

Investigations of Thermally-Controlled Mechanochemical Milling Reactions

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ABSTRACT: Mechanochemical milling reactions gained a lot of attention lately as a green and highly efficient path towards various relevant materials. The control over the fundamental reaction parameters in milling procedure, such as temperature and pressure of the reactor, is still in infancy and the vast majority of milling reactions is done with controlling just the basic parameters such as frequency and milling media weight. We demonstrate here how the milling under controlled, prolonged and variable heating programs accomplished in a new milling reactor introduces a new level of mechanochemical reactivity beyond what can be achieved by conventional mechanochemical or solution procedures, and also reduces the time and energy costs of the milling process. The methodology is demonstrated on four varied systems: C–C bond forming Knoevenagel condensation, selective C–N bond formation for amide/urea synthesis, selective double-imine condensation, and solid-state formation of an archetypal open metal-organic framework, MOF-74. The potential of this methodology is best demonstrated on the one-pot selective synthesis of four complex products containing combinations of amide, amine or urea functionalities from the same and simple acyl azide and diamine reactants. Principal control over this enhanced reactivity and selectivity stemmed from the application of specific heating regimes to mechanochemical processing accomplished by a new, in-house developed mechanochemical reactor. As even the moderate increase in temperature strongly affects the selectivity and the rate of mechanochemical reactions, the results presented are in line with recent challenges of the accepted theories of mechanochemical reactivity.

Introduction

Mechanochemical reactivity, i.e., chemical reactivity induced by application of mechanical force, developed into a viable, efficient, and potent alternative to the majority of conventional synthetic procedures.^{1,2,3} At this point, it has been applied for the preparation or transformation of a broad range of materials, from supramolecular materials^{4,5} and pharmaceutical co-crystals,⁶ diverse organic^{7,8,9,10,11} and organometallic compounds,^{12,13} discrete or porous coordination compounds, all the way to hard inorganic materials,^{14,15} nanoparticles,^{16,17} and intermetallic compounds.¹⁸ Mechanochemistry is dubbed Chemistry 2.0,¹⁹ as it opened a pathway towards numerous compounds not attainable by any other synthetic procedures.²⁰ Despite recent advances^{21,22,23,24,25} in understanding the impact of milling media on bulk reaction mixture^{26,27} and the energetics derived from kinetic and thermal energy in milling processes,^{28,29,30,31,32} fundamental knowledge about these basic reaction parameters is still largely lacking.⁹ The need for temperature control in the milling process has been emphasized as a central issue for mechanochemistry in several recent reviews,^{12,33} expecting it to overcome the activation energy barrier for some reactions and thus open a way towards a new level of chemical reactivity.³⁴ Milling at liquid-nitrogen temperature,

i.e., cryomilling, is now well established method for preparation of nanoparticles of metals or pharmaceutical materials, disruption of cell membranes, pulverization of thermally-sensitive materials, and also for preparation of amorphous drug forms.^{35,36,37,38} Only a few reports existing to date, however, show how milling at a sub-ambient or stable increased temperature of the milling vessel affects rates^{26,39} and selectivity⁴⁰ of mechanochemical milling reactions.

Here we show how the application of controlled and stable temperature regimes to mechanochemical milling leads towards chemical reactions not attainable by common mechanochemical or solution procedures. Thermal programming enabled selectivity in one-pot milling reaction between the 4-nitrobenzoyl azide (PNBA) and benzene-1,4-diamine (PDA) reactants, affording four different derivatives containing amido or urea groups, amide-amine, *N*-(4-aminophenyl)-4-nitrobenzamide (MA), diamide, *N,N'*-(1,4-phenylene)bis(4-nitrobenzamide) (DA), diurea, 1,1'-(1,4-phenylene)bis(3-(4-nitrophenyl)urea) (DU), and symmetrical or non-symmetrical amide-urea, 4-nitro-*N*-(4-(3-(4-nitrophenyl)ureido)phenyl)benzamide (AU) or *N*-(4-(3-(4-methoxyphenyl)ureido)phenyl)-4-nitrobenzamide (AUM), Figure 1. These products have found application in more than 100 patents including but not limited to potential antibacterial drugs,

ink composites, thermal recording materials, and optical properties modulators.^{41,42,43,44} In the herein studied thermally-assisted mechanochemical C-C bond-forming Knoevenagel condensation between vanillin and barbituric acid, the same methodology resulted not only in significant acceleration of the covalent bond formation but also in a change of mechanism on elevated temperatures and the product not available by conventional milling. Mechanochemical Schiff condensation between vanillin and PDA at elevated temperatures afforded doubly-condensed aldimines not readily accessible in conventional milling. Central to observed reactivity is a new modular mechanochemical reactor which enables multi-hour milling under changeable and precise temperature regimes (Figure 2 and ESI). Also, this methodology is not limited only to organic reactions; when applied to the mechanochemical formation of open coordination network, Zn-MOF-74,⁴⁵ highly crystalline MOF-74 was available after a several minutes milling, showing almost 10-fold acceleration despite using much milder milling conditions.

