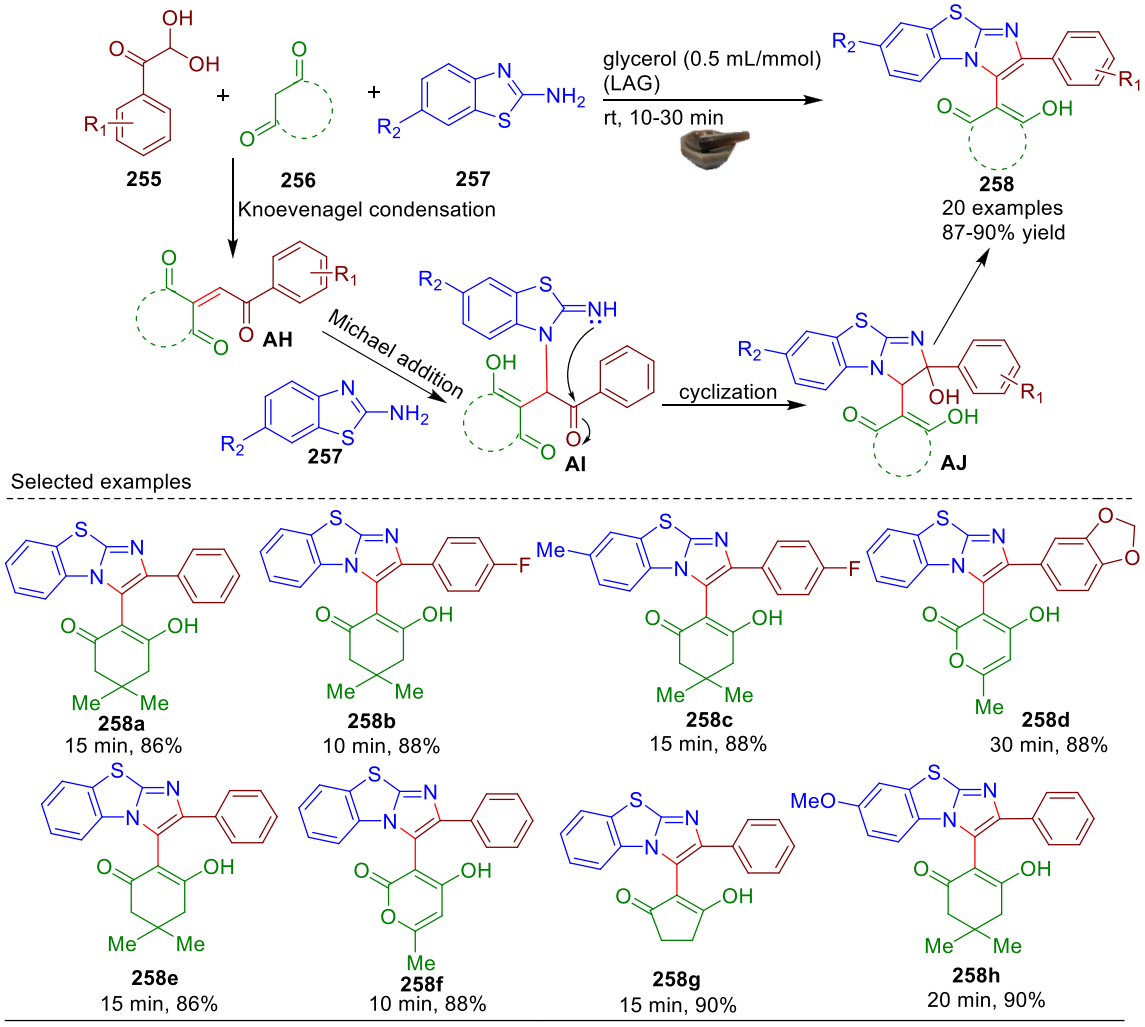
Benzo[*d*]imidazo[2,1-*b*]thiazole is an important sulfur-containing heterobicycle having *N*-atom at the ring junction that are the core structure of some natural alkaloids, agrochemicals, and pharmacologically active molecules [248]. Khurana and coworkers developed a simple one-pot synthetic protocol to access benzo[*d*]imidazo[2,1-*b*]thiazole derivatives (**258**) by grinding phenylglyoxal (**255**), cyclic enolizable carbonyl compounds (**256**), and 2-aminobenzothiazole (**257**) in glycerol as the LAG agent ($\eta = 1.13$ μL/mg of solid substrates) at room temperature (Scheme 46) [249]. The model reaction between phenylglyoxal, 2-aminobenzothiazole and 5,5-dimethylcyclohexane-1,3-dione



Scheme 44. I_2 promoted synthesis of 2-arylimidazo[1,2-*a*]pyridines (**250**, **251**) implementing automated grindstone chemistry [34].

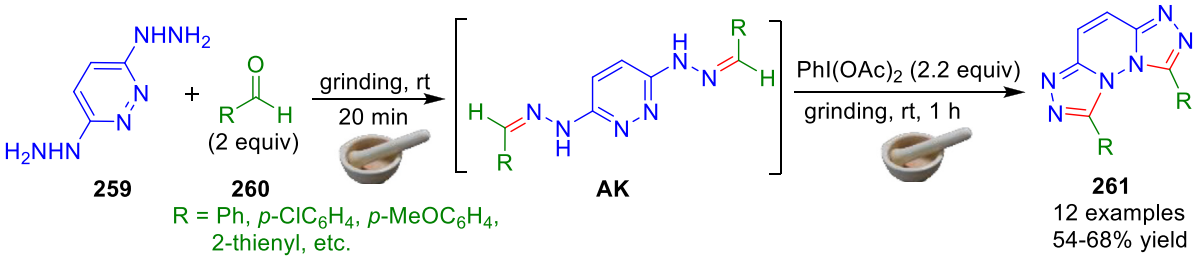


Scheme 45. Synthesis of imidazo[1,2-*a*]pyridine derivatives (**254**) under solvent-free and catalyst-free grinding conditions [247].



Scheme 46. Regioselective synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole (**258**) derivatives by grinding [249].

resulted in 86% yield within 15 min when ground using glycerol as the LAG agent, whereas, the same reaction required heating of 24 h in various solvents to afford **258a** in moderate yields in the solution phase. Other than glycerol, ethylene glycol, ethanol and PEG-400 were screened as LAG agents but the reactions took a longer time for completion. The amount of glycerol is optimized as 0.5 mL/mmol of the substrates. They proposed that mechanistic pathway involves Knoevenagel condensation of phenylglyoxal with 1,3-dicarbonyl compounds (**256**) to form an intermediate, **AH**. It then undergoes Michael type addition with 2-aminobenzothiazole



Scheme 47. Three-component synthesis of 3,6-disubstituted-bis-1,2,4-triazolo-[4,3-*b*:3′,4′- *f*]pyridazines (**261**) employing grindstone chemistry [252].

producing another intermediate, **AI**, which subsequently undergoes intramolecular cyclization (**AJ**) followed by dehydration to deliver the desired products (**258**). A library of 20 benzo[*d*]imidazo [2,1-*b*]thiazoles was prepared at room temperature in 87–90% yields by 10–30 min of grinding (entries **258a-h**).

3.6.3. Triazolopyridazines

1,2,4-triazolo[4,3-*b*]pyridazine derivatives, another fused heterocycle with *N*-atom at the ring junction, exhibit extensive pharmacological activities [250,251]. Aggarwal and coworkers reported a three-component reaction between 3,6-dihydrazinopyridazine (**259**), an aromatic or heteroaromatic aldehyde (**260**) and iodobenzene diacetate (IBD) to synthesize sterically hindered 3,6-disubstituted-bis-1,2,4-triazolo-[4,3-*b*:3′,4′-*f*]pyridazines (**261**) employing grindstone chemistry (Scheme 47) [252]. It was considered that both hydrazine functionalities of **259** react with 2 equiv of aldehydes (**260**) resulting in the intermediate **AK**, which was subsequently oxidatively cyclized by the addition of 2.2 equiv of hypervalent iodine, IBD to furnish the desired products (**261**) in moderate to good yields in 1 h. The solvent-free grinding approach afforded the desired compounds in 54–68% yields in one-pot, which is a significant enhancement as compared to the reported solution-phase multistep procedure (20–29%) for **261** [253].

