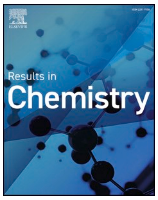
Results in Chemistry 18 (2025) 102675

Contents lists available at ScienceDirect

Results in Chemistry

journal homepage: www.sciencedirect.com/journal/results-in-chemistry



Recent advances in liquid assisted grinding chemistry: towards sustainable synthesis

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ARTICLE INFO

Keywords:
Mechanochemistry
Liquid-assisted grinding
Ion-assisted grinding
Neat grinding
Metal organic framework
Supramolecules

ABSTRACT

Mechanochemistry is undergoing a major renaissance in the fields of chemical and materials science, particularly in terms of synthesis. By injecting a small amount of a liquid into a reaction in a solid state, new mechanochemical technologies, including liquid-assisted grinding (LAG), where a liquid acts like a lubricant, facilitating the contact between solids in the substrate, thereby inducing solution-like areas where the molecules in the substrate solids can react. The screening of polymorphs, cocrystals, solvates, salts, and inclusion compounds has been accomplished through the use of LAG, a modification of conventional neat mechanochemical methods where reactivity is controlled and/or enhanced by the addition of a small amount of liquid. Nevertheless, insufficient research has been conducted on the application of this important technology in the synthesis of organic compounds. This article discusses the latest developments in LAG techniques and the potential of the most common forms of LAG for organic mechanosynthesis, as well as the solvent effect on the nature of the product obtained, the challenges to be overcome, optimal operating conditions, and solvent selection for the LAG processes.

Introduction

In recent years, chemical transformations induced by mechanical energy have become more and more popular, providing chemists and material scientists with new tools for improving synthetic chemical design [1]. This is among the top ten technologies that the International Union of Pure and Applied Chemistry (IUPAC) believes could revolutionize the world [2]. The typical way for carrying out mechanochemical reactions is to mill, grind, shearing reactants without using organic solvents or a catalytic proportion of solvent [3]. The approach integrates various green chemistry principles, such as employing ambient conditions, quick reaction kinetics, considerable decrease in solvent usage, and easy workup procedures [4]. Several chemical processes developed in the solution phase can be effectively replaced by this innovative approach, which frequently results in improved yields [5]. The prospects for mechanochemistry appear bright in conventional organic synthesis or organometallics as well as in a number of modern fields, such as biocatalysis, material chemistry, polymer chemistry, supramolecular chemistry, and the synthesis of active pharmaceutical ingredients (APIs) [6–9].

Conventional mechanochemical tools, such as a mortar and pestle in various sizes made of porcelain, granite, or agate (Fig. 1(A)), are used to accomplish chemical transformations, such as the synthesis of important organic compounds or intermediates and dyes [10]. Mechanochemical milling reactions are carried out by modern technologies, usually in mixer mills or planetary ball mills (Fig. 1(B)). The grinding balls inside the reaction jars in a planetary mill rotate on a planetary motion around an internal axis and simultaneously around an external axis during the milling process (Fig. 1(C)); in a mixer mill, the reaction jars are shaken quickly at a predetermined frequency (Fig. 1(D)), which causes the enclosed balls to shear, grinding the chemical components [11,12]. The jars and balls vary in size and are made of Teflon, zirconia, agate,

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https://doi.org/10.1016/j.rechem.2025.102675
Received 1 April 2025; Accepted 1 September 2025
Available online 3 September 2025

tungsten carbide, stainless steel (SS), and other materials. The milling speed for ball mills and the oscillation frequency for mixer mills are the other frequent variables (Fig. 1(E)). Mechanochemistry is carried out in continuous mode using twin-screw (TSE) and single-screw (SSE) extrusion. TSE uses two intermeshing, counter-rotating screws to continually drive solid reactants through a barrel (Fig. 1(F)).

The development of a neat or solventless methods of synthesis is an important step in green and sustainable chemistry due to their economy and environmental benefits. The Green Chemistry Institute Pharmaceutical Roundtable of the American Chemical Society for instance was founded to promote the application of green chemistry and engineering in the pharmaceutical industry [13]. Despite the desire for clean grinding, the reaction kinetics are often retarded when the substrates or intermediaries become stuck within the solid mass of the reaction mixture [14]. One easy way to help the solid substrates at the solid-liquid interphase is to inject a small amount of solvent to create a pasty mass. LAG has been widely utilized to produce a variety of important organic compounds with conventional solvents including methanol (MeOH), ethanol (EtOH), *N*,*N*-dimethylformamide, and water (H_2O). Additionally, to accelerate mechanochemical processes, solid matrices can be used as grinding auxiliaries (silica alumina, sand, salts, polyethylene glycol, zeolites, and so on) [15–17].

For the quantification of the solvent used in relation to the solids in a LAG approach an empirical parameter η is described [18]. η is the ratio of the volume of liquid added (in μL) to the mass of the reacting materials (in mg), this shows the proportion of the liquid additive to the reactants' total mass [19–21]. As a result, the added liquid in LAG is often less than 1–2 μL/mg. For instance, a normal solution-based reaction $\eta >$ 12 μL/mg, whereas neat grinding is indicated by $\eta = 0$ μL/mg. According to a landmark study done in 2002 by Shan et al., small solvent additions increased the rate of hydrogen-bonding-driven cocrystallizations under mechanochemical conditions [22]. The mechanochemical processes involved in this synthetic approach were first named solvent-drop grinding, but other research groups have dubbed it kneading [14–19]. In mechanochemical processes, the term liquid-assisted grinding (LAG), was first used by the Friscic group [20] and is currently the most used. The term "liquid" has replaced "solvent" to underline that the reactants for mechanochemical reactions may or may not be soluble in liquid phase. These modifications benefit typically include higher reaction yields and rates, greater chemical reactivity, control of product polymorphism, and a higher degree of products crystallinity [23]. The liquid utilized additionally affects the powder products' microstructure and degree of crystallinity (Fig. 2) [21–24].

There has been a steady growth in the number of research employing LAG for its distinctive advantages in organo-synthesis [25], in addition to its particularly successful employment in solid-state pharmaceuticals via the screening of polymorphs, cocrystals, solvates, salts, and inclusion compounds [26–28].

Mack and co-workers showed the effect of solvent polarity on the palladium-catalyzed alkyne-alkyne coupling product under liquid-assisted mechanochemical conditions [29]. Shortly after, the Browne group selectively fluorinated *β*-diketones under LAG conditions [30]. The chemoselectivity of the reaction was modified by the application of LAG or by neat grinding. It is commonly known that the mobility required for the organic ligands and the metal ions to carry out the intended coordination reactions is provided by the solvents [31]. In specific mechanochemical processes, applying high mechanical force

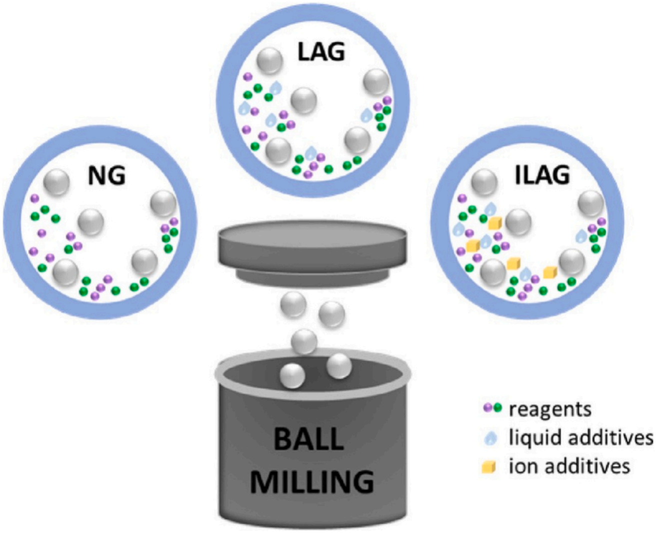


Fig. 2. Mechanochemical methods: Liquid Assisted Grinding (LAG), Ion and Liquid Assisted Grinding (ILAG), Neat Grinding (NG) [24].

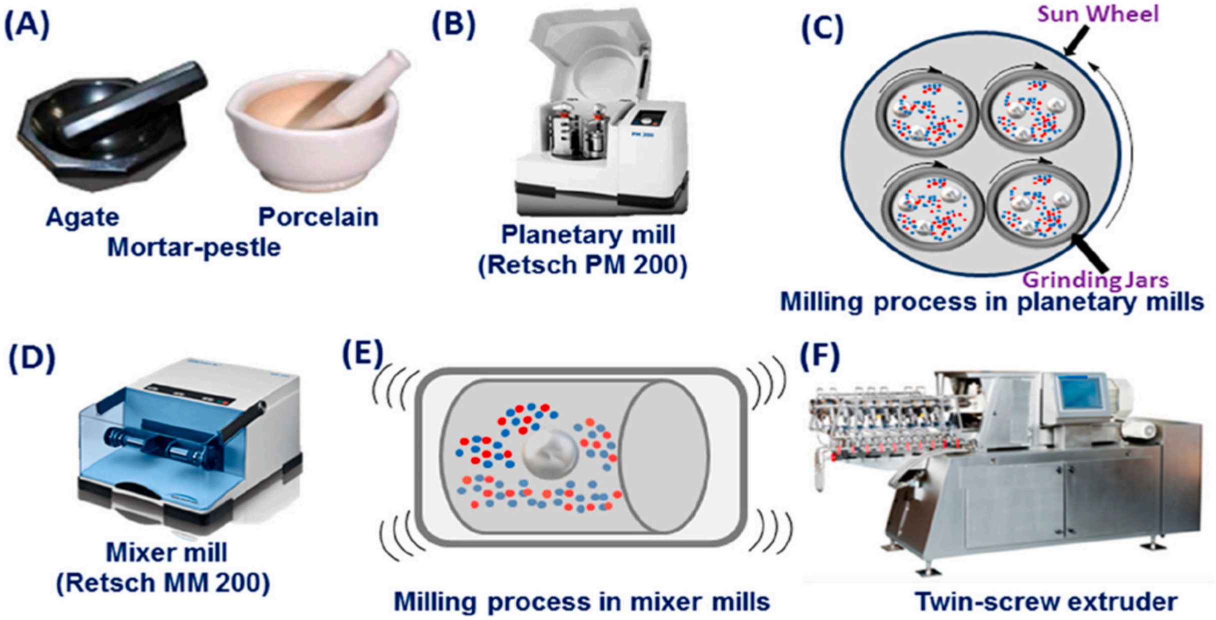


Fig. 1. Common tools for mechanochemistry (Adapted from Banerjee et al.,) [12].

during ball milling, heating, adding salt catalysts and liquid, and extrusion are required to provide extra impetus to initiate the reaction [32]. Although neat grinding is the most straightforward process, the synthetic range is more constrained, leading to partial conversion and amorphization of the final product [33]. Bennett et al. have shown the amorphization of activated open metal-organic frameworks (MOFs) under solvent-free grinding conditions. However, the presence of the liquid hindered amorphization and boosted reactivity by acting as a space-filling agent [34]. The primary goal of this study is to highlight and consolidate recent development in organic-mechanosynthesis and associated fragments and functionalities utilizing a LAG approach, as well as to forecast the LAG technology's continued progress.

Liquid assisted mechanochemical mediated synthesis of metal-organic frameworks

MOFs are a type of indispensable crystalline porous and polymeric materials with continuous frameworks that comprise metal ions covalently bonded together by organic bridging ligands or linkers in a three-dimensional structure [1,2]. Currently, the most popular method of producing MOFs in the laboratory is solvothermal synthesis, which requires a large volume of organic solvents, longer reaction duration, enormous waste generation and functionalization difficulties. From a sustainability standpoint, this is neither an environmentally friendly nor economically viable way to produce MOFs on a large scale. However, the development of safer, more environmentally friendly reactions and methods has received significantly more attention in organic synthesis than in coordination chemistry and MOF synthesis. Several research groups have recently started to address the need for novel, environmentally friendly processes to produce metal-organic material.

Over the last decade, mechanochemistry has emerged as a sustainable method for synthesizing some MOFs, offering a unique approach that is difficult to achieve using conventional methods. For instance, neat grinding of anhydrous $CoCl_2$ with 2,2'-Bipyridine (bipy) in an attempt to produce the coordinated polymer $[CoCl_2\ (bipy)]_n$ yielded no product. But when ethanol (EtOH) was added in modest amounts to the reaction mixture, the polymer $[CoCl_2(bipy)]_n$ was rapidly obtained in high yield [35]. Similarly, the addition of a small volume of water increased the solid-state reaction between ethylenethiourea (etu) and Ag (etu). LAG provided quantifiable yields in less than a minute, whereas the neat reaction took a longer time to reach complete conversion [36].