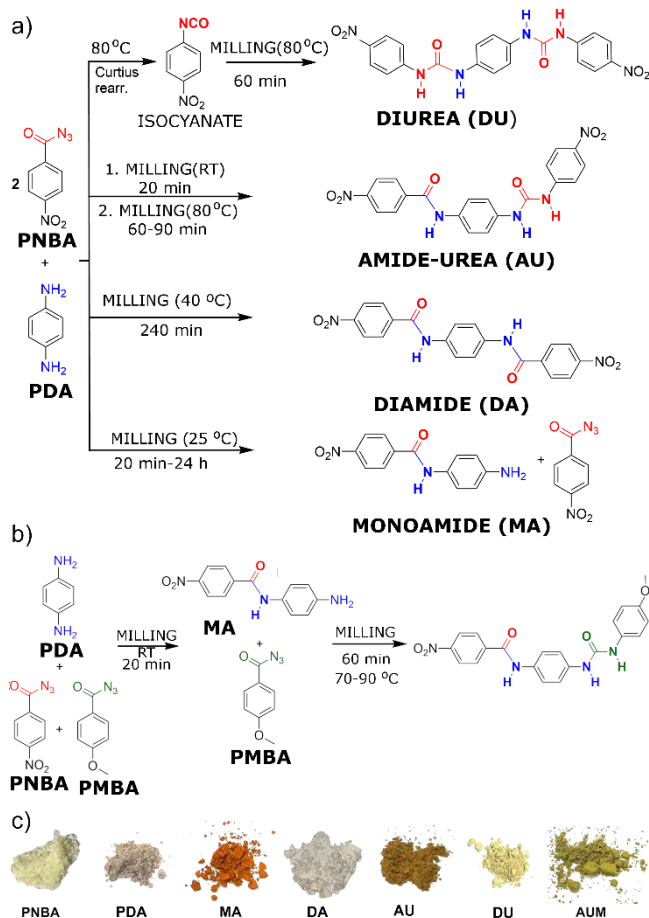


Figure 1. a) and b) Schematic representation of mechanochemical selective C–N bond formation reactions between *p*-nitrobenzoyl azide (PNBA) and *p*-phenylenediamine (PDA) under controlled heating regimes; c) reactants and obtained products.

Experimental section

General mechanochemical synthetic procedures. Mechanochemical syntheses were performed in IST-636 (InSolido Technologies, Croatia, Zagreb) mixer mill operating at 30 Hz with two stainless steel balls (7 mm diameter, 1.4 g each), but the setup for thermal control is also suitable for other mixer mills. If not stated otherwise, the inner milling vessel (14 mL) was made of stainless steel. We have also used aluminum, polytetrafluoroethylene (PTFE) and poly(methyl methacrylate), PMMA, for specific purposes, such as in situ monitoring of thermally-controlled milling. The general milling procedure is universal. For example, for the amide/urea system, PDA (28 mg, 0.25 mmol) and PNBA (100 mg, 0.5 mmol, melting point was not determined since the PNBA rearrange into isocyanate at elevated temperatures) were each positioned in the separate parts of the milling vessel to prevent their contact before the milling commenced. The additive (toluene, 30–35 μ L) was added to the PNBA side. CAUTION: Care should be taken when working with acyl azides, as they may be explosive. In the scope of our work, we have not experienced any explosive decomposition when using the conditions stated above. However, acyl azide reagents should not be heated without toluene or similar low vapor-pressure liquid before milling.

The reactor vessel was filled with argon gas, mounted on the insulated hands of the mill, and thermally-controlled milling was started. The temperature for each respective experiment was logged and controlled by LogOS software (InSolido Technologies, Croatia, Zagreb). After the milling was finished, the reactor vessel was allowed to cool down, and the product was carefully collected from the reactor vessel and analyzed. For more details on the yields and analysis results, please check SI.

Results and discussion

For the proposed study we developed thermally-controlled mechanochemical reactor inspired by the water-heated milling reactor devised by Kaupp,^{46,47,48} whose modification was described in more details in recent work of Mack group, where the similar setup was used to study enantioselectivity in 4-*tert*-butylcyclohexanone under sub-ambient temperatures.^{40,49} To avoid circulation of liquid during the mill operation, broaden the temperature range, and ensure fast and responsive heating system, we developed here an insulated reactor vessel equipped with a 75 W band heater, in which the temperature may be elevated, varied during the milling or held stable for hours of milling (Figure 2a). For a detailed description on the construction of thermal reactor vessel and the temperature controller, please check SI, Section 4). The temperature of the milling reactor in motion was controlled using a proportional–integral–derivative (PID) controller and a solid-state relay, enabling long periods of uninterrupted milling under precise, stable and variable temperature programs of up to 250 °C (Figures 2b and S6), with a deviation of ± 0.2 – ± 5 °C, depending on the milling reactor material (Figure S2). In general, when the reactor vessel is made of a material with good thermal conductivity, such as aluminum or steel, the deviations are lower since the feedback to PID controller is much faster (SI, Section 4). Importantly, the milling system *in operando* is a challenging object for precise heating, as the milling at 30 Hz involves G-force shocks of ca. 30 G on the equipment (Figure S7) and the internal heating may vary

throughout time considerably when the composition of reaction mixture changes.²⁸ These changes usually occur due to the formation of new material with different elastic properties, but also due to the changes in the rheology of the sample and possible sticking of the material to one side of the jar, resulting in the direct impact of milling media with reactor walls and a change in heating regime.²⁸ PID controller system used herein (SI, Section 4) ensured rapid adaptation and corrections in the heating regime during the milling, continuously lowering the deviation from the target temperature as milling continued.