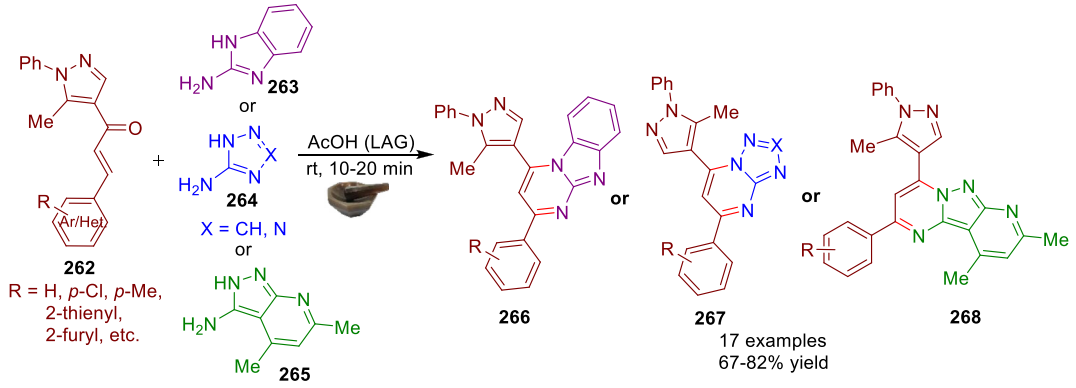
3.6.4. Azolopyrimidines

Both pyrimidine and pyrazole are significant pharmacophores and their fused systems (e.g. pyrazolyl-pyrimidines) are the scaffolds of medicinal interests [254]. Gomha and coworkers efficiently exploited the grindstone technique to prepare an array of pyrazolylbenzo [4,5]imidazo[1,2-*a*]pyrimidines (**266**), pyrazolyl-triazolo[1,5-*a*]pyrimidines or pyrazolyl-tetrazolo[1,5-*a*]pyrimidines (**267**), and bis-azolopyrimidines (**268**) (Scheme 48) [255]. The acetic acid catalyzed grinding reaction of pyrazolylchalcones or its bis-pyrazolyl-chalcones (**262**) with the appropriate heterocyclic amines such as 2-aminobenzimidazole (**263**), aminotriazole (**264**), aminotetrazole and 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**265**) under solvent-free conditions resulted in the formation of respective products (**266**–**268**) in a period of 10–20 min with high yields. Using the reaction conditions, a total of 17 derivatives were synthesized by the group. They also conducted antimicrobial activity assay of the title compounds and a couple of them displayed comparable antibacterial activity as the marketed drug *penicillin G* and *streptomycin*.

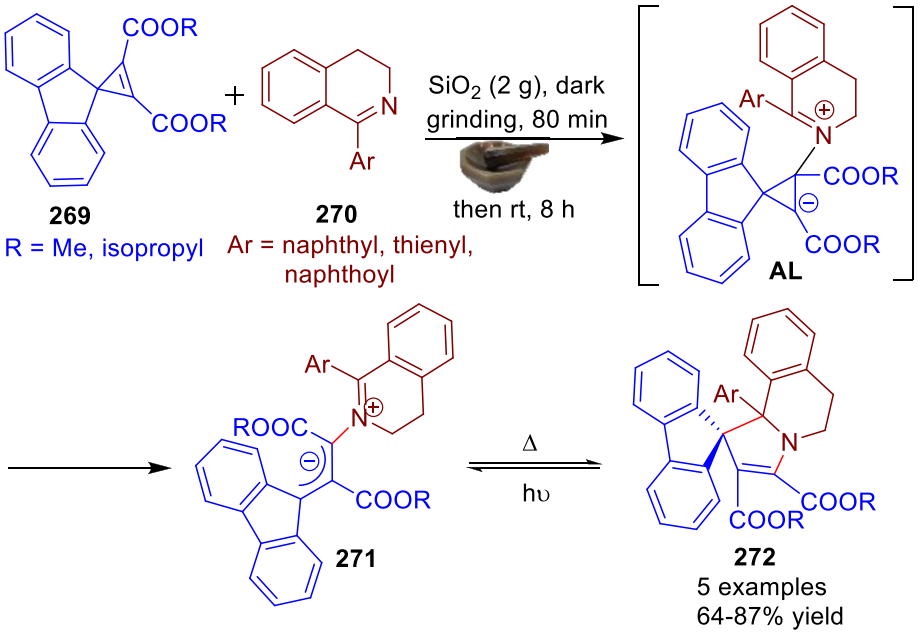
3.7. Spirocycles

Spirocycles with hetero-atoms such as spirooxindoles, spiroindole-thiazolidinones are the core units of a number of pharmaceuticals and natural products [256,257]. Grindstone chemistry was successfully employed for the facile synthesis of various spirocycles [27,35,258–260]. In an interesting approach, Ahmed and coworkers demonstrated a grinding protocol towards the synthesis of photochromic tetrahydroindolizines (THIs) (**272**) and also studied the substituent effect on their photochromic properties (Scheme 49) [258]. Grinding a mixture of spirocyclopropenes (**269**), 1-substituted aryl-3,4-dihydroisoquinolines (**270**) in the presence of silica gel (2 g) as the grinding auxiliary in a mortar-pestle delivered five THIs (**272**). A 40 min of grinding followed by 2 h rest period, further 40 min grinding and standing for 8 h delivered the desired products, dialkyl-5′,6′-dihydro-10′b-substituted-1′H-spiro[fluorine-9,1′-pyrrolo[2,1-*a*]isoquinoline-2′,3′-dicarboxylate (**272**) in 64–87% yields. The photochromic THIs were formed via electrophilic attack of **269** to the *N*-heterocycle dihydroisoquinoline derivatives (**270**) and consequently opened via a cyclopropyl-allyl intermediate (**AL**) to give the colored betaines (**271**), which is thermally closed to give **272** via 1,5-electrocyclization pathway. The newly synthesized THIs offered diverse photochromic behaviors.

In another study, Bazgir and coworkers reported a one-pot, pseudo four-component mechanochemical protocol to furnish



Scheme 48. Usefulness of pyrazolylchalcone synthons towards the synthesis of pyazolopyrimidines (**266**–**268**) by hand-grinding [255].



Scheme 49. Grindstone mediated synthesis of photochromic tetrahydroindolizines (THIs) (**272**) [258].

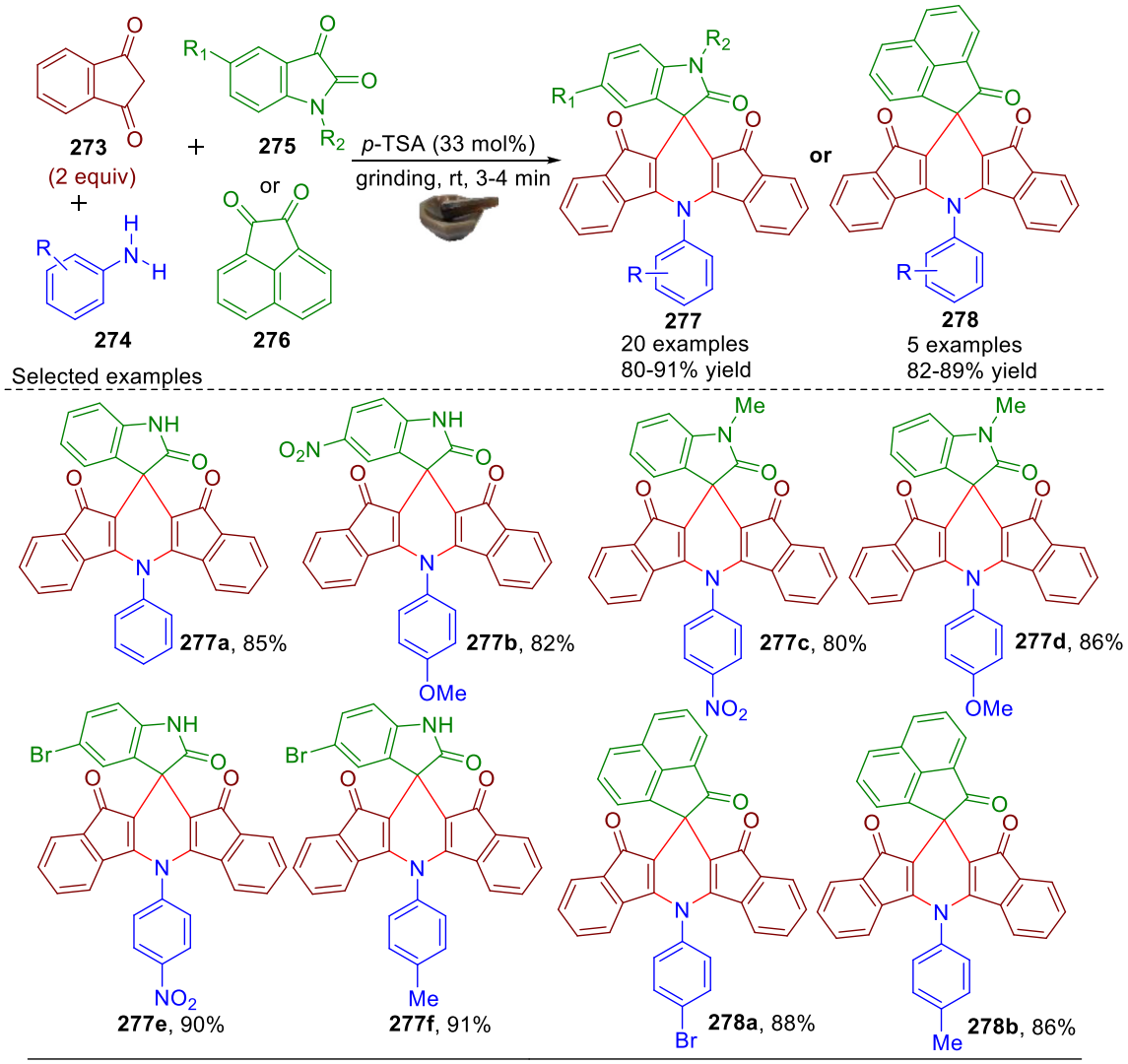
spiro[diindenopyridine-indoline]triones (**277**) or spiro [acenaphthylene-diindenopyridine]triones (**278**) (Scheme 50) [259]. The protocol involves the grinding of 1,3-indandione (**273**), aromatic amines (**274**), with isatins (**275**) or acenaphthylene-1,2-dione (**276**) in the presence of *p*-TSA as the catalyst to furnish the products (**277** or **278**) in high yields. The pilot experiment carried out by grinding isatin, aniline, and 1,3-indanedione in the presence of 30 mol% of *p*-TSA for 3–4 min afforded the corresponding product (**277a**) in 85% yield, while without *p*-TSA, the yields of products were low (<40%) even after 30 min of grinding. This method was validated using substitutions in isatin and anilines with both EDGs and EWGs delivering 20 examples of the title compounds, spiro[diindenopyridine-indoline]triones (**277a-f**) in high to excellent yields (80–91%). Also, a small library of 5 derivatives of spiro[acenaphthylene-diindenopyridine]triones (**278a,b**) was prepared in a similar manner in high yields (82–89%). The method was tested in a gram scale (0.1 mol, 60 g of reaction mass) with the synthesis of **277a** in a glass bowl using a mechanical stirrer to obtain 85% yield in just 5 min.