Furthermore, LAG not only accelerates mechanochemical processes but also permits host-guest complexes to reversibly self-assemble. For instance, Braga et al., [37] found that a liquid addition significantly affects the production of inclusion compounds polymer $[CoCl_2(dace)]\infty$ in the 1-D coordination polymer. Similarly, milling $CoCl_2$ and dace with water (LAG) resulted in a hydrated material $[CoCl_2(dace)]\infty\cdot nH_2O$. However, adding organic liquids like acetone, 2-propanol, or DMSO resulted in the reversible incorporation of solvent guests into the polymer host structure. Several studies have shown that using LAG and ILAG techniques may significantly improve the reactivity of metal oxides [38,39]. For example, milling zinc oxide (ZnO) with fumaric acid (H_2fum) for 30–60 min does not result in the formation of a new compound. However, milling or grinding with appropriate amount of liquid additives allows for the quick formation of structurally distinct coordination polymers. Similarly, when ZnO and H_2fum are milled with 3 or 4 equivalents of water produces the one-dimensional coordination polymers $Zn(fum)\cdot 4H_2O$ and $Zn(fum)\cdot 5H_2O$, respectively. Furthermore, milling in the presence of ethanol (EtOH) or methanol (MeOH) results in the synthesis of hitherto unidentified phases, which have been shown to be the hydrated 2-D coordination polymer $Zn(fum)\cdot 2H_2O$ and the anhydrous 3-D polymer Zn(fum) respectively. After milling with various liquid additives, it was observed that the volume of H_2O has correlation to the formation of distinct metal-organic phases (Fig. 3**).** This is because high hydrogen bonding liquids like EtOH or MeOH lower the thermodynamic activity of water, allowing for the production of low-hydration materials. Consequently, liquids that do not effectively reduce water activity, including acetonitrile, or 2-propanol, result in highly hydrated materials [38–40]. Interestingly, LAG syntheses provide four unique structures by changing the solvent phases in this instance.

Furthermore, adding only a small amount of liquid can significantly expedite the coordination polymer synthesis from carbonates or oxides. For instance, Adams et al. [41] showed the formation of coordination polymers employing LAG or the solvent-free milling reaction of transition metal carbonates with organic linkers' protonated hydrochloride salts, including bipy. Similarly, Yuan et al., showed that changing the liquid additive may influence the formation of metal-organic compounds. They investigated the mechanochemical reaction between

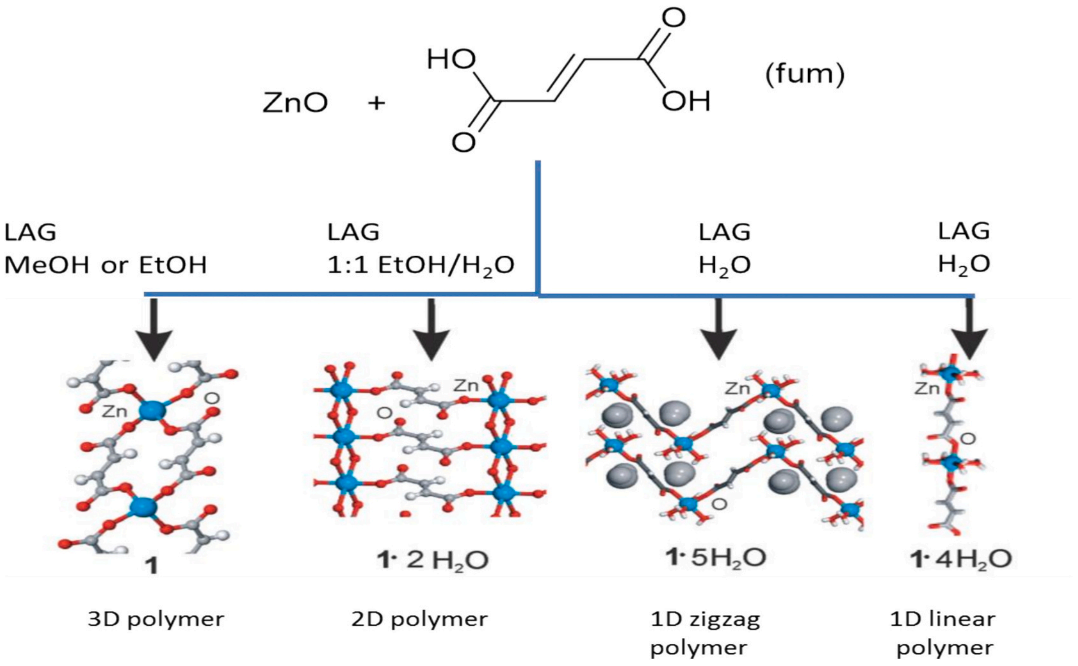


Fig. 3. Reaction of zinc oxide and fumaric acid using various solvents [38].

terephthalic acid and zinc carbonate under LAG conditions [42]. When zinc terephthalate dihydrate was milled with MeOH, a 3-D close-packed monohydrate framework (Fig. 4) was formed, whereas milling with H_2O produced a 1-D coordination polymer. In contrast, grinding with DMF produced an open structure made up of two-dimensional sheets connected by terephthalate linkers with a square-grid topology (Fig. 4).

In another work, Lewinski group and coworkers employed LAG to develop a mechanochemical mediated synthesis of MOF-5 material (IRMOF). The interaction between zinc-oxo carboxylate containing pre-assembled Zn_4O^{6+} units and terephthalic acid resulted in the formation of MOF-5 [43]. When a catalytic amount of DMF were added, the reactants were completely converted to MOF-5, with a high surface area of 1831 m^2/g. The neat process employing the benzoate-based cluster performed poorly (Fig. 5). Similarly, Užarevic et al. [44] used a similar technique to synthesize zirconium-based UiO-66-NH_2 and UiO-66 frameworks, using 12-hexanuclear coordinated zirconium oxo-clusters. MOFs were easily constructed using LAG of pre-assembled hexanuclear clusters terephthalic acid and methacrylate or benzoate ligands. The UiO-66 framework may be easily constructed via a one-pot approach consisting of terephthalic acid, zirconium(IV) propoxide and water. The approach allowed for quick and straightforward access to frameworks that were difficult to synthesize in solution [45]. The employment of water as a liquid component in LAG synthesis eliminated the need for DMF. It resulted in materials with excellent catalytic activity and porosity for the hydrolysis of nerve gas analogues.

Stolar et al. [46] employed in-situ X-ray diffraction (XRD) to explore the influence of nineteen solvents on HKUST-1 production. When compared to neat grinding (NG), polar liquid additive such as nitromethane, and weakly polar liquid including toluene, hexane, dichloromethane, chloroform, have no positive effect on the mechanochemical processes. However, protonic liquid additives, on the other hand, greatly enhanced the synthesis of HKUST-1. Polar protic solvents such as alcohols, are excellent at hastening the production of HKUST-1, resulting in the accelerated reaction rate and highest yield. With the addition of methanol, the formation of HKUST-1 was detected in the reaction mixture practically instantly, and after five minutes of grinding, the maximal conversion was attained. Whereas, when the same amount of isopropanol or EtOH was employed as LAG, the conversion was slower, and the process took around 20 min to complete. The results show that protic liquids are more effective than polar aprotic liquid additives in increasing the production of HKUST-1. Examples of these liquid additives are N,N-diethylformamide (DEF), DMF, acetone, and acetonitrile. These findings suggest that the mechanochemical production of HKUST-1 is significantly influenced by the coordination capacity of liquid additives.

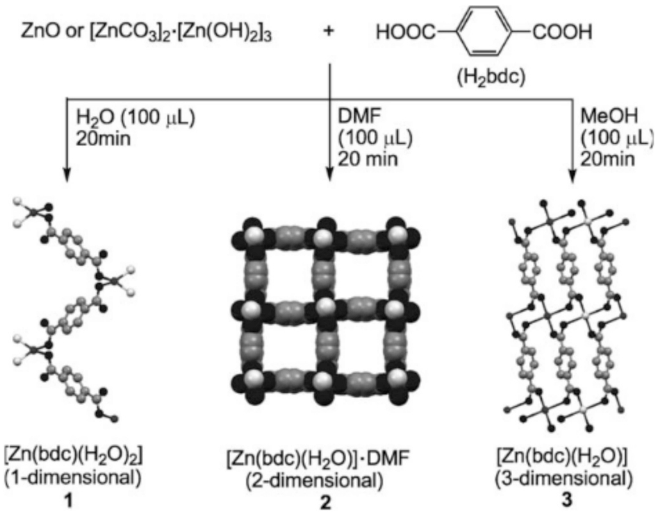


Fig. 4. Liquid mediated synthesis of Zn-(MOF)1–3 [42].

In another study, Yang et al. [47] employed a mixture of $H_2O/EtOH$ as a liquid auxiliary to examine the influence of solvent concentrations on the production of $Cu_3(BTC)_2$. The polymer $Cu_3(BTC)_2$ can be obtained under solvent free condition using H_3BTC and anhydrous copper acetate ($Cu(OAc)_2$) since $Cu(OAc)_2$ contains crystal water, which functions as an auxiliary solvent, and can therefore increase the crystallinity of a product. The addition of a suitable quantity of additional solvent to the system enhances both the fluidity of the reactant and the crystallinity of the product. In this case, increasing the quantity of solvent from 50 to 400 μL improves the product crystallinity. Wang et al. reported the application of LAG in the synthesis of high-quality metal organic framework (MOF-74) M_2(dobdc) analogues (M = Mn, Mg, Ni, Co, Zn, Cu, dobdc^{4-} = 2,5-dioxidobenzene-1,4-dicarboxylate) in the presence of metal nitrate salts at room temperature using Hünig's base ((*N*, *N*-diisopropylethylamine). The Hünig's base had dual responsibilities in the reaction, first as a base to enable the MOF formation and as a liquid to facilitate mechanical grinding. They characterized the MOF with PXRD and FTIR which showed that the prepared MOF exhibited high crystallinity and surface area [48]. The method was further optimized by the same author in another studies. The mechanochemical grinding of Mg $(NO_3)_2\cdot 6H_2O$, Et_3N, produced a crystalline Mg_2(*m*-dobdc)-MC within 5–10 min under optimal conditions. The study described here is an uncommon instance of a mechanochemically produced MOF exhibiting better gas sorption qualities than material produced using conventional solvothermal methods [49].

Pilloni et al. reported the use of LAG at room temperature to synthesize iron (III) carboxylate MOF that was isostructural with MIL-100 (Fe). They characterized the MOF using PXRD, FTIR and scanning electron microscope for morphology. The thermal stability was evaluated with TGA, and the adsorption performance of the MOF against the removal of 4,6-dimethyldibenzothiophene (4,6-DMDBT) from 4,6-DMDBT/n-heptane solutions mimicking a diesel fuel was also evaluated and compared to iron trimesate Basolite F300, a commercially available sample. Besides showing better crystallinity, optimal thermal stability, and higher surface area and pore volume, it was also revealed that the synthesized MOF outperformed Basolite F300 [50].

Ion-liquid assisted mechanochemical mediated synthesis of metal-organic frameworks

The ILAG approach has been employed in recent times to enhance the mechanochemical synthesis of MOFs by employing both ions and liquids concurrently [51]. Additionally, the usage of metal oxides can be more difficult than that of hydroxides and carbonates, which are frequently employed as surrogates for LAG synthesis of MOFs. For example, the synthesis of zeolitic imidazolate frameworks (ZIFs) from ZnO was attempted, but neither LAG nor neat grinding resulted in complete conversion [52]. The reactivity of metal oxide can be improved using ILAG, which involves performing LAG with a catalytic quantity of an inorganic salt. The ILAG approach was originally used to develop pillared MOFs using zinc terephthalate (open square grid sheets) separated by 1,4-diazabicyclo[2.2.2]octane (DABCO) as the pillaring ligand [53]. Under LAG conditions, attempt to synthesize the pillared MOF using ZnO, terephthalic acid and DABCO was unsuccessful. This differs from fumaric acid-based pillared MOFs, which were easily obtained via LAG. However, addition of stochiometric amount of nitrate ions, such as ammonium or alkaline metal nitrate, LAG efficiently generated the anticipated MOF within 30 min. A distinct pillared MOF of zinc terephthalate sheets based on hexagonal Kagome-topology was produced by substituting sulfates for nitrates in this ILAG process, indicating the vital roles of the ILAG in regulating the MOF's topology.