Sharma and coworkers recently developed a catalyst-free hand grinding strategy towards a domino multicomponent reaction to afford 2-amino-2-oxospiro[indoline-3,4′-pyran]-3′-carbonitriles (**282**) in excellent yields (Scheme 51) [260]. The reaction involves the grinding of isatin or acetanaphthelenequinone (**279**), malononitrile or ethylcyanoacetate (**280**) and enolizable 1,3-dicarbonyl compounds (**281**) to afford the desired spirocycle (**282**) in excellent yields. During the optimization studies with isatin, malononitrile and dimedone, they observed multiple unidentifiable products when all the substrates were ground together without any catalyst. Therefore, a stepwise domino reaction strategy was adopted by grinding isatin and malononitrile for 10 min followed by the addition of the third component, dimedone to the reaction mixture and grinding it for another 15 min to afford the desired product (**282a**) in 94% yield. LAG using different solvents such as water, glycerol and PEG-400 did not affect any improvement in the product yield, and thus, the neat condition was adopted for other derivatives. By varying substrates 19 derivatives of 2-oxospiro [indoline-3, 4′-pyran]-3′-carbonitriles (**282**) were prepared in 87–95% yields. However, reactants like 1-methyl isatin, 2-cyanoacetamide and acyclic 1, 3-dicarbonyl compounds such as ethylacetoacetate gave trace amounts of the products (entries **282g**,**h**) due to the electronic effects. The authors proposed that the reaction proceeds by the formation of Knoevenagel condensation product **AM**, which undergoes subsequent Michael addition (**AN**), intramolecular cyclization (**AO**) and tautomerization to furnish the desired products, **282**. The products were obtained in sufficiently pure form by simple filtration avoiding tedious workups or column chromatographic purification steps. The feasibility of the protocol was further demonstrated by the gram scale (5 mmol) production of (**282a**) in 92% yield. The green metrics of this protocol are E-factor 0.054, atom economy 85% other than simple experimental set-up establishing the usefulness of the grindstone method in the effortless synthesis of these heterocycles in a short time.

Recently Gobinath et al. reported another spirocycle synthesis in one-pot with the aid of mortar-pestle grinding [35]. The syntheses of 10-phenyl-3,4,6,7-tetrahydro-1*H*-spiro [acridine-9,20-indoline]-1,3,8-trione derivatives (**286**) were achieved via a pseudo-four-component reaction by grinding of isatins (1 equiv) (**283**), 1,3-cyclohexanedione (2 equiv) (**284**) and substituted anilines (1 equiv) (**285**) under solvent-free conditions for 10 min grinding catalyzed by *p*-TSA (Scheme 52) [35]. The method gave excellent yields of the spirocycles, **286** (78–95%) derived from aromatic amines with both EWG and EDG delivering a short library of 10 compounds. On cytotoxic screening of the products, the derivative of *p*-methoxyaniline was found to be highly active against MCF-7 cancer cell lines.

3.8. Diversity oriented heterocycle synthesis

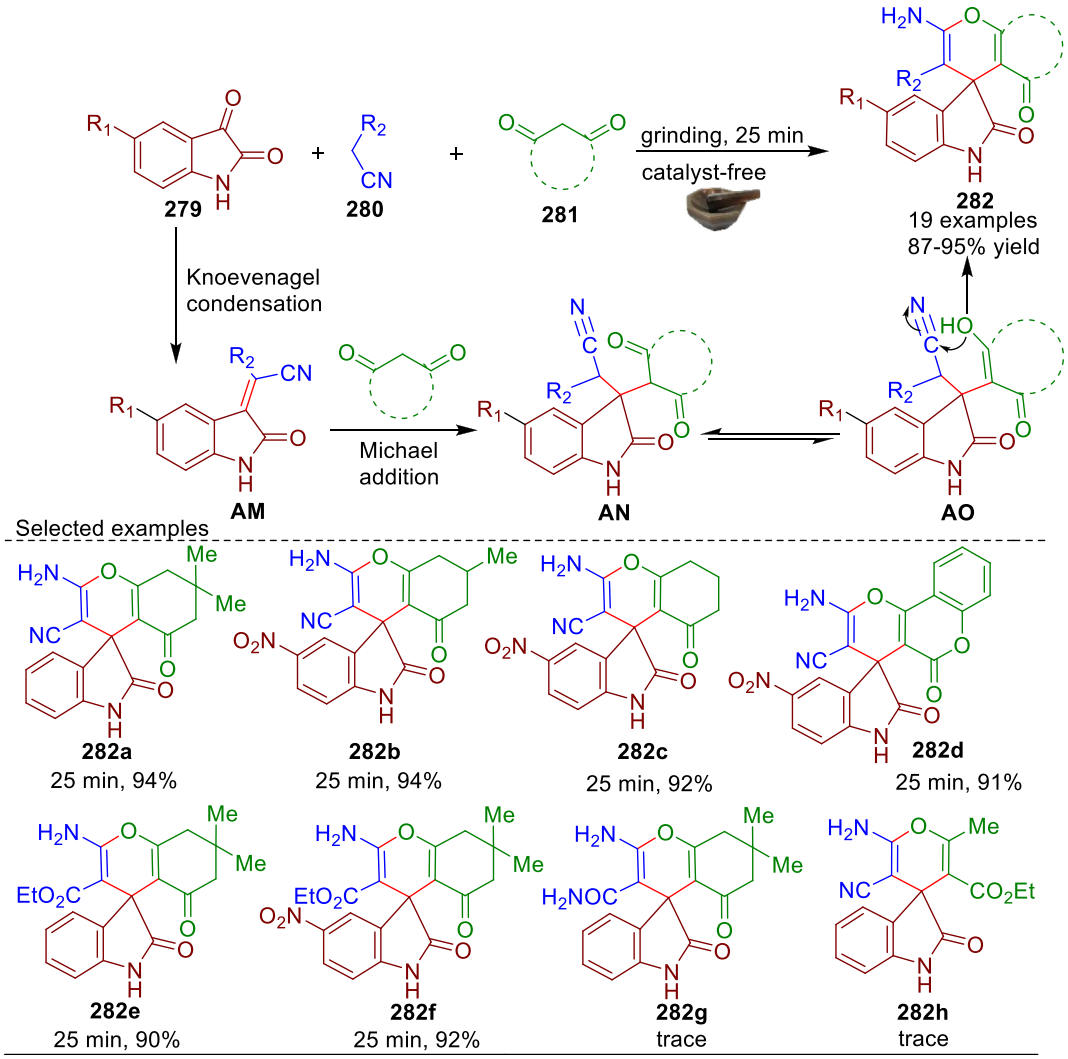
A few grinding protocols are available for the synthesis of more than one heterocycles using the same methodology by a simple change of one of the key substrates. In one such approach, an interesting chemodivergent multi-component synthesis of pyrroles (**289**) and tetrahydropyridines (**290**) were developed by Dhinakaran et al. via mortar-pestle grinding [261]. The catalyst-free grinding of ethyl (*E*)-3-(aryl/alkyl amino)acrylates (**287**), 2,2-



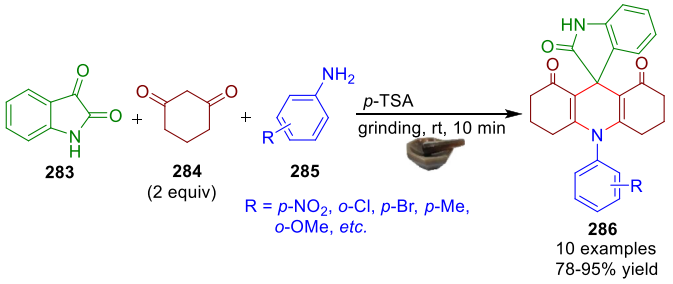
Scheme 50. Synthesis of spiro[diindenopyridine-indoline]triones (**277**) and spiro[acenaphthylene-diindenopyridine]triones (**278**) using grindstone technique [259].

dihydroxy-1-arylethan-1-ones (**288**) and malononitrile afforded either the expected tetrasubstituted pyrroles, **289** or unexpected tetrahydropyridines, **290** as the major product under the same reaction condition by the electronic effect in (*E*)-3-(aryl/alkyl amino) acrylates (**287**) (Scheme 53) [261]. The representative reaction involving 2,2- dihydroxy-1-phenylethan-1-one, malononitrile and ethyl (*E*)-3-((4-bromophenyl)amino)acrylate showed the superiority of hand-grinding (yield of **289a** is 85% after 10 min of grinding) over solvent-phase reactions using solvents like EtOH, $CHCl_3$, H_2O etc. under refluxing conditions (yields of **289a** is 80% in EtOH after 30 min; 40% in H_2O after 6 h; 50% in $CHCl_3$, after 6 h). Interestingly, under optimized grinding conditions, they observed unexpected chemoselectivity governed by the substitutions in the *N*-aryl ring of enamine **287**. In the cases of *N*-phenyl, *N*-heterocycle and *N*-phenyl ring with electron-withdrawing substituents in enamine **287**, the cyclization involving the secondary amine group and the carbonyl is favoured leading to the formation of polysubstituted pyrroles (**289**). On the other hand, *N*-phenyl rings with electron-donating substituents favor cyclization involving the secondary amine group and the nitrile functionality to afford tetrahydropyridines (**290**). As per the plausible mechanism, initially, the pseudo-aldehyde, **288** and malononitrile furnish 2-(2-oxo-2-arylethylidene)malononitrile (**AP**), the Knoevenagel condensation product, which further undergoes Michael addition with enamine **287,** resulting in the formation of the intermediate, **AQ**. If a phenyl with EWG is present in *N*-aryl ring in **AQ**, the cyclization involving the secondary amine group and the carbonyl is favoured and reaction proceeds via path (a), leading to the formation of polysubstituted pyrrole **289** (Scheme 53). On the other hand, the presence of EDG in the *N*-aryl ring of the intermediate **AQ** favours the attack of the secondary amine group to one of the nitrile functionalities leading to the six-membered cyclic product **290** via path (b) (Scheme 53). The method was validated by changing the *N*-substituents in enamine and 10 examples of pyrrole, **289** as the major product and 12 examples of tetrahydropyridines**, 290** as the major products were prepared in 70–85% yields.

Fahmi et al. developed a grindstone technique for the synthesis of a variety of nitrogen-based heterocycles with promising biological activities by the condensation of α,β-epoxyketones (**291**) with various amine derivatives involving imine formation followed by cyclization via the opening of epoxy ring (Scheme 54) [262]. Firstly, grinding **291** with hydrazine or phenylhydrazine for 5–7 min under solvent-free conditions in a porcelain mortar-pestle at room temperature afforded the stable pyrazoline-4-ol derivatives (**292**) with a yield of 80–93%. The same reaction in the conventional approach by refluxing in ethanol takes 7–14 h



Scheme 51. A hand grinding mediated domino multicomponent synthesis of 2- amino-2-oxospiro[indoline-3,4′-pyran]-3′-carbonitriles (**282**) [260].

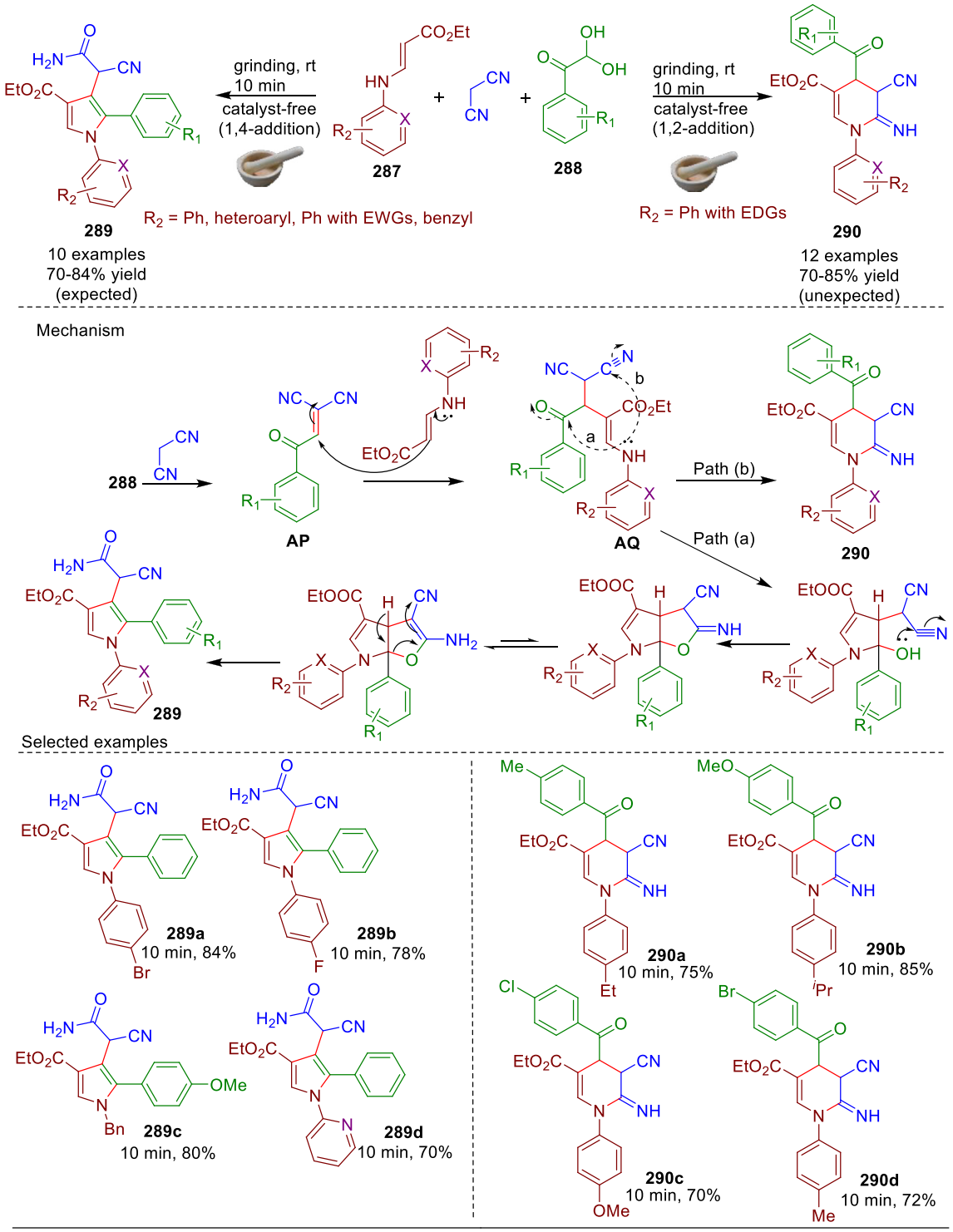


Scheme 52. A one-pot synthesis of 10-phenyl-3,4,6,7-tetrahydro-1*H*-spiro[acridine-9,20-indoline]-1,3,8-trione (**286**) derivatives via a pseudo-four-component cyclocondensation reaction [35].

yielding 59–83% of **292**. Next, grinding **291** with urea/thiourea in a porcelain mortar-pestle for 3–10 min in the presence of a few drops of acetic anhydride afforded imidazoline derivatives (**293**) with a yield of 81–86%, which otherwise would take 2–3 h to complete in refluxing ethanol to afford relatively lower yields (71–80%) of **293**. Subsequently, reacting **291** with semicarbazide in a mortar-pestle afforded 1,2,4-oxadiazin derivative (**294**) and pyrazole derivative (**295**) with a yield of 60% and 80%, respectively.