Subsequently, Beldon and coworkers carried out another mechanochemical reaction using LAG and ILAG under which a series of zinc oxide and imidazole based ZIFs were produced. Various solvents including DMF, DEF, and EtOH in combination with salt additives ($NH_4CH_3SO_3$,

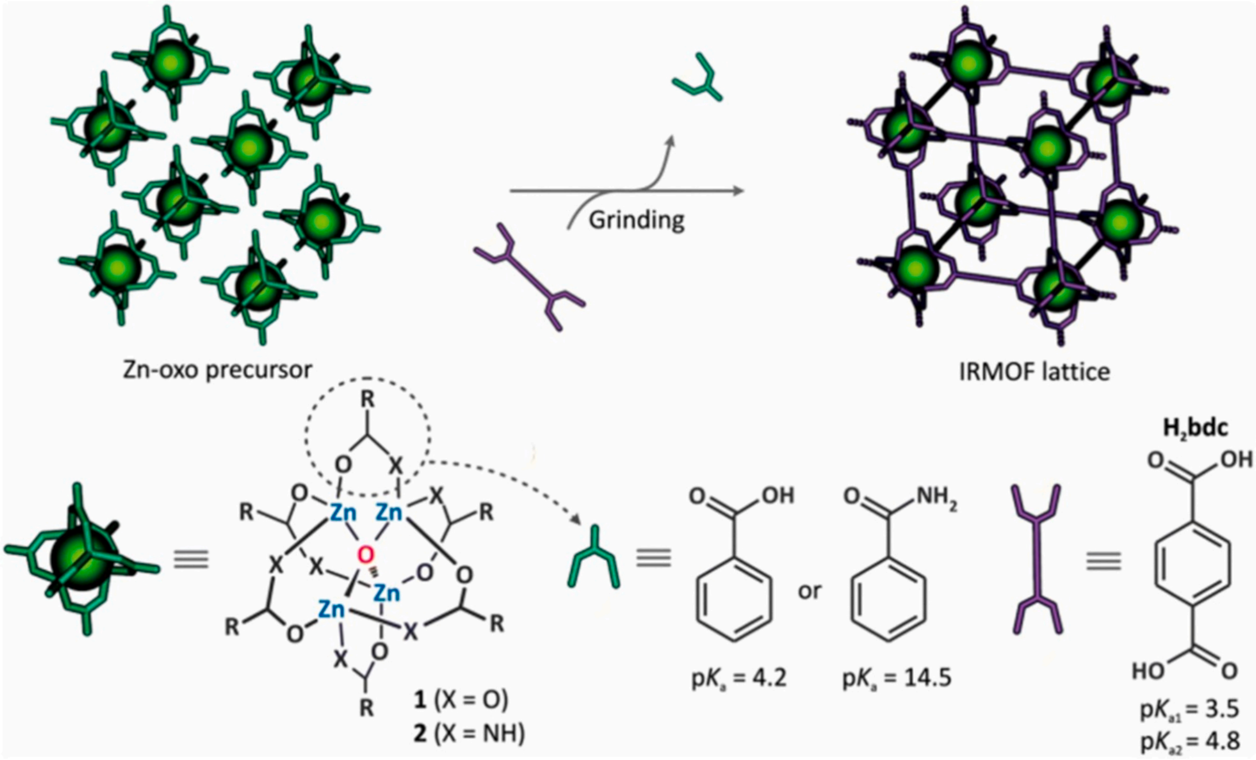


Fig. 5. Production of the archetypal IRMOF [43].

NH_4NO_3, $(NH_4)_2SO_4$), for the ILAG process were employed. The ammonium salt alone was found to enhance the production of ZIFs, even in the absence of liquid (Fig. 6**)**. Furthermore, ILAG also enabled the quantitative synthesis of both microporous and densely packed ZIFs using just stoichiometric amounts of reagents at room temperature [54]. The ZIF products topology was shown to be actively driven by the ILAG. These products were formed in less than 30 min at room temperature. The ILAG approach was crucial in enabling the synthesis of ZIF-8, as its conventional solution-based synthesis generates an abysmal yield and needs excess amounts of solvent or concentrated aqueous ammonia and long reaction times [54].

The application of a small amounts of organic liquids facilitates the synthesis of MOFs under mechanochemical conditions. The liquid added serves many functions, including (i) entering pores and stabilizing the resultant framework, (ii) dissociating intermediates and increasing MOF activation, and (iii) accelerating product formation [52–54].

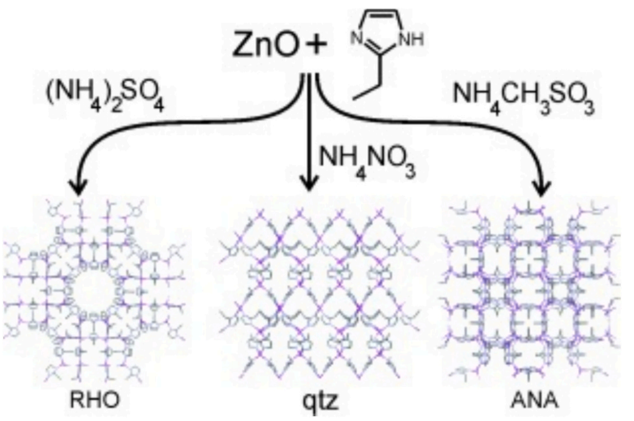


Fig. 6. Mechanochemical reactivity of ZnO towards HEtIm: (**A**) $(NH_4)_2SO_4$ with ILAG (**B**) NH_4NO_3 or $NH_4CH_3SO_3$ with ILAG in the presence of EtOH (**C**) $NH_4CH_3SO_3$ and DMF with ILAG) [54].

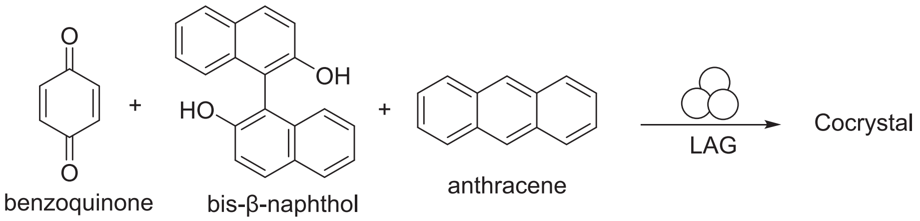
Preparation of supramolecules/ multicomponent assemblies using LAG

The use of mechanical force to produce new supramolecular assembly such as cocrystal (Scheme 1**)**, otherwise known as mechanochemistry or solid-state grinding, is a greener and intriguing approach that does not involve the usage of excess solvents [55–59]. (See Scheme 2.)

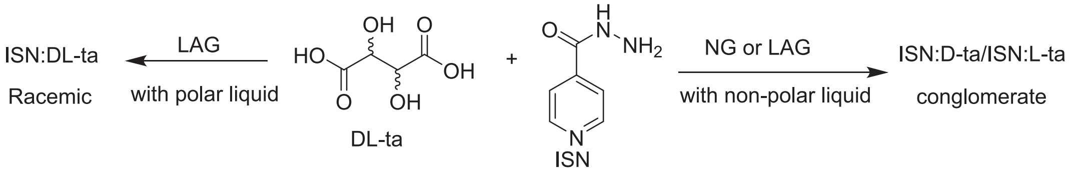
It is an improvement in the conventional neat or solvent-free grinding [60]. In 2021 Chaudhari et al. prepared a cocrystal of the antiretroviral drug ritonavir with conformer of amino acid *L*-tyrosine using LAG. This drug and coformer are poorly water soluble and were ideal candidates for LAG. They characterized the new solid form using Fourier-Transform Infrared (FTIR), Powder X-ray Diffraction (PXRD), solid state Nuclear Magnetic Resonance (SSNMR), and Differential Scanning Calorimetry (DSC). They showed that the cocrystal formed through LAG demonstrated good tableting behavior compares to the active pharmaceutical ingredient (API). They reported an 11.24 % increase in solubility of the new cocrystal compared to the parent API. Stability improvements over a month at 40 °C and 75 % relative humidity (RH) and 25 °C and 60 % RH and a 3.73-fold improvement in dissolution profile in 1 h was also reported, resulting in overall improvement in the physicochemical properties of the API [60].

In 2020, Nikam et al. reported the use of LAG to prepare a pharmaceutical cocrystal of Nebivolol hydrochloride a drug used to manage hypertension with GRAS coformers such as nicotinamide and 4-hydroxy benzoic acid to improve the aqueous solubility, stability, and dissolution profiles. They used PXRD, DSC and FTIR to confirm the formation of the cocrystal. The dissolution profiles of the cocrystals were faster with higher equilibrium solubility than the parent drug. The cocrystals of Nebivolol hydrochloride with nicotinamide and 4-hydroxy benzoic acid showed a solubility of 2.802 mg/mL and 1.808 mg/mL respectively, compared to the API alone that showed solubility of 0.792 mg/mL [61].

Furthermore, Huang and coworkers developed a modified green two steps liquid assisted grinding co-assembly to prepare tetracene and



Scheme 1. Synthesis of multicomponent crystal through LAG [57].



Scheme 2. Formation of a conglomerate through NG/LAG with non-polar liquids and a racemate using LAG with polar liquids for an equimolar mixture of isoniazid and *DL*-tartaric acid [75].

octafluoronaphthalene cocrystals that were difficult to obtain using a solution approach (Fig. 7**)**. They confirmed the efficiency of the procedure by making 80 mg of the product in 20 s and applied it in gram scale quantities. Their result revealed that the cocrystal exhibited green emission of tetracene with greater photoluminescence quantum yield of 13.75 % compared to pure tetracene with 0.47 % aggregation-caused quenching. They reported that the cocrystal can easily be dispersed into water to form aqueous inks with high luminescent properties that can be used to hand-paint patterns of luminescent materials to make green-emissive films with transparent and flexible properties [62].

In 2021, Myz et al. reported the preparation of a cocrystal of betulin-adipic acid by co-grinding with 1,4-dioxane. They introduced various solvents in small amounts to elucidate their roles in the cocrystal synthesis when compared to dry grinding. They concluded that LAG was the favorite route to obtain cocrystals with betulin and when solvent evaporation was employed solvates were obtained preferentially. The formation of the cocrystal through LAG was established using FTIR, PXRD, and thermal analysis and showed that the hydrate of the cocrystal was formed when liquid-assisted grinding was performed using water miscible solvents. They confirmed that the hydrate wasn't stable under thermal analysis but rather changed into the anhydrous form followed by decomposition [63].

Panzade and Shendarkar used liquid assisted grinding approach to formulate a cocrystal of zaltoprofen and nicotinamide [64]. Zaltoprofen is a water insoluble drug that is used to treat acute and chronic inflammation and rheumatoid arthritis. This solubility challenge makes it difficult to obtain its cocrystal using solvents. They reported a rise in the melting points and solubility of the 1:1 and 1:2 cocrystals that were characterized using PXRD, DSC, FTIR and SEM. The micromeritic of the cocrystal was also enhanced compared to the individual components. Most importantly, there was a rise in dissolution profile of the cocrystal of about 99.47 % compared to zaltoprofen (48.83 %), the formulated multicomponent solid was also found to be stable during storage [64].

In 2021, Mithu et al. prepared a pharmaceutical cocrystal of ketoconazole with fumaric and succinic acid using LAG. They evaluated the use of neat grinding and noticed that it resulted in the generation of co-amorphous solid, while LAG formed cocrystal. They confirmed the formation of the cocrystal through DSC, PXRD, FTIR and Raman spectroscopy analysis. The in-vitro dissolution evaluation revealed that the cocrystals exhibited a higher drug dissolution behavior of greater than 80 % compared to the single component that was reported to be less than 40 %. Their work showed that the cocrystal prepared using LAG

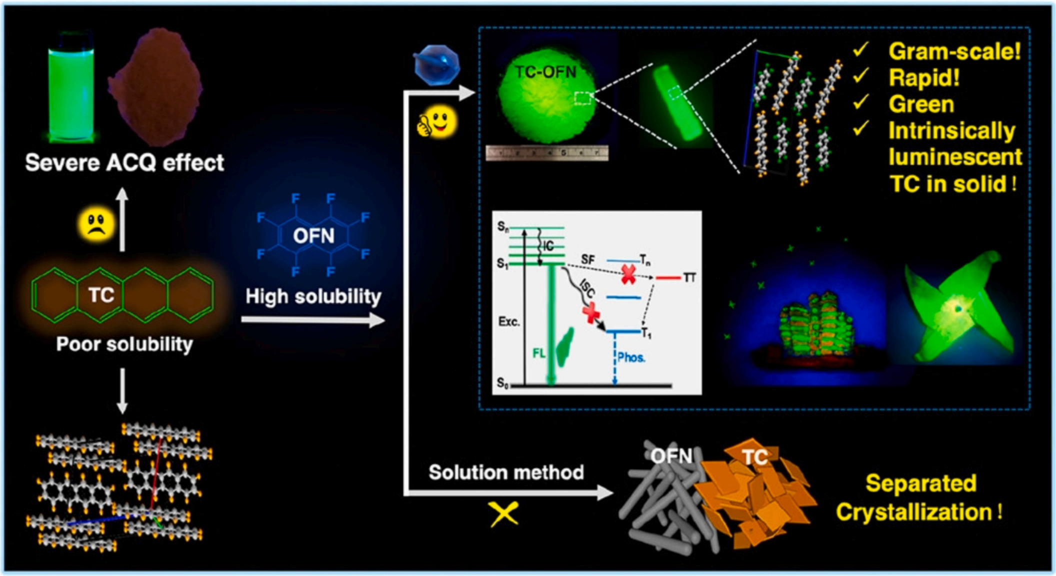


Fig. 7. Illustration of the use of LAG to synthesize tetracene and octafluoronaphthalene cocrystals that were difficult to obtain in solution [62].

improved the solubility of the drug and can be a potential means to increase the drug bioavailability [65].