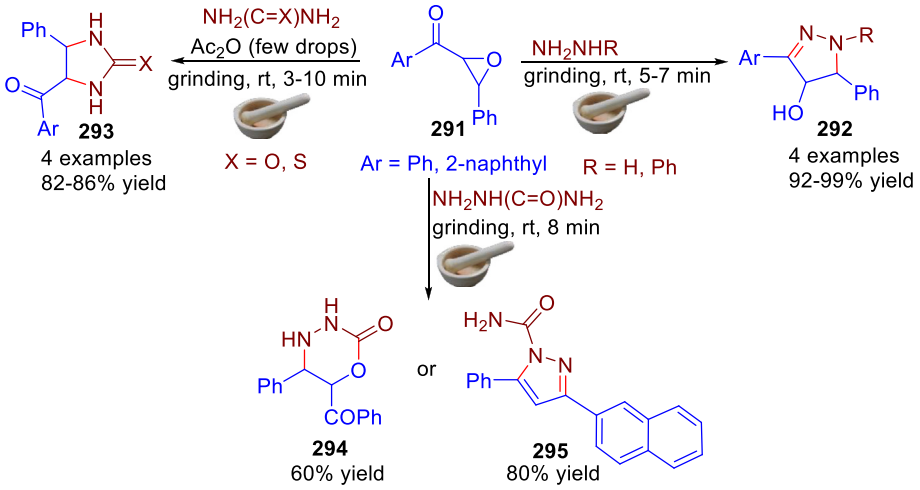
Abdel-Aziem and coworkers synthesized a library of new pyrazolopyridazines (**298**), pyrazoles (**300**), and pyrimidines (**302**) by a cyclocondensation reaction of 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one (**296**) with various substituents such as hydrazonoyl halides (**297**), hydrazines (**299**) and 2-amino-heterocycles (**301**), respectively, via a mortar-pestle grinding (Scheme 55) [263]. For pyrazolopyridazines (**298**) synthesis, a weak base, sodium carbonate, was used during grinding, whereas, pyrazoles (**300**) could be obtained in catalyst-free conditions and synthesis of pyrimidines (**302**) required catalytic amount of AcOH for successful conversion. These compounds were also synthesized in conventional media by heating in ethanol. There were obvious advantages for grinding technique such as operational simplicity, solvent-free conditions, facile work-up coupled with high to excellent yields. The anticancer activity of the synthesized compounds was checked for *in vitro* antiproliferative against different human tumor cell lines such as melanoma, leukemia and cancers of the brain, lung, colon, ovary, prostate, breast and kidney. The results displayed that pyrazolo[3,4-*d*]pyridazines derivatives (**298**), pyrazole (**300**) exhibited powerful anticancer activity.

Abdullah and Rabeaa demonstrated the synthesis of some pyrazole-derived heterocycles using diversity oriented synthesis involving condensation of a heteroaromatic amine, **303** with

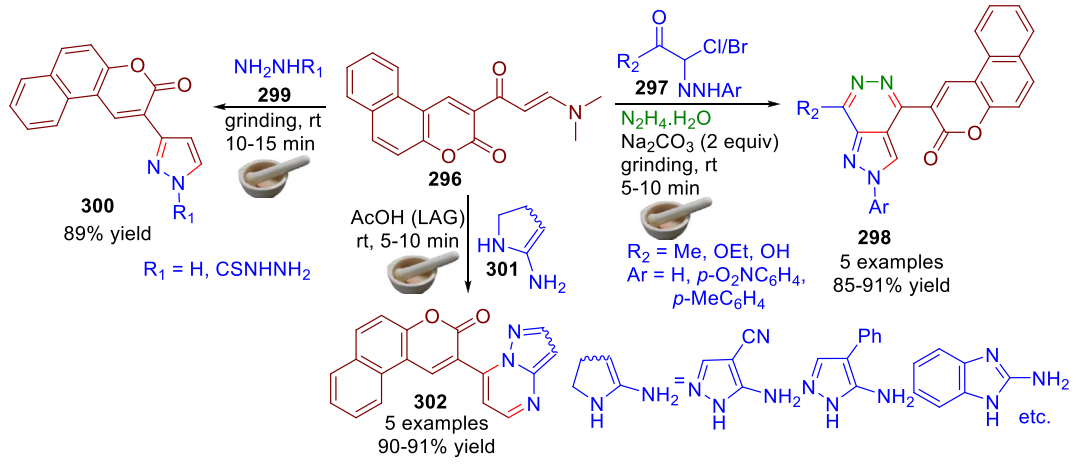


Scheme 53. A chemodivergent multi-component synthesis of pyrroles (**289**) and tetrahydropyridines (**290**) using grindstone technique [261].

various aromatic aldehydes (**304**) and then treating the corresponding Schiff's bases (**305**) with sodium azide to convert to tetrazoles (**306**) and also with various anhydrides (**307**) to obtain oxazepine derivatives (**308**) using a simple hand-grinding technique (Scheme 56) [264]. The Schiff base (**305**) of 4-aminoantipyrine (**303**) and aromatic aldehydes (**304**) are used as precursors for the synthesis of oxazepine and oxazepane derivatives. Schiff bases **305** upon neat grinding with sodium azide in the absence of any catalyst or additive produced tetrazole derivatives (**306**) in excellent yields within 12–15 min. Again, the conversion of **305** to oxazepine derivatives (**308**) were more facile and six derivatives were obtained from phthalic, maleic and succinic anhydride (**307**) within 5–10 min of grinding in 83–93% yields.



Scheme 54. Synthesis of various nitrogen-based heterocycles by condensation of α,β-epoxyketones (**291**) with various amine derivatives in a mortar-pestle [262].



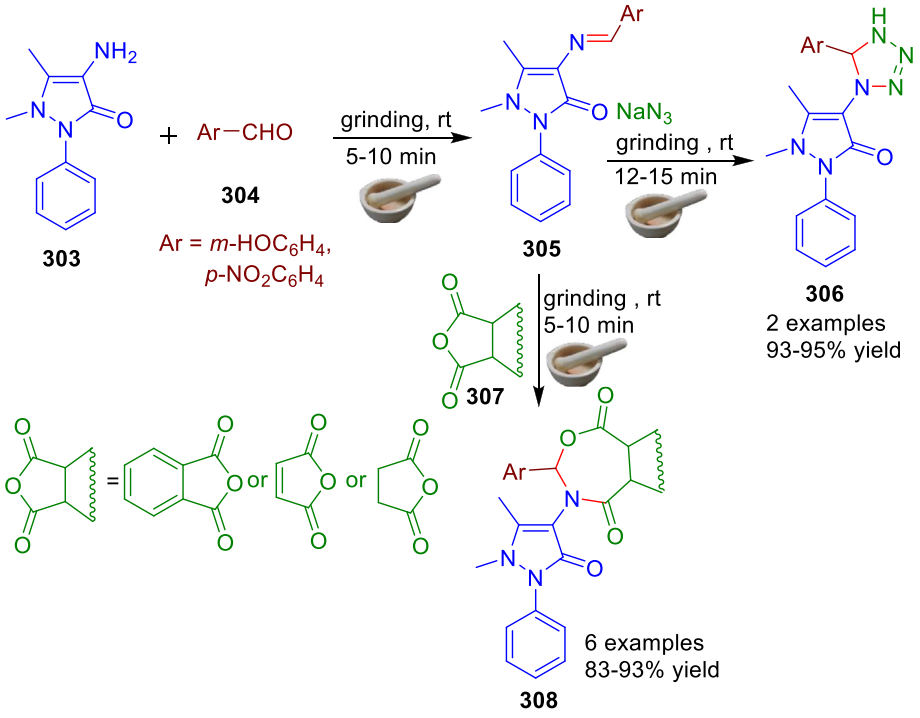
Scheme 55. Synthesis of new pyrazolopyridazines (**298**), pyrazoles (**300**), and condensed pyrimidines (**302**) via grinding of 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one with different reagents [263].