In 2023, D'Abbrunzo et al. reported the application of mechanochemical competitive milling to prepare multicomponent solvate and hydrate of theophylline with water and 2-pyrrolidone. They explored the possibility of generating theophylline in its neat form in the presence of a binary liquid mixture, where both liquids result in solvate formation when used individually. They employed various molar ratios of theophylline-to-liquid and many water: 2-pyrrolidone ratio to comprehend the transformation between the solvates. This verified a substantial competitive effect of miscible liquids when employed in combination with mechanochemical synthesis, which was attributable to the existing interactions between the liquids that are preferred when compared to the interaction of the single liquid with the solid. They also carried out interconversion evaluation involving hydrates/monosolvate and sesquisolvate. Their results showed that water:2-pyrolidone mixture negatively affected the multicomponent phase because it decreased the odds of inclusion of liquids in the crystal. They noticed the preferential incorporation of 2-pyrrolidone over water and concluded that the chance of formation of solvate in the presence of liquid mixture is a function of multifaceted interplay of physicochemical and kinetic properties [66].

Fernandes et al. prepared two new cocrystals of theophylline with 4-aminosalycylic acid and 4-aminobenzoic acid using LAG and characterized it using single crystal XRD, SSNMR spectroscopy, and Density Function Theory (DFT) calculations. They revealed that the crystal structure of theophylline and 4-aminosalycylic acid exhibited an infinite planar arrangement held by hydrogen bond interactions while in the structure involving 4-aminobenzoic acid, the amino group was not involved in hydrogen bonding **(**Fig. 8**)** [67].

Li and coworkers reported the formation of eight drug-drug cocrystals solvates piroxicam and clonixin (two non-steroidal anti-inflammatory drugs), using LAG with different solvents. They noticed that five of the cocrystal solvates are isostructural with similar packing arrangements and unit cell parameters. The solvents in the crystal structures behave as binders instead of space-fillers. They concluded that some properties of the solvents like the polarity, hydrogen bond donor and accepting abilities played major roles in formation of the solvates. They further characterized the solvates with Thermogravimetric Analysis (TGA), DSC and NMR. From their thermal result, the solvents were instrumental in stabilizing the crystal structures. They concluded that solvents with moderate polarity form complexes with the two drug molecules through hydrogen bond interactions [68].

In 2024, MacGillivray et al. applied multicomponent milling through LAG to decolorize a sample of an orange-red zwitterionic cocrystal of pyridine 2,4-dicraboxylic acid and acetaminophen using *trans*-1,2-bis(*n*-pyridylethylene and for $n = n$' = 3 or 4). They observed the removal of the bright orange color after grinding the cocrystal and the coformer in 1:1 stoichiometric ratio in a drop of EtOH, and also the dismantling of the solid to a binary cocrystals of pyridine 2,4-dicraboxylic acid and *trans*-1,2-bis(*n*-pyridylethylene as confirmed using PXRD **(**Fig. 9**).** They attributed the dismantling to stability, especially difference in melting points as a result of packing arrangements of the solids as revealed by DSC analysis [69].

Mingxia He and coworkers applied LAG to synthesize a cocrystal of pyrazinamide and a series of alkyl dicarboxylic acids such as maleic acid and gallic acid using drops of methanol, anhydrous EtOH and isopropanol. They experimentally extracted the terahertz spectra of the cocrystals and obtained the typical structural attributes of the supramolecular synthons. They explored solid-state DFT to calculate the relationship between specific collective vibrational modes and terahertz absorption peak. According to their analysis of lattice potential energy, Form I is more stable than Form II, demonstrating the stability of PZA-MA cocrystal polymorphs [70].

LAG is one of the emerging methods used to date in the preparation of pharmaceutical salts [71]. A study by Suresh et al. reported the synthesis of a salt of a marketed antibacterial drug known as ofloxacin using diphenic acid as a conformer [72]. The crystal structure of the salt revealed a proton migration from the conformer, resulting in the formation of the salt through charge-mediated NH^+-O hydrogen bond interactions. The authors further demonstrated that the formation of the salt significantly improved the physicochemical properties of ofloxacin, such as intrinsic dissolution rate and aqueous solubility [72].

Production process of salts by LAG reactions can be affected by several factors, including the nature and volume of the LAG additive, the grinding frequency, the milling assembly materials, and the time of milling. In that perspective, Harris et al. reported the formation of quininium aspirinate a new drug-drug salt, by combining quinine (an antimalarial) and aspirin (a nonsteroidal anti-inflammatory drug). LAG of a 1:1 M ratio of the two components was performed using different solvents (H_2O, EtOH, toluene, and *n*-heptane). Only the product from using EtOH was able to form a single crystal in tetrahydrofuran, where the structure demonstrated that a hydrogen bond had formed between the two components. Finally, the H_2O solubility of quininium aspiranate was improved three times than the commercial quinine sulphate [73]. The amount of solvent employed during LAG has an implication on the outcome of the reaction. Prado et al. used two antimalarial drugs to demonstrate the effect of water addition in the formation of the drug-drug salt. They reported a hybrid salt containing α-artesunate and mefloquine interacted via a hydrogen bond between the carboxylic acid and the basic sites of the latter (the pyridine and/or the piperidine) as a consequence of the mechanochemical process used to create the salt with $\eta = 1$ μLmg^{-1}. While the product with $\eta = 0.5$ μLmg^{-1} reveals a mixture of the two components as a salt and maybe ionic species that

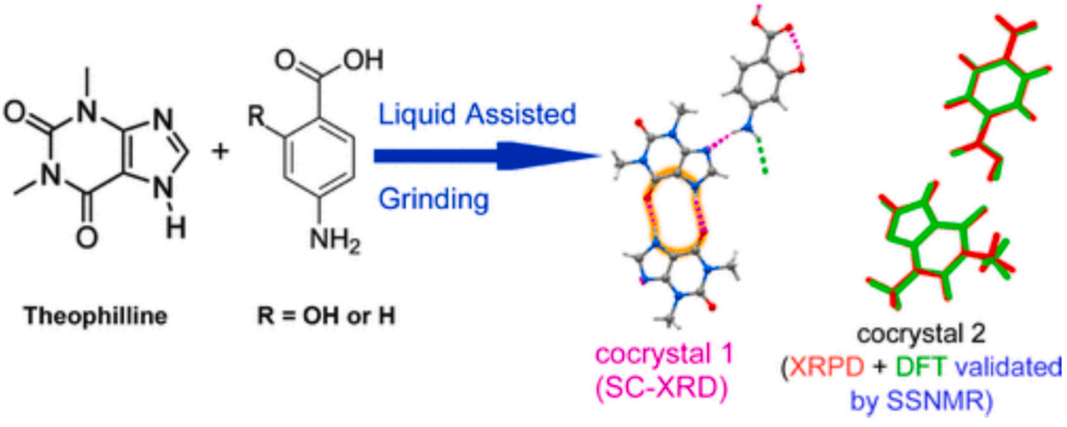


Fig. 8. Preparation of cocrystals of theophylline with 4-aminosalycylic acid and 4-aminobenzoic acid using LAG [68].

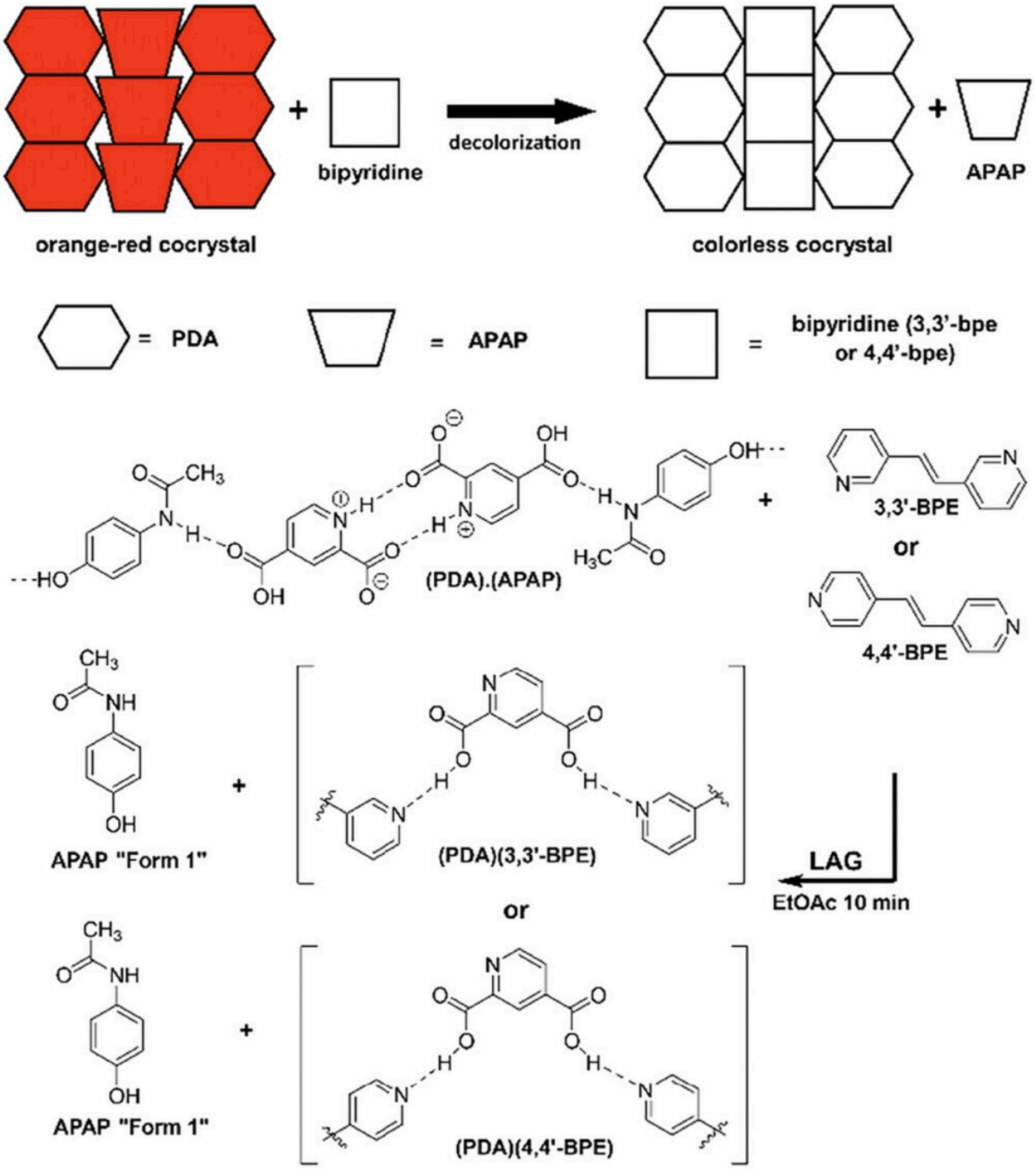


Fig. 9. Decolorization of orange-red zwitterionic (PDA)·(APAP) through LAG multi-component milling [69]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

may not interact, the other two attempts with $\eta = 0$ and 0.1 μLmg^{-1} only show a physical mixture of the precursors [74]. Finally, the polarity of the liquid used in the preparation of salts is crucial in predicting the outcomes of the product. For example, grinding achiral isoniazid (ISN) and *DL*-tartaric acid (*DL*-ta) in the presence of non-polar liquids as LAG, a conglomerate is formed; while when polar liquids are used, racemic salt is produced. This highlighted the impact of solvent polarity and dipole moment in LAG reactions [75].

Polymorphic studies are extremely important for academic researchers and the pharmaceutical industry since each polymorph has unique physicochemical features [76]. LAG is one of the techniques used to investigate the polymorphic transformation of molecules [77]. The polymorphism of sofosbuvir, a drug used in the treatment of hepatitis C, was investigated by vibration ball mill under different LAG experimental conditions by Chatziadi et al. [78]. Upon milling for 30 min with varying LAG additive, the original form which is the most thermodynamically stable form at ambient temperature transformed into an amorphous phase. In addition, the transformation can occur through different intermediate, and it is influenced by the time of milling and nature of the liquid additive [77]. The material used for the milling assembly has a significant impact on the formation and interconversion of polymorphs in a mechanochemical reaction. Germann et al. demonstrated the preparation of a pharmaceutical cocrystal of adipic acid and nicotinamide that generated different polymorphs by changing the milling material (jar material, balls size and number) which allowed for repeatable and reversible interconversion of cocrystal polymorphs [79].

Recent works exploring the polymorphs formation and transformation have revealed that mechanochemical approaches especially LAG, produce multiples metastable polymorphs that are not accessible through cocrystallization in solution. This was corroborated by Belenguer et al. who reported three crystalline polymorphs using a disulfide system [80] (Fig. 10). Interestingly, each polymorph can only be obtained under specific mechanochemical conditions providing a nuanced understanding of the apparent thermodynamic stability.

Furthermore, a multicomponent crystal system was reported by Kulla and co-workers consisting of pyrazinamide and pimelic acid. Two novel cocrystal polymorphs (Form I and Form II) were prepared mechanochemically and the formation was traced in real time using an in-situ synchrotron PXRD. Selective choice of liquid additive helped to control the two polymorphic forms. From slurry experiments and

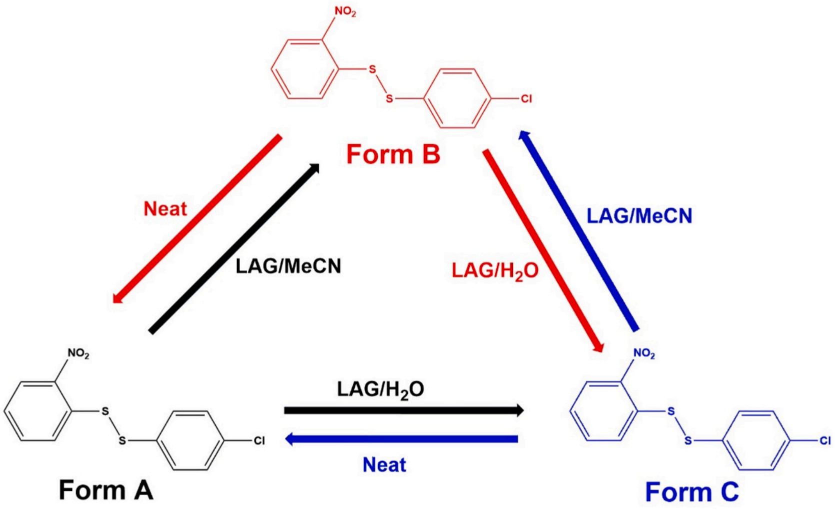
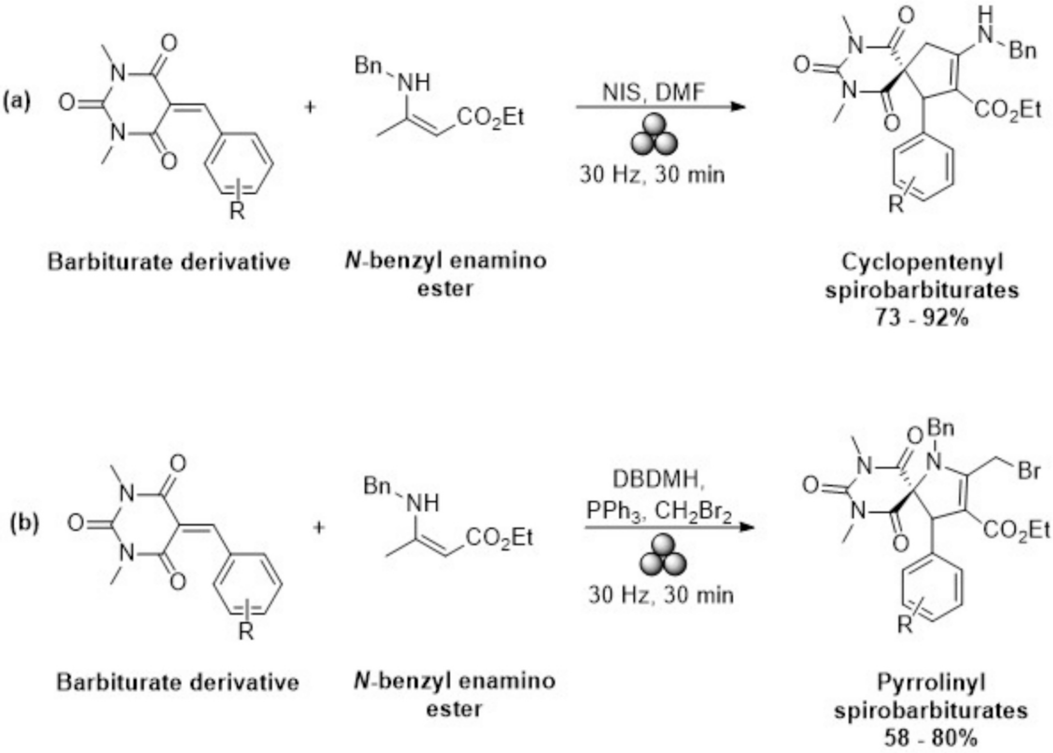


Fig. 10. Polymorph interconversion between three polymorphs of a disulfide system under well-defined mechanochemical conditions (adapted from [79]).

dispersion-corrected DFT calculations, it appears that Form I is the thermodynamically stable form at room temperature. In addition, the choice of milling jar demonstrated a significant effect on the aging stability of the polymorphs where Form II polymorph prepared in Perspex (PMMA) vessels, tripled its lifetime compared to material prepared in steel milling vessels [81]. In pharmaceutics, it is essential to identify every potential polymorph of a pharmaceutical compound in order to formulate better medications with the intended effects. LAG is an interesting tool in accessing unknown polymorphs of a pharmaceutical compound [77,82].

LAG assisted organic reactions (Synthesis of heterocycles)

The demands for greener processes for the production of biologically important heterocycles with high yield and purity has become more and more prevalent [83]. Environmentally friendly procedures entail aspects such as substituting organic solvents, cutting down on chemical waste production, ensuring effective disposal, reusability, and economic viability [84,85]. Chromatography-free product separation techniques have been introduced to address the problems of high purity and yield. This has resulted in the development of reaction routes that are easy to operate and satisfy the requirements of organic and pharmaceutical chemists [86]. With the growing interest in finding more environmentally friendly ways for organic transformation, mechanochemical technologies are becoming more applicable for this aim [87]. Some of the mechanochemical methodologies reported involve carbon-carbon and carbon-heteroatom bond formations. As a result, mechanochemistry is being used in MCRs and heterocycle synthesis involving C-2 selective



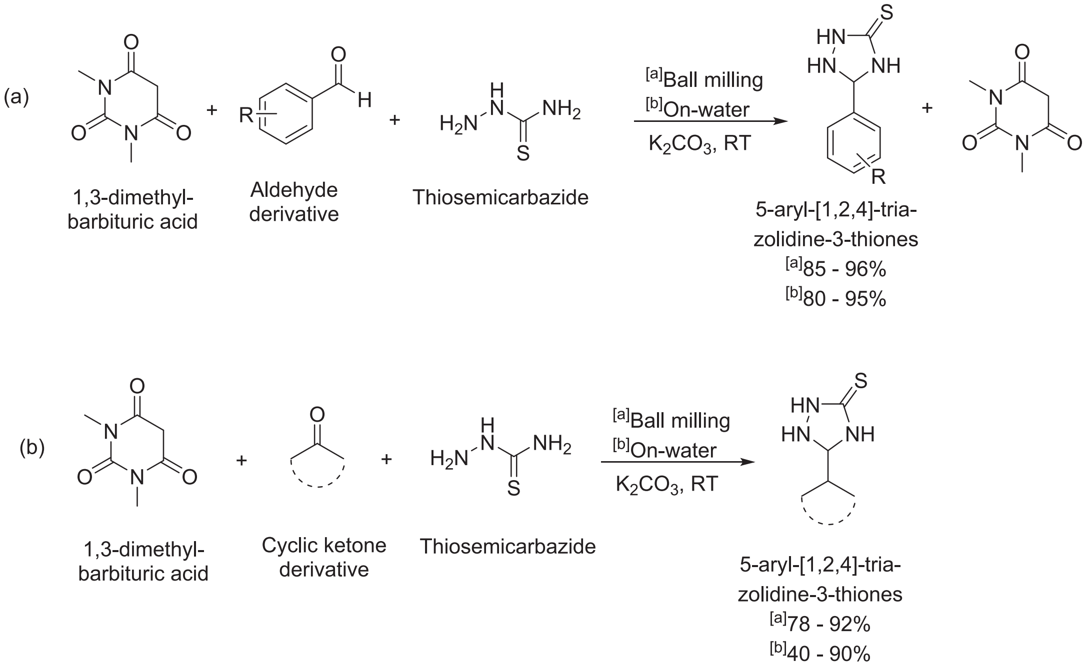
Scheme 3. Synthesis of cyclopentenyl and pyrrolinyl spirobarbiturates under ball-milling conditions.

arylation of indoles [88], multicomponent synthesis of polysubstituted pyrroles as well as *trans*-2,3-dihydropyrroles [89]. A further component of mechanochemical transformation is liquid-assisted grinding, which increases reaction yield and chemo-selectivity [90]. Xu et al. developed a novel and controllable protocol for the spirocyclization of unsaturated barbiturates with enamino esters under ball-milling conditions to generate cyclopentenyl and pyrrolinyl spirobarbiturates (Scheme 3) [91]. The study was conducted using a Retsch MM400 mixer mill containing four stainless steel balls (6 mm in diameter). Their observations showed that the milling at 30 Hz, 5-benzylidene-1,3-dimethylbarbituric acid (0.2 mmol), *N*-benzyl enamino ester (0.24 mmol), *N*-iodosuccinimide (NIS) (1.2 eq.) and dimethylformamide (DMF) as LAG solvent (30 μL) in 30 min promoted the chemoselective synthesis of cyclopentenyl spirobarbiturates in 73–92 % yield (Scheme 3(a)). Whereas in solvent-free conditions, the mechano-reaction generated 46 % yield of adducts using iodine (1.0 eq.) as the promoter, and 69, and 74 % yield of adducts using 1.0, 1.2 and 1.4 eq. of NIS respectively. The chemoselective production of pyrrolinyl spirobarbiturates was conducted under the same conditions but was promoted using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (1.0 eq.), required the addition of triphenylphosphate (PPh_3) (1.0 eq.) as additive, and used dibromomethane (CH_2Br_2) (30 μL) as LAG solvent (Scheme 3(b)). The procedure afforded pyrrolinyl spirobarbiturates in 58–80 % yield. The use of sodium and potassium carbonate as additives did not enable the formation of the desired adduct and conducting the reactions under solvent-free conditions generated low yield of adducts (trace - 22 %).

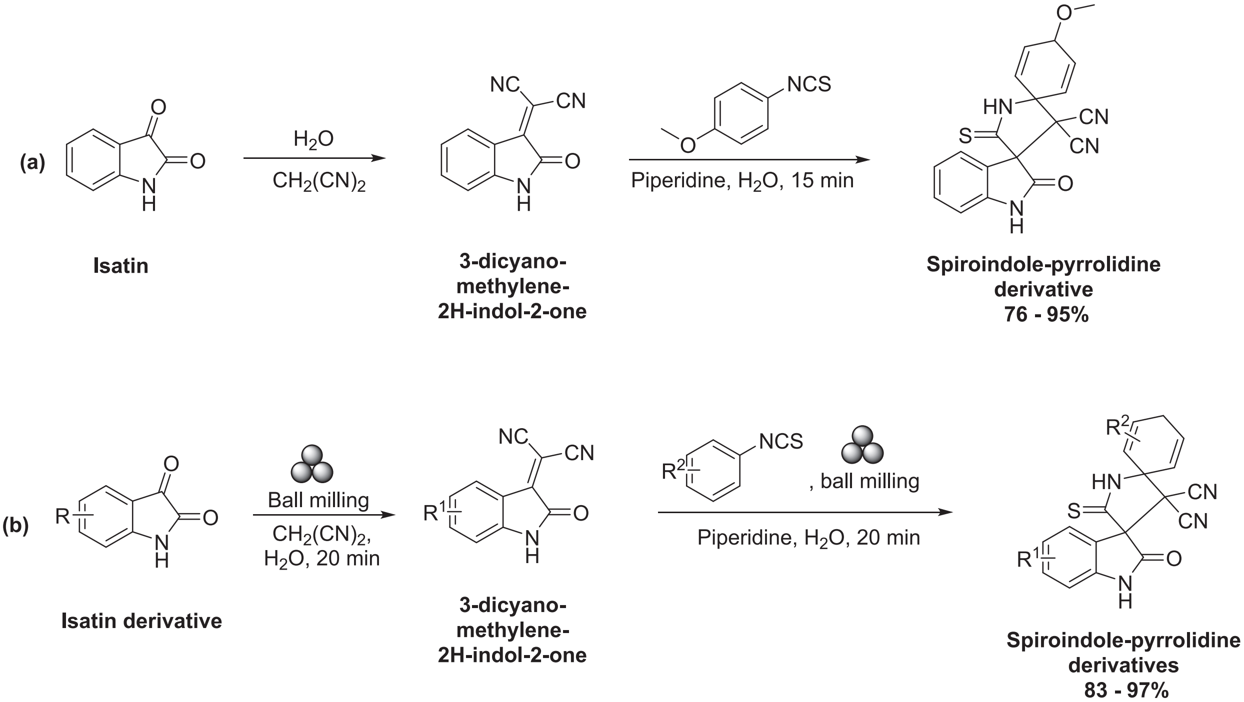
Similarly, Dutta and co-workers reported the successful LAG methodology for the one-pot synthesis of 5-aryl/spiro-1,2,4-triazolidine-3-thiones (Scheme 4) [92]. The study showed a quick and eco-friendly procedure that could lead to the expansion of the range of homogeneous reusable reaction media. The LAG procedure consisted of a mixture of an aromatic aldehyde or cyclic ketone (1 mmol), 1,3-dimethylbarbituric acid (0.156 g, 1 mmol), thiosemicarbazide (0.091 g), potassium carbonate (0.138 g, 1 mmol) and 1 mL of distilled water (Scheme 4(a)). The mixture was milled in a stainless steel (5 mL) equipped with 10 stainless balls (2 mm diameter) at 300 rpm for 10 min at room temperature. The procedure afforded adducts in 88–94 % isolated yield in 2–3 min. In addition, they also established a procedure for the synthesis of the aforementioned family of compounds in aqueous media, which is equally effective but takes somewhat longer (25–30 min). The synthesis involved stirring at 25 °C a mixture of 1,3-dimethylbarbituric acid (1 mmol), aromatic aldehyde (1 mmol), potassium carbonate (1 mmol), thiosemicarbazide (1 mmol) in 5 mL of H_2O. The procedure afforded adducts as precipitate which were separated via gravity filtration to afford pure adducts in 80–95 % (Scheme 4(a)). The filtrate containing the base and 1,3-dimethylbarbituric acid was for the isolation of 1,3-dimethylbarbituric acid. Using cyclic ketones under the same conditions (Scheme 4(b)), the preparation of 5-aryl-[1,2,4]-triazolidine-3-thiones generated 78–92 % employed ball milling in 3–4 min and 40–90 % using "on-water" conditions in 30–40 min. These findings illustrated the efficiency of mechano-synthesis and liquid-assisted ball milling synthesis over the "on-water" conditions for the synthesis of spirocycles.