4. Derivatization of heterocycles

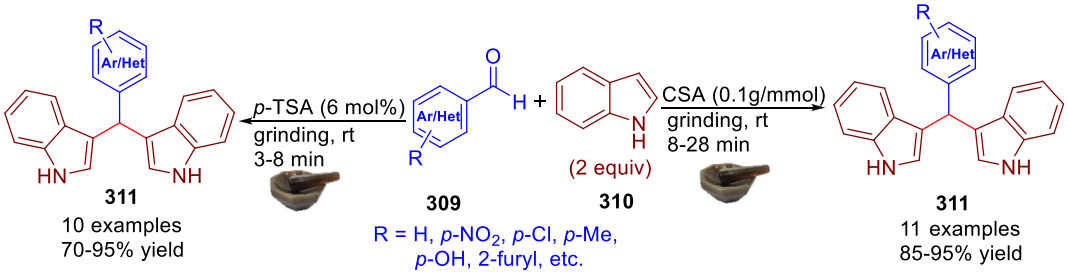
The appropriate derivatization of preassembled heterocyclic cores is an important tool to accomplish the synthesis of targeted drugs or new chemical entities for activity screening in the fields of biology, pharmaceuticals, and agrochemicals. Although there are limited attempts as compared to the construction of heterocycles, the grindstone technique is successfully employed in the derivatization of heteroaromatic systems as well. In this section, the available literature on grindstone-aided derivatization of heteroaromatics will be discussed.

Bis(indolyl)methanes are important for their immense anticancer activities [265–267]. 3,3′-Diindolylmethane is a novel mitochondrial H + -ATP synthase inhibitor that can induce p21Cip1/Waf1 expression by induction of oxidative stress in human breast cancer cells [265]. A standard and convenient method for the synthesis of bis(indolyl)methanes is the Friedel–Crafts reaction between indoles and carbonyl compounds in the presence of an acid or base. A solvent-free grindstone process for the synthesis of bis(indolyl)methanes (**311**) was described by Sadaphal et al. involving the condensation reaction of aromatic aldehydes (**309**) and indole (**310**) in a 1:2 ratio in the presence of cellulose sulfuric acid (CSA) as the solid-acid catalyst (Scheme 57) [268]. The initial investigations revealed that bis(indolyl)methanes (**311**) formation takes a longer time (30–90 min) in the solution phase using common solvents such as ACN, MeOH, EtOH in the presence of catalysts such as $ZrCl_4$, $ZrOCl_2$, [Hmim][HSO_4], Ph_3CCl, whereas, a small amount of CSA (0.1 g/mmol of aldehyde) as the catalyst under grinding condition effectively form the title products in >90% yield within 8 min. The catalyst CSA was prepared easily by treatment of chlorosulfonic acid on cellulose in hexane under stirring conditions and isolated by filtration. Total 11 examples of **311** were prepared in 85–95% yields. After the reaction, CSA was filtered and reused without much loss in reactivity. Earlier, Pasha and coworkers reported a similar hand-grinding method for the synthesis of bis(indolyl)methanes (**311**) by grinding indole with various aldehydes (**309**) using a catalytic amount of *p*-TSA (6 mol%) in a mortar-pestle for just 3–8 min (Scheme 57) [269].

Brahmachari and Das demonstrated the mechanosynthesis of *gem*-(β-dicarbonyl)arylmethane derivatives (**315**) via C-3 alkylation of indoles (**314**) via L-proline catalyzed MCR involving 1,3-dicarbonyl compounds (**312**) and aromatic aldehydes (**313**) as the other substrates (Scheme 58) [32]. The reactions were conducted in a watch glass grinding with a spatula under solvent-free conditions at room temperature. Initial studies showed that the grinding of benzaldehyde, 4-hydroxycoumarin and indole to afford bis-indole



Scheme 56. Diversity oriented conversion of 4-aminoantipyrine (**303**) to tetrazole (**306**) and oxazepine (**308**) derivatives using grindstone technique [264].

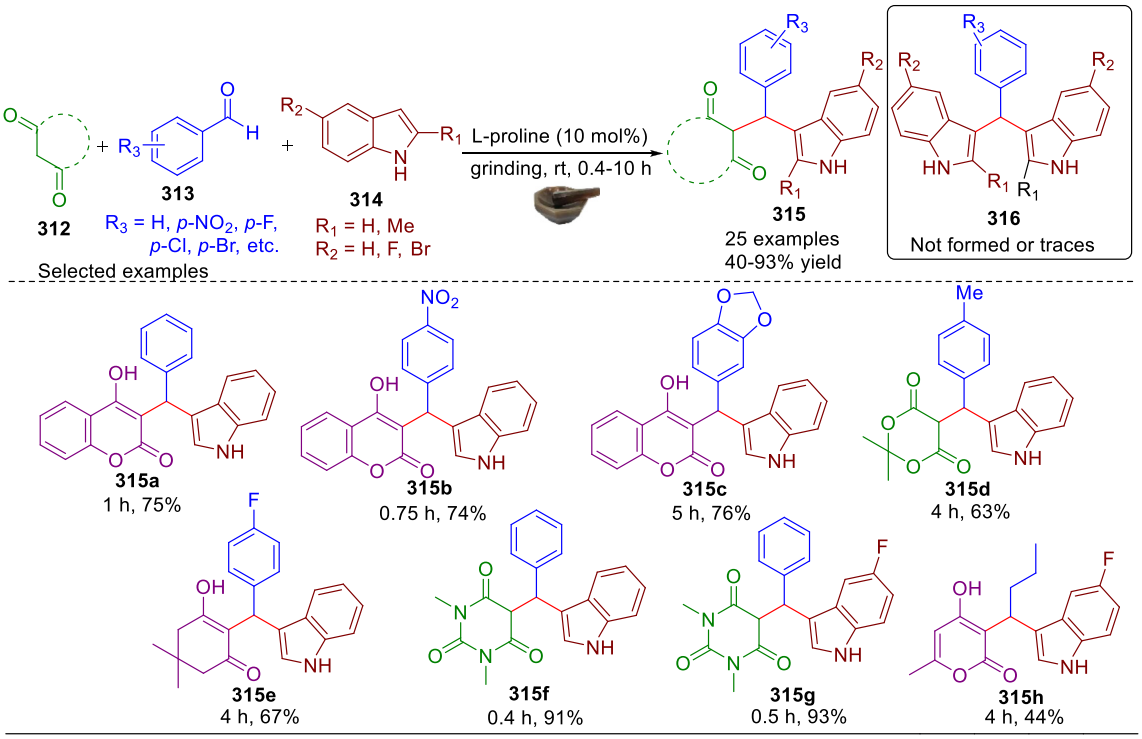


Scheme 57. Solvent-free grindstone process for the synthesis of bis(indolyl)methanes (**311**) [268,269].

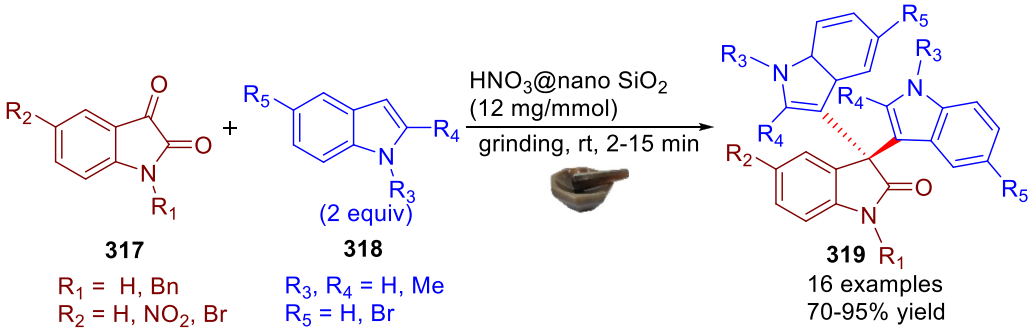
derivative (**316**) instead of the desired product (**315a**) when Lewis acid ($AlCl_3$, $ZrOCl_2$, $Bi(NO_3)_3$) or the ionic liquid ([Hmim][HSO_4]) are used as the catalysts, whereas, organocatalyst, L-proline could catalyze the formation of the title product, **315a** in 75% yield within 1 h. This atom-economic grinding procedure afforded moderate to high yields of non-racemic products (**315**), which displayed varying optical rotations. However, they did not report the enantiomeric excess (*ee*) of the reactions in their article. The scope and generality of the protocol was explored by reacting a variety of aromatic aldehydes containing electron-donating or electron-withdrawing substituents in the aromatic ring with 4-hydroxycoumarin (or other carbonyl compounds, **312**) and substituted indoles (**314**) and the corresponding products (entries **315a-g**) were obtained in moderate to high yields (53–93%). Aliphatic aldehydes like butyraldehyde also took part in the reaction with a low yield (44%) of the desired product (entry **315h**). The Michael addition from the indole moiety to the Knoevenagel adduct of **312** and **313** furnishes the desired products.

In another recent work on C-3 activation of indoles, Nikoofar and coworkers presented a solvent-free procedure for the synthesis of both symmetrical and unsymmetrical di(indolyl)indoline-2-ones (**319**) by grinding isatin (**317**) with indoles (**318**) with a solid acid catalyst, HNO_3@nano SiO_2 (12 mg/mmol) in mortar-pestle (Scheme 59) [270]. The catalyst was prepared by stirring commercial nano SiO_2 (2.5 g) with conc. HNO_3 (1 mL) in dry $CHCl_3$ at room temperature for 3 h. The requirement of catalyst is confirmed by conducting a model reaction which showed the formation of only 21% of the title compound in the absence of any catalyst even after 100 min under the neat condition as compared to 94% yield of the product within 5 min if HNO_3@nano SiO_2 (12 mg/mmol) is used as a catalyst in the mixture. A library of 16 derivatives of di(indolyl) indoline-2-ones (**319**) was prepared in 70–95% yields within 2–15 min of grinding. Notably, the reaction could also be performed with the same ease in the solution phase (such as ACN, MeOH and EtOH) resulting in excellent yields of **319** (90–95%) within 40–60 min. A remarkable decrease in reaction times for grinding method is attributed to local heat generation during pulverization by a pestle than the simple collision of two substrates in the solution phase, indicating the superiority of the grinding protocol over the conventional method.

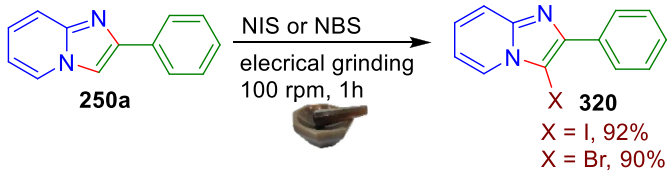
Halogenation of heteroaromatic ring is a useful tool for further functionalization, such as cross-coupling reactions. In one such approach, Banerjee and group demonstrated a late-stage halogenation at C3-position of 2-arylimidazo[1,2-*a*]pyridine (**250a**) as an



Scheme 58. L-Proline catalyzed mechanochemical C-3 alkylation of indole to form *gem*-(β-dicarbonyl)arylmethane derivatives (**315**) by mortar-pestle grinding [32].



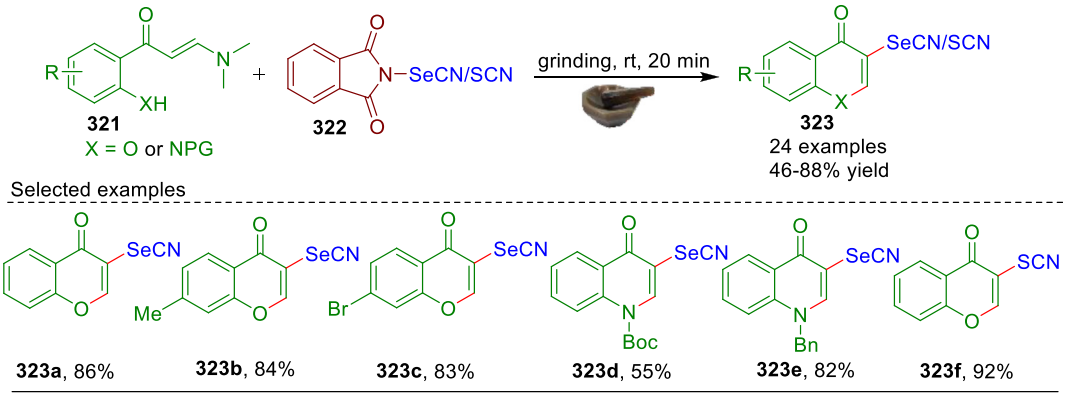
Scheme 59. Synthesis of symmetrical and unsymmetrical di(indolyl)indoline-2-ones (**319**) by grinding isatins and indoles or pyrrole with HNO_3@nano SiO_2 [270].



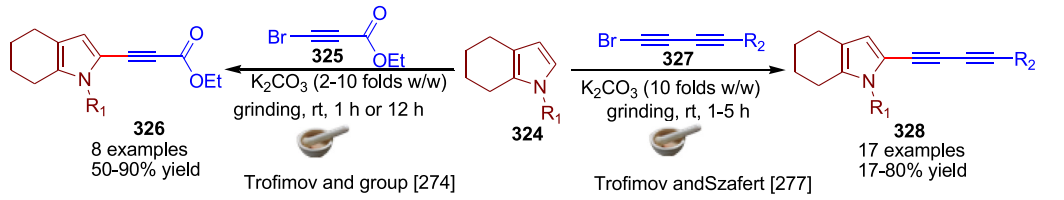
Scheme 60. Late stage halogenation at the C3-position of 2-arylimidazo[1,2-*a*]pyridine (**250a**) using an electrical grinder [34].

extension of their work on the synthesis of imidazo[1,2-*a*]pyridines (Scheme 60) [34]. 2-Phenylimidazo[1,2-*a*]pyridines (**250a**) was subjected to C–H halogenation in the heteroaromatic ring by grinding with *N*-iodosuccinimide (NIS) and *N*-bromosuccinimide (NBS) in an electrical grinder at 100 rpm for 1 h to afford corresponding Br-or I-substituted imidazo[1,2-*a*]pyridines (**320**) in excellent yields (90% and 92%, respectively).

Organic selenocyanates are important functionality for various selenium-containing compounds, which exhibit a range of bioactivities [271]. The development of mild and metal-free methods for syntheses of organic selenocyanates is of current research focus [272]. In this direction, Xiao et al. used an electrophilic selenocyanating reagent *N*-selenocyanatophthalimide (PhthSCN) (**322**) for the synthesis of 3-selenocyanato-substituted chromones (or quinolones, **323**) from 2-hydroxyphenyl enaminones (**321**) by a tandem cyclization selenation in mortar-pestle (Scheme 61) [273]. The reaction condition was standardized by using 2-hydroxyphenyl enaminone, *N*-selenocyanatophthalimide (**322**) as model substrates which afforded **323a** with yields of 44–71% after 12 h when carried out in the solution phase using different solvents such as CH_2Cl_2, DCE, THF, ACN, toluene, and DMF. However, the same reaction in grinding condition afforded **323a** with a yield of 86% within 20 min. The other selenocyanating reagent, selenocyanobenziodoxolone also afforded the desired product (**323a**) but in lower yield (72%). This protocol displayed a broad substrate scope with regards to phenylenaminones with various electron-donating or electron-withdrawing groups as well as phenols (entries **323a-c**) or *N*-protected anilines (entries **323d**,**e**) which took part in the reaction with equal ease. The generality of



Scheme 61. Synthesis of 3-selenocyanato-substituted chromones (or quinolones, **323**) from 2-hydroxyphenyl enaminones (**321**) using *N*-selenocyanatophthalimide (PhthSeCN) (**322**) by employing grindstone chemistry [273].



A)

Entry	R_1	Time (h)	Yield (%)
1.	H	1	50
2.	Me	1	80
3.	Bn	1	90
4.	Me, BuO	12	62

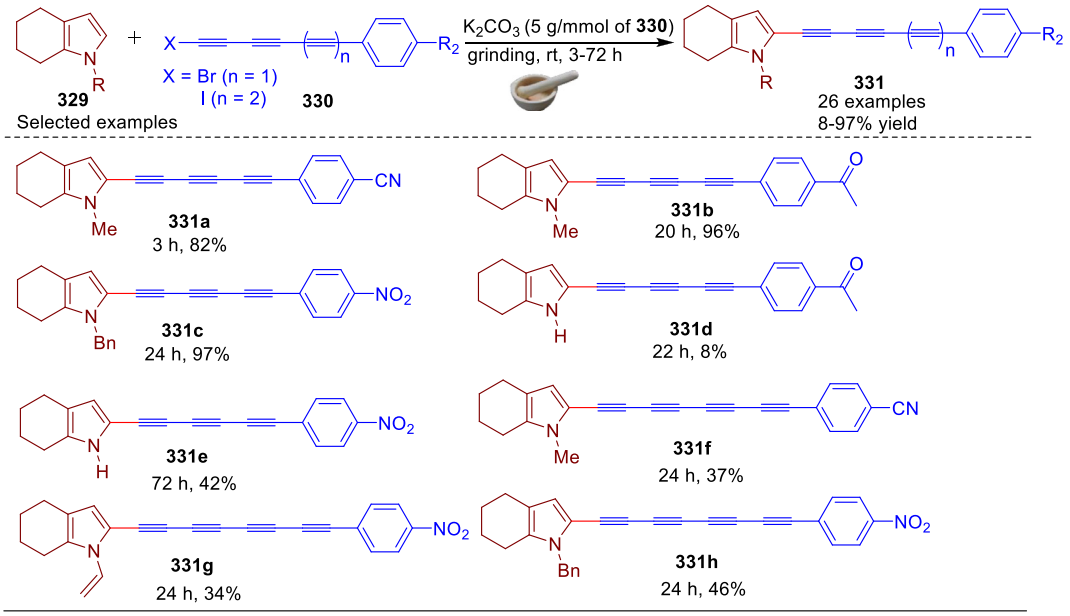
B)

Entry	X	R_1	R_2	Time (h)	Yield (%)
1.	Br	Me	COOMe	1-5	77
2.	Br	vinyl	COOBn	1-5	43
3.	Br	Bn	COOBn	1-5	80
4.	Cl	H	*p*-$EtO_2CC_6H_4$	24	36
5.	Br	H	*p*-$EtO_2CC_6H_4$	24	17

Scheme 62. Synthesis of alkynyl substituted 4,5,6,7-tetrahydroindoles (**326**,**328**) [274,277].

the protocol was demonstrated by a few examples of thiocyanation of enaminones with PhthSCN (entry **323f**), which gave the corresponding thiocyanated products in good to excellent yields. The method was validated in the gram-scale synthesis of organic selenocynates.