Salami and co-workers reported the Michael condensation of 3-dicyanomethylene-2H-indol-2-ones or 5-bromo, 3-dicyanomethylene-2H-indol-2-ones with isothiocyanate derivatives under aqua and mechanochemical conditions which allows for the simple synthesis of several novel derivatives of spiro pyrrolidine compounds (Scheme 5) [93]. In their study, they described an environmentally benign procedure for the Michael and Knoevenagel condensation with high yield, operational simplicity, and short reaction time. The procedure involved the milling of 4-methoxyphenyl isothiocyanate (1 mmol), and 5-bromo, 3-dicyanomethylene-2H-indol-2-ones/3-dicyanomethylene-2H-indol-2-ones (1 mmol) with 2–3 drops of piperidine in a stainless steel (13.2 mL) equipped with two balls (6 mm in diameter) of the same material for 20 min at 25 Hz. The purification steps afforded the desired adducts in 83–97 % yield (Scheme 5(b)). The methodology proved to be more advantageous as it reduced the reaction time and generated higher yield compared to normal aqua conditions (Scheme 5(a)). The resulting spirocyclic compounds are essential building blocks for the diversity-oriented synthesis of spiro heterocyclic libraries that may be used as bioactive molecules since they contain a variety of functional groups.

A range of heterocycles have been accessed by different groups of investigators employing LAG. Bora et al. used LAG in mechanochemical domino MCRs in the presence of Bronsted acid catalyst to access a range (20 examples) of heterocycles among which were 2-amino-3-cyano-4H-



Scheme 4. Synthesis of 5-Aryl/Spiro-[1,2,4]- triazolidine-3-thiones using aromatic aldehydes **(a)** and cyclic ketones **(b)** using ball milling and on-water, respectively.



Scheme 5. Synthesis of spiroindole pyrrolidine derivative under aqueous media **(a)** and mechanochemical activation **(b)**.

chromenes (Scheme 6) whose yields were 86–98 %, in 5–10 min at ambient temperature. The reaction conditions and yields were quite attractive and also the scope of the protocol in view of the variety of substrates and products [94].

A LAG protocol was established by Jiang et al. for the rapid preparation of polysubstituted pyrroles, heterocyclic compounds exhibiting several biological activities. The protocol is catalyst free, has a wide scope of application and employs MeOH as the liquid additive in a one-pot three-component reaction (Scheme 7) [95].

Yadav and Parvin developed a multicomponent LAG methodology in which 2-hydroxy1,4-naphthoquinone, 5-aminopyrazoles and α,β-unsaturated aldehydes, were reacted to provide styryl linked benzo [*H*]pyrazolo[3,4-b]quinoline-5,6(10*H*)-diones. The water-assisted synthesis enables good yields, short reaction times, is greener and has a simple work up procedure [96]. (Scheme 8) shows the product endowed with several bioactive moieties, pyrazole, naphthoquinone, styryl, and 1,2-naphthoquinone.

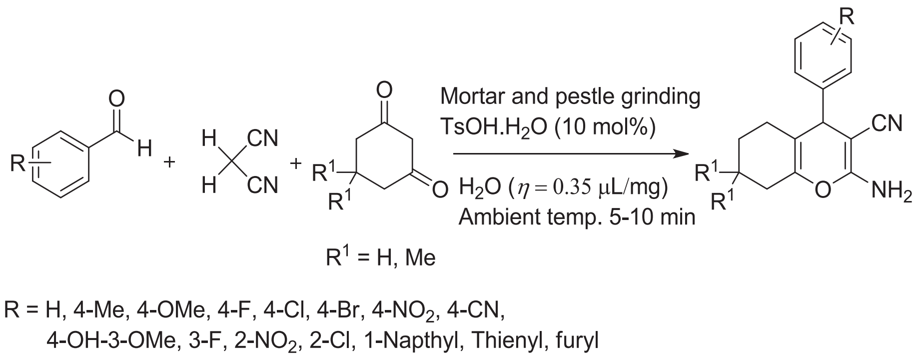
The synthesis of 1,4,5,8,9,11-hexaazatriphenylenehexacarbonitrile a compound with a potential application in organic light-emitting material, was enhanced in terms of time, yield, and sustainability considerations in a LAG protocol employing water as additive (η = 0.1). Diaminomaleonitrile was condensed with hexaketocyclohexane to provide the product at room temperature (Scheme 9) [97].

Isoindolo[2,1-*a*]quinazolines and chromenes are heterocycles drawing significant attention in natural product and synthetic chemistry [98–100]. Lohar et al. developed a protocol for the synthesis of Chromenes and isoindolo[2,1-*a*]quinazolines using LAG and 2,2,2-trifluoroethanol (TFE) catalyst [101]. The procedure proved to be environmentally benign resulting in excellent yield of the product in high purity within the shortest reaction times (Schemes 10 and 11).

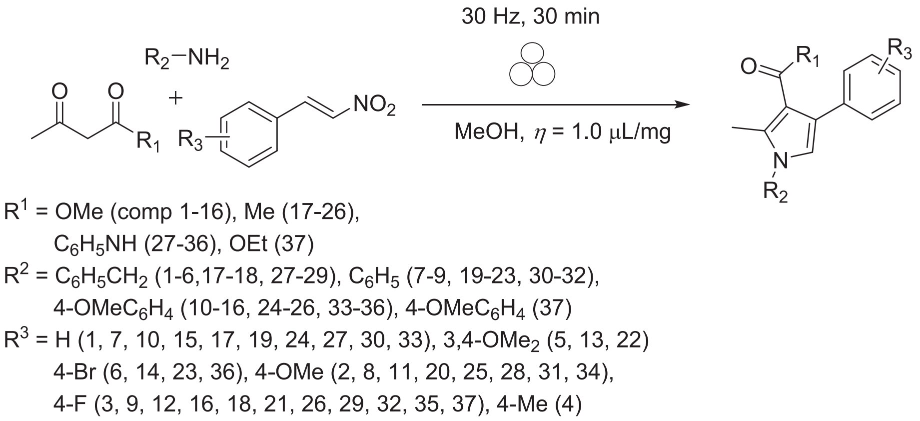
An iodine-enhanced mechanochemical synthesis of 2-arylimidazo [1,2- *a*]pyridines afforded desired products with some substrates amenable to both neat and LAG condition (for solid reactants) in which EtOH was the liquid additive (Scheme 12) [102]. The protocol which proved to be greener, atom economic and simple was employed to perform a scalable synthesis of the gastroprotective drug Zolimidine.

A multicomponent LAG method (acetic anhydride as liquid additive) afforded the environmentally cleaner, simple and atom economic synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (azlactones) which are part of a class of heterocycles that have exhibited biological activity such as antimicrobial, anticancer, anti-inflammatory, immune suppressive, and can also be used as synthons for other molecules (Scheme 13) [103].

Penaska and co-workers accessed chiral pyran derivatives through LAG in a protocol which enabled the diastereo-divergent and

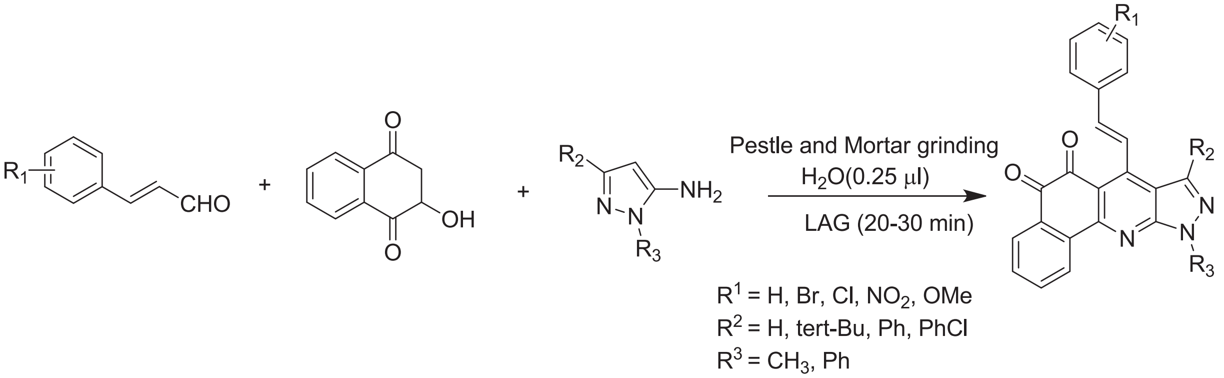


Scheme 6. Synthesis of 2-amino-3-cyano-4*H* chromenes under LAG conditions



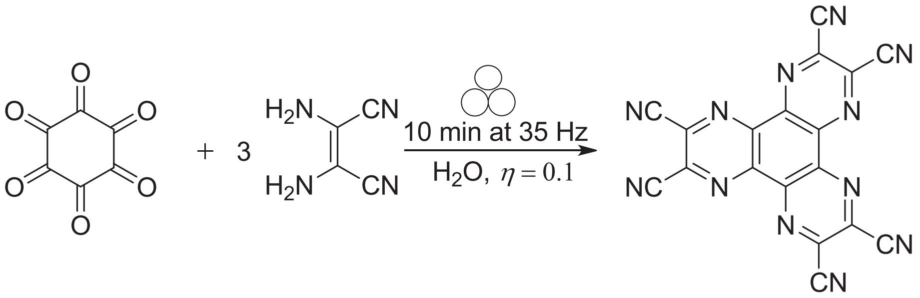
R^1 = OMe (comp 1-16), Me (17-26), C_6H_5NH (27-36), OEt (37)
R^2 = $C_6H_5CH_2$ (1-6,17-18, 27-29), C_6H_5 (7-9, 19-23, 30-32), 4-OMeC_6H_4 (10-16, 24-26, 33-36), 4-OMeC_6H_4 (37)
R^3 = H (1, 7, 10, 15, 17, 19, 24, 27, 30, 33), 3,4-OMe$_2$ (5, 13, 22) 4-Br (6, 14, 23, 36), 4-OMe (2, 8, 11, 20, 25, 28, 31, 34), 4-F (3, 9, 12, 16, 18, 21, 26, 29, 32, 35, 37), 4-Me (4)

Scheme 7. LAG mediated synthesis of polysubstituted pyrroles.

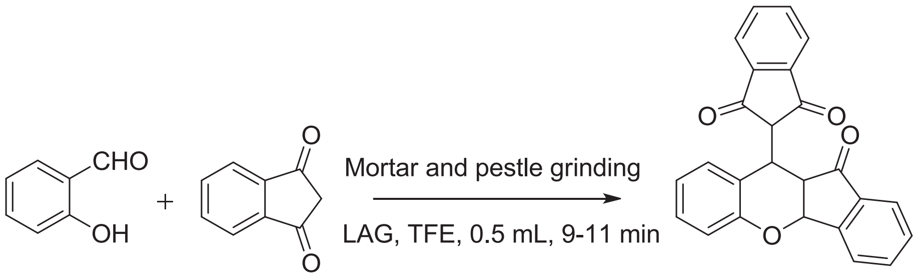


R^1 = H, Br, Cl, NO_2, OMe
R^2 = H, tert-Bu, Ph, PhCl
R^3 = CH_3, Ph

Scheme 8. LAG styryl linked benzo[*H*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-diones.



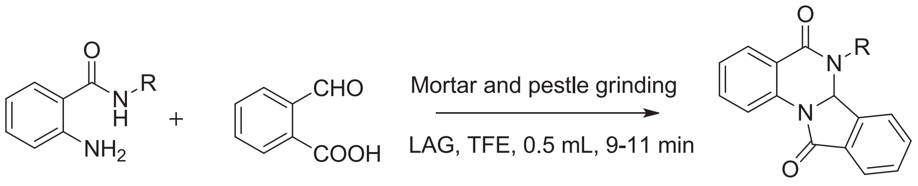
Scheme 9. LAG synthesis of 1,4,5,8,9,11-hexaazatriphenylenehexacarbonitrile.