The cross-coupling reactions are scantily explored using the grindstone technique. In one such study, Trofimov et al. demonstrated a transition metal-free chemo- and regio-selective ethynylation of 4,5,6,7-tetrahydoindoles (**324**) with 3-halopropynoates (**325**) by grinding them in a china dish with solid K_2CO_3 to afford ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates (**326**) in good to excellent yields (Scheme 62) [274]. The C-2 alkynylation of indole usually requires a transition metal for the cross-coupling [275]. However, Trofimov and group achieved this under aerobic conditions at room temperature by the hand-grinding approach. Notably, 2–10 folds amount of K_2CO_3 (by weight) with respect to tetrahydoindoles (**324**) was used, which acts as a base and provides a grinding media for successful C-2 selective cross-coupling. Their previous effort of ethynylation of 4,5,6,7-tetrahydroindole on active Al_2O_3 surface via hand-grinding was not highly chemoselective [276]. They checked that the reactions did not proceed in the solution phase (diethyl ether, $CHCl_3$) or without the addition of K_2CO_3, and generally took 1 h for completion by hand-grinding, affording moderate to high yields (50–90%) of the products (entries 1–3, Table A, Scheme 62). Notably, the presence of bulky substituents (like CH(Me)OBu) on C1 of pyrrole did not affect the regioselectivity but took a longer time (12 h) for completion (entry 4, Table A, Scheme 62). Later the same group developed another method for the C–H butadiynylation via cross-coupling reaction of substituted 4,5,6,7-tetrahydroindoles (**324**) with 1-halobutadiynes (**327**) under mild, solvent- and transition metal-free conditions (Scheme 62) [277]. Multialkynyl cross-coupling reactions have been a topic of research interest for the last few decades [278]. The starting substrates, 1-halobutadiynes (**327**) were prepared from brominated esters of propiolic acid via Cadiot-Chodkiewicz cross-coupling with trimethylsilylacetylene in the presence of $Pd(PPh_3)_2Cl_2$/CuI. Again 10 times of K_2CO_3 against the substrate was used for solid-phase C-2 selective cross-coupling reaction. A drop in the yield was observed if the grinding matrix was changed to Al_2O_3. The influence of halogen in the reaction kinetics of the cross-coupling reaction was tested with 1-halobutadiynes taking Br or I as the halogen. The conversion was seen after 1 h, but Br-butadiyne appeared reacting faster than I-butadiynes with tetrahydroindole. The substrate scope was checked by varying substituents (R_1) at *N*-atom of tetrahydroindole (**324**) and the products (**328**) were obtained with moderate to high yields ranging from 43% to 80% by grinding reaction mixture up to 5 h (entries 1–3, Table B, Scheme 62). Next, they studied the influence of the phenyl spacer situated



Scheme 63. Synthesis of long-chain hexatriynyl- and octatetraynyl-substituted tetrahydroindoles (**331**) [279].

between the butadiyne fragment and an ester group on the coupling reaction using 1-bromobutadiyne and 1-chlorobutadiyne. In both cases, the reaction time was longer (24 h), delivering low yields of the products (entries 4 and 5, Table B, Scheme 62).

To further extend the scope, Szafert, Trofimov and coworkers synthesized long-chain hexatriynyl- and octatetraynyl-substituted pyrroles (**331**) by grinding *N*-substituted pyrroles (**329**) with 1-haloalkynes (**330**) in the presence of K_2CO_3 as the catalyst as well as solid support (Scheme 63) [279]. This time 5 g of K_2CO_3 per mmol of polyalkyne (**330**) was used for the smooth conversion to the title products **331** via C2–H activation of the aromatic ring of tetrahydroindoles. It was observed that the reactions of 1-bromohexatriynes and N-substituted tetrahydroindoles worked well, and the products were obtained with yields up to 97% with the reaction times ranging between 3 and 24 h (entries **331a-c**). However, the reactions with unsubstituted tetrahydroindole gave products with low to moderate yields (8–52%) (entries **331d**,**e**) after a long time of grinding (19–72 h). Again, reactions with 1-iodotetraynes were found sluggish and took 24–48 h for completion. A limitation of the method is that the reactions with unsubstituted tetrahydroindoles are slow and low-yielding.

5. Summary and future perspective

Mechanochemistry, i.e. the chemical transformations achieved by mechanochemical force, is a tool to conduct solvent-*less* reactions and has been recognized by IUPAC as one of the ten world-changing technologies. While mechanical milling is a superior and more versatile technique, a pair of mortar-pestle is the simplest tool for mechanochemical activation, and the technique, called "grindstone chemistry," has benevolent characteristics like simple instrumentation and operational simplicity. Since its formal introduction by Toda et al. in the last century [22], "grindstone chemistry" has traveled a long stride forward, particularly in recent years, and has been employed in a myriad of organic transformations. This includes but is not limited to traditional C–C bond formation, Schiff base and its derivatives, various name reactions, multicomponent reactions, and several of them led to the construction of heterocycles by cyclocondensation. Moreover, valuable materials and intricate structures including co-crystals, composites, dyes, MOFs, COFs, etc. were prepared by the grindstone method. It is postulated that the grinding of reacting components under the neat conditions or in the presence of a small volume of solvent as LAG agent allows the formation of a liquid/semi-liquid interphase with a high density of uniformly distributed reactants in close contacts to propel the reaction to completion mostly in just a few minutes. Keeping the main focus on the use of mortar-pestle grinding for the construction and derivatization of heterocycles, this review article captured a brief account on the other areas of applications to provide the entire spectrum on the scope of "grindstone chemistry" to the readers.

As seen in section 3, a variety of heterocycles could be efficiently synthesized by simple hand-grinding that include heterocycles with a single heteroatom (like pyrroles, furans, thiophenes, pyridines, chromenes, etc.), with two heteroatoms (like 1,3-benzazole, pyrimidines, quinoxalines, etc.), or even spirocycles, fused heterocycles etc. often with the aim of synthesizing new and important heterocyclic scaffolds with biological and medicinal importance. Although there is a limited number of attempts, the derivatizations of preassembled heterocyclic cores were also accomplished by grindstone technique that include halogenation, selective alkylation of the heteroaromatic rings, C–H activation etc. In several cases, the solvent- and catalyst-free transformations were achieved in a shorter time with higher yields ticking the check-box of several green matrices. For example, the grindstone method of Das et al. [34] for marketed drug, zolimidine with an E-factor of 1.77 is much greener and cheaper than a fancy solution-phase method by Bagdi et al. [76] with an E-factor of 14.22. In several other cases, the use of green-solvents like EtOH, PEG, H_2O or an ionic-liquid as LAG agents offered faster reaction kinetics and higher yields. Notably, facile aerial oxidation due to "open-air" grinding, easy separation products by simple filtration, easy recovery of heterogeneous catalysts are some of the common features of grindstone chemistry. However, manual grinding by a person is a labor-intensive process and concerns like "does the reaction kinetics depend on the physical power or the grinding speed?" or "how long the hand-grinding can be continued?" or "what is the scalability?" are some concerns often raised on manual-grinding. The solution to these problems is

automation in the grinding process and the electrical grinders are already used for the laboratory-scale synthesis of heterocycles [34]. So, despite some challenges "grindstone chemistry" has shown immense prospects as a viable alternative of the solution-phase methods.

From a future perspective, the use of hybrid techniques such as heating-grinding (by a heat gun) or grinding under LED lights are some possible advanced which may be achieved to overcome some current synthetic challenges in grindstone like cross-coupling reactions, C–H activation in the near future. Moreover, with automation in mortar-pestle grinding, a large grindstone apparatus can be envisaged for industrial-scale preparation of APIs (e.g. zolimidine), in a direction of practical implementation of grindstone chemistry to achieve sustainability.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

M.B. thanks DST-SERB, India (project no. EMR/2016/002253) for financial support.

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