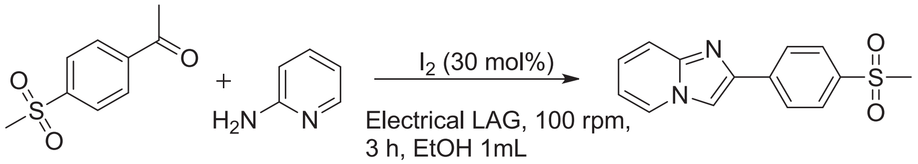
Scheme 10. LAG synthesis of chromene scaffolds.

enantioselective synthesis of these important heterocycles (Scheme 14) [104]. Employing the oxa-Diels-Alder and either mono- or bi-functional organocatalysts, diastereoisomers could be targeted. The LAG protocol afforded the desired products efficiently and rapidly in almost quantitative yields and with high enantiomeric purity.

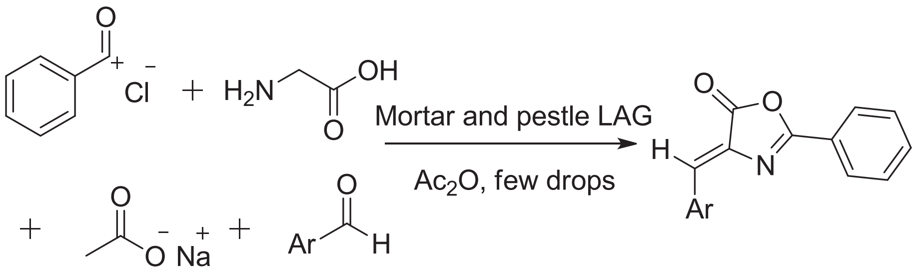
A mechanochemical activation technique using high-speed ball milling (HSBM) for isocyanide-based multicomponent reactions (IMCRs) was successfully applied by Juriasti and Polinda [105]. Under



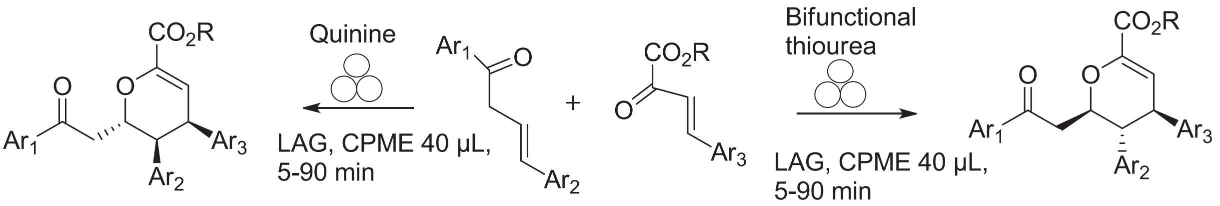
Scheme 11. LAG synthesis of isoindolo[2,1-*a*]quinazolines.



Scheme 12. LAG synthesis of 2-arylimidazo[1,2- *a*]pyridines.



Scheme 13. LAG synthesized 4-arylidene-2-phenyl-5(4*H*)-oxazolones.

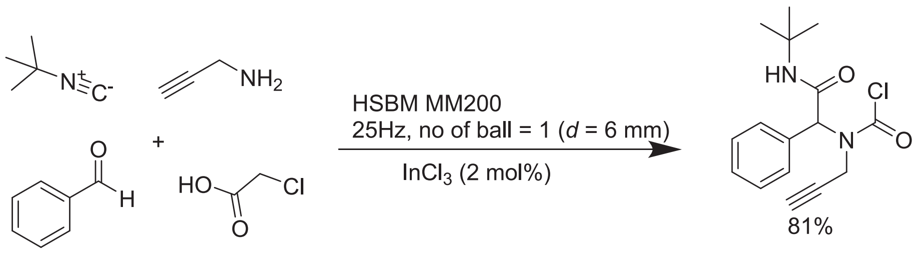


Scheme 14. LAG synthesis of pyran derivatives.

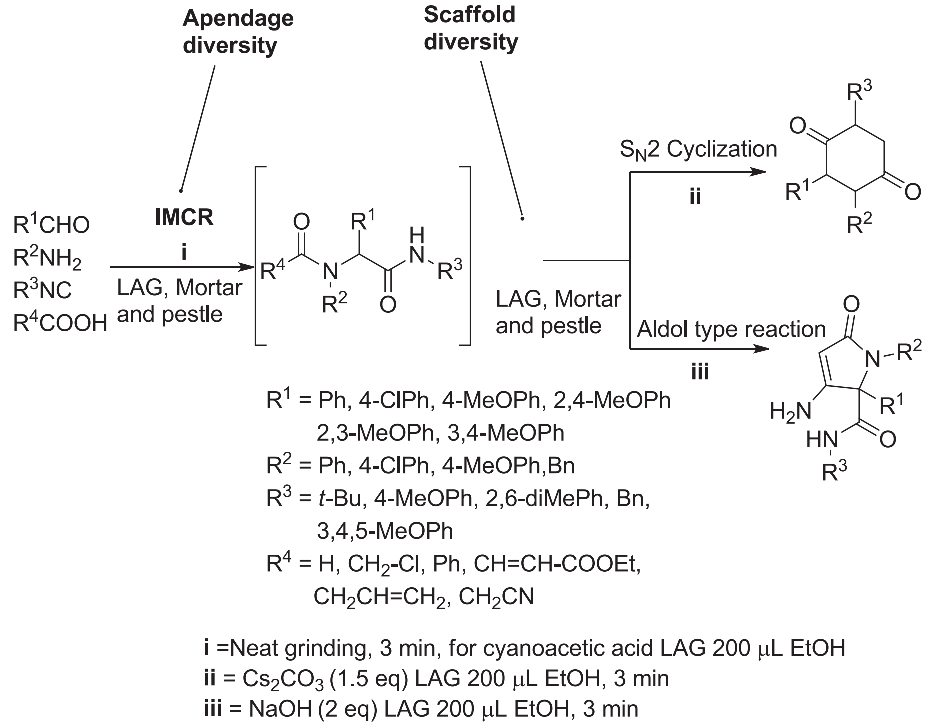
LAG circumstances, the Ugi adduct was synthesized in a Retsch Mixer Mill MM200 ball mill by equimolar reaction of tert-butyl isocyanide, propargylamine, benzaldehyde, and chloroacetic acid with indium(III) chloride (2 mol-%) serving as a catalyst (Scheme 15). The Ugi adduct was obtained in a 59 % yield when the reaction was first carried out under neat conditions. However, when 50 μL of MeOH is used in the reaction, the yield increases to 74 %. In this sense, adding 75 μL (η = 0.44 μL mg–1) and 100 μL (η = 0.59 μL mg–1) of methanol to the LAG resulted in a significant increase in yield of 81 %.

Pharande and co-workers employed LAG Ugi four-component isocyanide-based multicomponent reaction (IMCR) to access privileged heterocycles *α*,*β*-unsaturated-*γ*-lactams and tri-substituted 2,5-diketopiperazines (DKPs) employing LAG to access the targeted heterocycles (Scheme 16) [106]. The overall reaction from the start to the privileged heterocycles was six minutes. The protocol employing EtOH as the liquid additive is versatile, has a wide scope, with high yield.

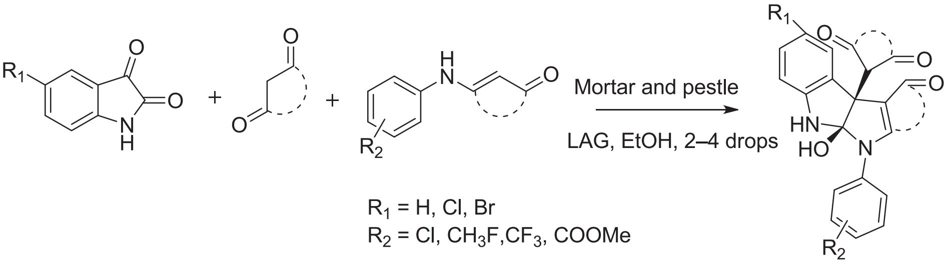
In the light of the established pharmaceutical characteristics of pyrimidine and indole moieties Maury et al. used LAG as a greener and efficient method to access potentially biologically active molecules containing both entities, indoloindole pyrimidines (Scheme 17) [107]. The protocol did not include a catalyst but had a facile work up that was rapid, generated high yield of adducts, and had a wide scope of



Scheme 15. LAG synthesis of Ugi adduct.



Scheme 16. LAG synthesis of α,β-unsaturated-γ-lactams and tri-substituted 2,5-diketopiperazines



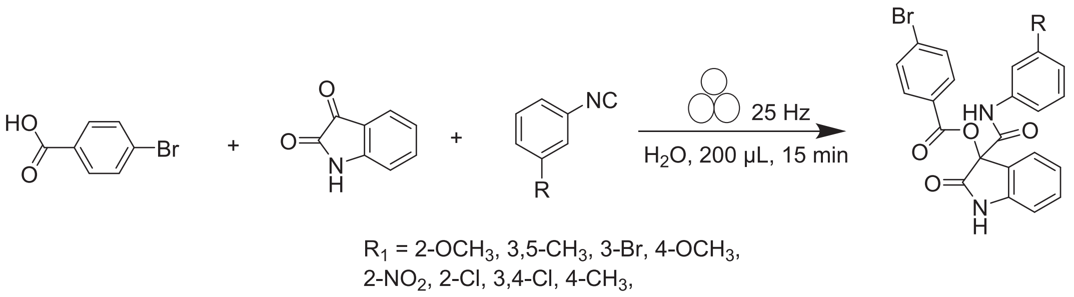
Scheme 17. LAG synthesis of indoloindole pyrimidines.

application as well as functional group range.

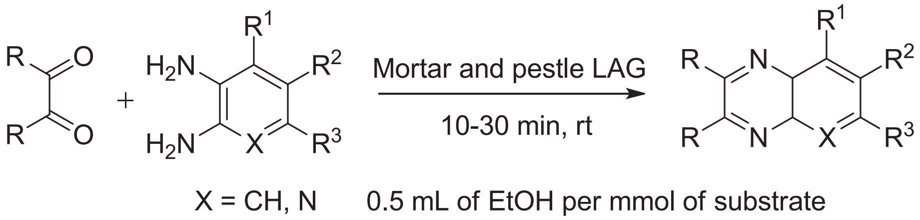
Similar to this, Salami and co-workers [108] employed isatin, benzoic acid, and substituted isocyanides to develop a simple, effective, safe, and cost-effective synthesis of a small library of biologically relevant oxindole derivatives using a protocol based on the Passerini Multicomponent reaction (MCR) (Scheme 18). Passerini reactions were conducted under mechanochemical activation in 10–15 min with high yields using water as the LAG. In particular, the procedure enables the modular synthesis of a variety of compounds with significant atom economy, shorter reaction times, cleaner reactions with higher yields, and ease of experimentation [108,109].

Bhutia and co-workers [110] used LAG to achieve the synthesis of quinoxalines (Scheme 19). Condensation of 1,2 dicarbonyl compounds and aromatic and heteroaromatic 1,2-diamines afforded the target compounds in an environmentally benign way, in excellent yields and short reaction times [111]. The quinoxaline moiety is present in several commercial drugs and biological activities of quinoxaline derivatives encompass anti-inflammatory, antimicrobial, anticancer, antifungal, and antiviral [112].

Bagchi et al. developed a LAG protocol to access dihydrobenzo[*f*] pyrano[3,2-*c*]chromenones with benzaldehydes, malononitrile, and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one as starting materials in a domino



Scheme 18. Water assisted synthesis of oxindole derivatives under mechanochemical conditions.



Scheme 19. LAG synthesis of quinoxalines.

one pot reaction (Scheme 20) [113]. The protocol in which isopropyl alcohol (IPA) was employed as the liquid additive proved to be wide in scope, atom economic, greener, and facile.

In a bid to harness the therapeutic and fluorescent properties of thiazoles and barbituric acid, Mahata and co-workers developed a LAG protocol to synthesize barbituric acid linked diphenyl-1,3-thiazole hybrids (Scheme 21) [114]. Arylglyoxal, thioamides and barbituric acid were reacted under LAG condition affording the hybrids in 30 min. The methodology has a wide scope, environmentally benign, and affords facile purification among other advantages.

A mechanochemical protocol to access heterocyclic compounds 5,5-diarylhydantoin, thiazole, imidazole thiadiazine, and triazinthione derivatives in a one pot synthesis was described by Fahmy et al. (Scheme 22) [115]. EtOH or *n*-butanol was employed as the liquid auxiliary and thiamine as a catalyst to access the compounds which exhibited potential as insecticidal agents.

A study of the poly(ethylene) glycols (PEGs) as LAG additives in the mechanochemical synthesis of 3,5-disubstituted hydantoins was carried out by Mascitti and co-workers (Scheme 23) [116]. The study revealed that the cyclisation was directly influenced by the quantity of the PEGs and the use of the LAG agents afforded cleaner reaction profiles in comparison to dry grinding.

Guha et al. reported a LAG synthesis of iminoiodinanes from various cyclic secondary amines. (Scheme 24) [117]. The protocol involved a catalyst, a base, and an acid free and employed 2-methyl tetrahydrofuran (0.5 μL/mg) as the liquid additive.

A facile LAG route for the conversion of amides into carbarmoyl isatins, imides, and benzamides in high yields was developed by Friscic and co-workers (Scheme 25) [118]. In solution the Cu-catalyzed conversion normally required high temperatures or did not even take place. The high temperatures in solution allowed competing reactions which were not present in the LAG reaction and conversions when they occured were lower.

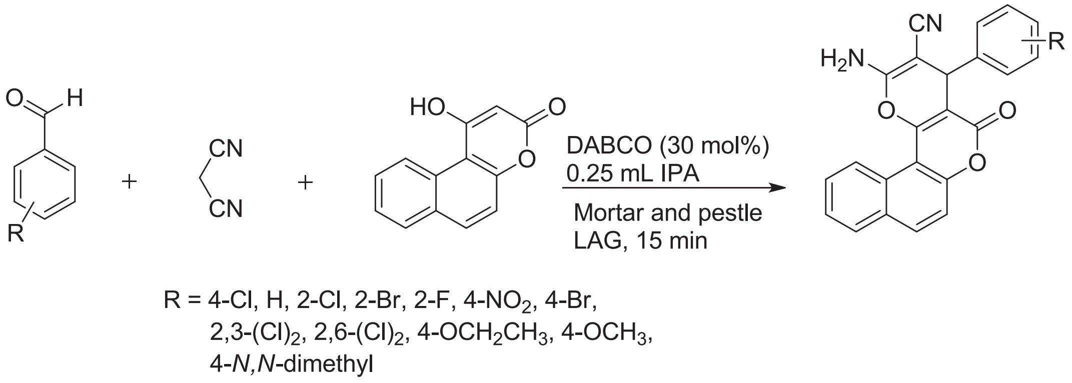
Kuntikana et al. reported a LAG synthesis of 3-arylideneaminoquinazolin-4(1*H*)-ones from aldehydes/ketones and *o*-aminobenzhydrazide (Scheme 26) [119]. The protocol offered a number of advantages over other approaches which included high yields, wide scope of reactants and convenient synthesis of products in high atom economy.

A LAG protocol associated with the advantages of being catalyst free, greener, affording products quickly and in excellent yields was developed by Banerjee and co-workers to access 2-substituted and 1,2-disubstituted benzimidazole derivatives, and also 2-aryl benzothiazoles (Scheme 27) [120]. Of the substances investigated as the liquid auxiliaries, EtOH proved to be the best and considered ahead of MeOH which afforded similar yields but has a poorer safety profile.

Summary and conclusion

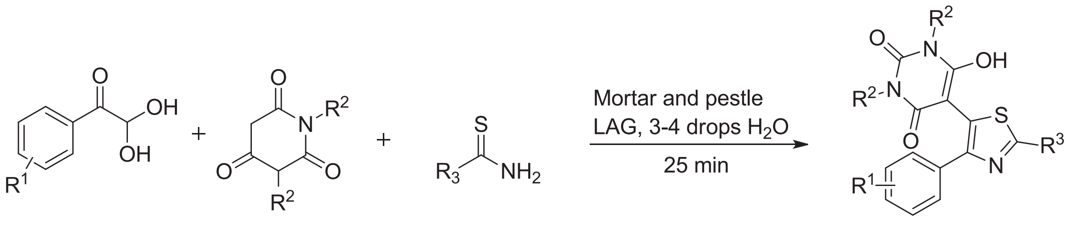
The application of LAG in mechanochemical processes is a growing field as evidenced by the increased number of publications in the last two decades. The benefits of liquid-assisted mechanochemistry are identical to those of the neat approach, with the extra benefit being that the liquid-assisted procedure is typically substantially quicker, leading to significantly shorter reaction times. The LAG methodology was first presented in organic co-crystal formation studies to speed up cocrystal formation. However, it quickly became clear that this methodology offered additional advantages over neat grinding procedures, such as higher product crystallinity, control over polymorph formation, higher yield, and a much wider range of reactants and products. In many cases, the yield of product obtained through mechanochemistry, or LAG conditions is essentially quantitative and usually greater than that of classical solution synthesis. The presence of several equilibria in solution reactions can lead to low yields and the generation of various undesirable products. In contrast, in mechanochemical synthesis, the solid-state reactants have a higher chemical potential than their solution counterparts, which in turn increases the resultant yield [121,122].

Generally, the primary drawback of liquid-assisted mechanochemical synthesis, aside from pragmatic concerns like product purification and equipment design, is a lack of sufficient understanding regarding its mechanism and scope of application. It will be beneficial to record reactions that take place as well as those that don’t under any mechanochemical conditions as mechanochemical synthesis advances. This reveals not just whether a reaction has occurred, but also how quickly it has occurred. Despite the many benefits of mechanochemistry, there are obstacles and restrictions that must be overcome before it can be completely embraced as a common practice. The primary one is a lack of



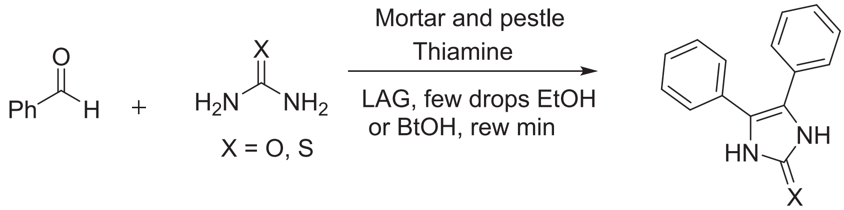
R = 4-Cl, H, 2-Cl, 2-Br, 2-F, 4-NO_2, 4-Br, 2,3-$(Cl)_2$, 2,6-$(Cl)_2$, 4-OCH_2CH_3, 4-OCH_3, 4-*N,N*-dimethyl

Scheme 20. Synthesis of dihydrobenzo[*f*] pyrano[3,2-*c*]chromenones under LAG conditions

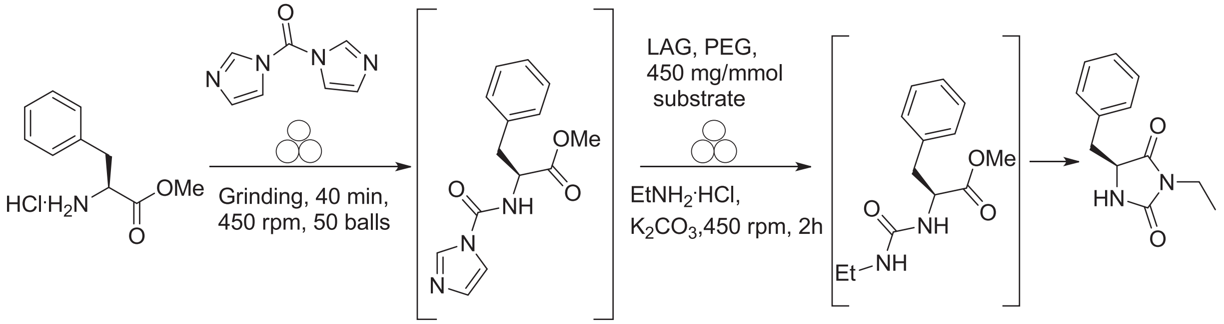


R^1 = H, 4-F,4-CF_3, 4-NO_2, 4-OMe,
3,4-methylenedioxy, 3-OMe
R^2 = Me, H
R^3 = C_6H_5, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-$NO_2C_6H_4$,
4-OMe-C_6H_4, 4-Me-C_6H_4, C_5H_4N

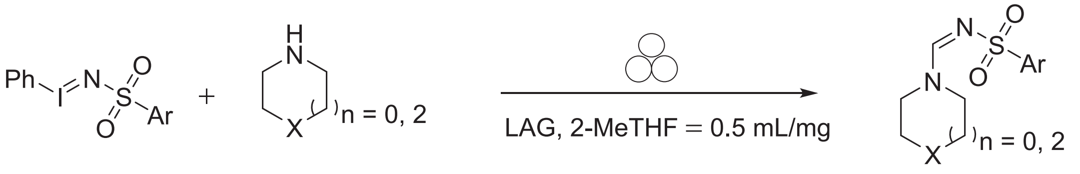
Scheme 21. LAG synthesis of barbituric acid linked diphenyl-1,3-thiazole hybrids.



Scheme 22. LAG synthesis of 5,5-diarylhydantoin

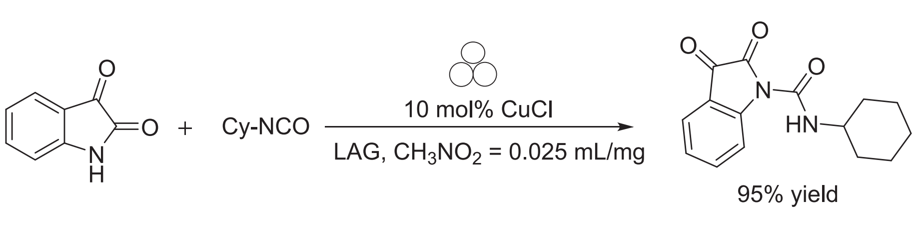


Scheme 23. LAG synthesis of a 3,5-disubstituted hydantoin.

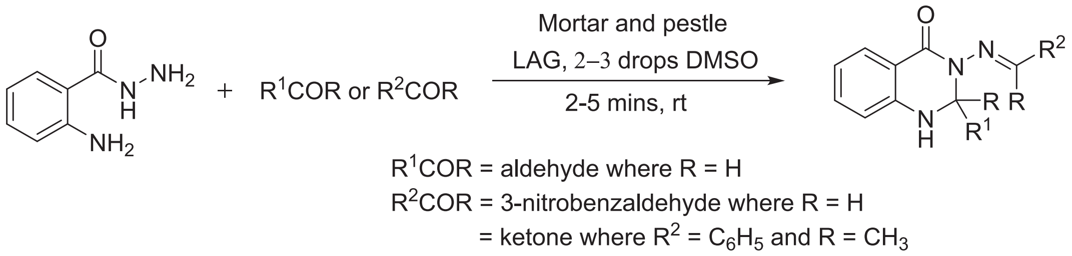


X = CH_2, S, O, N-Boc

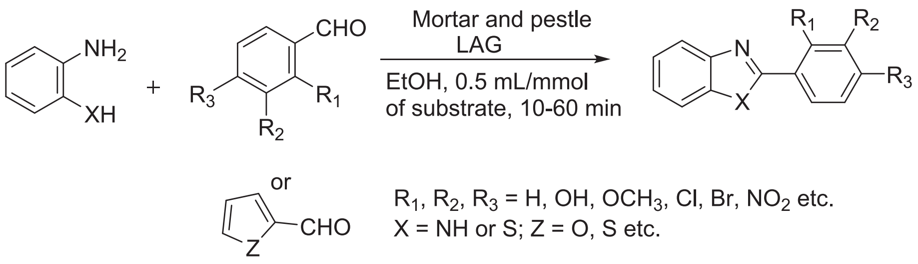
Scheme 24. LAG synthesis of iminoiodinanes.



Scheme 25. LAG synthesis of *N*-cyclohexyl-2,3-dioxoindoline-1-carboxamide.



Scheme 26. LAG synthesis of 3-arylideneaminoquinazolin-4(1*H*)-ones.



Scheme 27. LAG synthesis of 2-heteroaryl benzazoles.

adequate and universal awareness regarding the method's entire scope of application. This can only be addressed through inquiries into a broader spectrum of reaction types.

Furthermore, a deeper comprehension of the function of the liquid employed in the mechanochemical process might be beneficial for future advancements. The notion that the liquid will function as a solvent for one or more of the reactants seems to be the primary factor in the great majority of cases when deciding which liquid to employ and whether the reaction will be successful. However, many of the neat mechanochemical processes documented in the literature may be better understood as liquid-assisted mechanochemical reactions, due to the possibility that liquid reaction byproducts could serve as a solvent during the reaction or just because of the existence of traces of atmospheric moisture. Before asserting a mechanochemical synthesis to be "solvent-free," researchers must consider the reaction as a whole because either of the two outcomes could occur. Many mechanochemical processes that are described as "solvent-free" require lengthy milling periods; in this case, it would be intriguing to find out if the reaction may proceed much faster under LAG conditions. Liquid-assistance should be taken into consideration for all mechanochemical reactions, as there are numerous examples of liquid mechanochemical processes in shortening the reaction time. Although these reactions would obviously not be completely "solventless, however, since they maintain all of the benefits of mechanochemical synthesis while employing less solvent than traditional solution reactions should make this approach the preferred choice.

CRediT authorship contribution statement

Sodeeq Aderotimi Salami: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Data curation, Conceptualization. **Melody H. Manyeruke:** Writing – review & editing, Writing – original draft, Methodology. **Charles Izuchukwu Ezekiel:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Urbain Nshokano Ndagano:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Justin Bazibuhe Safari:** Writing – review & editing, Writing – original draft, Methodology. **Sefiu Olaitan Amusat:** Writing – review & editing, Writing – original draft, Methodology. **Rui W.M. Krause:** Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

This research was funded by National Research Foundation of South Africa, grant number 116109. 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.

Data availability

No data was used for the research described in the article.

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