We aimed to test several different synthetic systems to determine the generality of the new reactor and also the suitability of temperature-assisted milling for the synthesis of different types of organic or coordination materials.

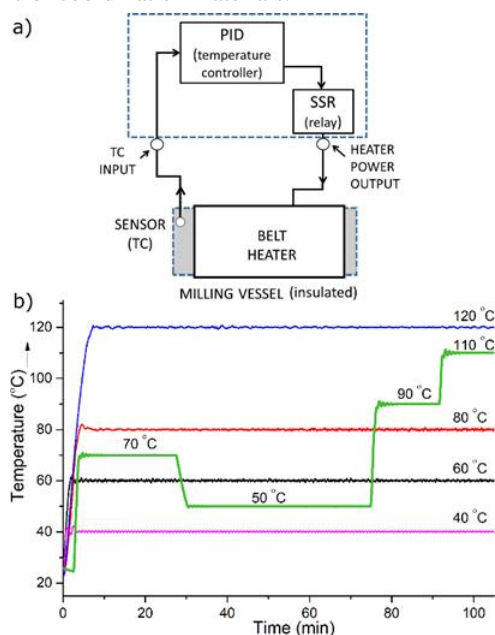


Figure 2. a) Feedback PID adaptive control mechanism enabling stable multi-hour mechanochemical reactions at controlled temperatures; and b) thermal data during milling reactions (30 Hz; stainless steel reactor of 14 mL volume, weighing 140 g, with two 7 mm steel balls inside) at various temperature programs. Green liner represents a complex multi-stage program involving cooling and heating of reaction jars without stopping the milling procedure.

Selective formation of amide and urea derivatives by thermally-controlled mechanochemical reactions

As an initial system, we chose the mechanochemical reaction between the PNBA and PDA. Our recent study on mechanochemical behaviour of PNBA discovered that no matter on the duration of milling or milling media used, the only product of 1:1 (PNBA:PDA) mechanochemical reaction performed at room temperature was monoamide MA, formed through a nucleophilic substitution of azide group by the amino group and formation of the monoamide.⁵⁰

The mechanochemical preparation of ureas using cyanates, isocyanates, or isocyanate equivalents was previously reported.^{51,52,53,54,55} Although it could be expected based on estimated energetics of milling,³² the Curtius rearrangement of acyl

azide into isocyanate and consequent formation of urea products did not occur in standard mixer mill, suggesting that the activation barrier for Curtius rearrangement is too high for conventional milling procedures. Such rearrangements are rarely studied in milling processes, but very recently Porcheddu and coworkers demonstrated mechanochemical Lossen transposition for preparation of hydantoins and unsymmetrical ureas.⁵⁶ We aimed to explore here whether the milling under elevated temperatures can overcome the energy barrier for Curtius rearrangement and result in the formation of thus far inaccessible urea functionality from the acyl azide.

All amide-urea selective syntheses were performed from the same starting mixture containing PNBA (melting point not possible to determine, it transforms to isocyanate at temperatures above 70 °C) and PDA (melting point 145 °C) in 2:1 molar ratio. Reactants were placed at different sides of the milling vessel to avoid their contact before the milling starts. A small portion of toluene additive ($\eta=0.25$ $\mu\text{L}/\text{mg}$) was added to PNBA side, which was chosen for its low vapour pressure and stability at elevated temperatures. Acyl azides are potentially explosive so special caution must be taken while heating these compounds (see Experimental section, General mechanochemical synthetic procedures). In LAG of PDA and PNBA without external heating, the temperature of the reaction mixture raised from 21.1 °C to 25.2 °C, but gradually fell to 23.6 °C and remained stable for following 25 minutes (Figure S8), meaning that the composition of the reaction mixture has stabilized, and the reaction is finished. As we discussed above, this behaviour complies to a recent report on energetics in milling assessed by high-precision RTD device, where the temperature profiles of milling reactions proved highly dependent on the composition of reaction mixture and interaction between the milling balls and the milled material.²⁸ The NMR analysis of the isolated bright orange solid revealed it to be a 1:1 mixture of MA together with the remaining PNBA (Figure S23, Section 6, SI), indicating that the formation of MA passivized the remaining amino group, most likely due to the lowered nucleophilicity of this amine group after the first amidation. Activation of remaining amino group and formation of diamide DA did not occur even after 24 hours of uninterrupted milling no matter on milling media size, and NMR analyses showed that the reaction mixture, containing MA and PNBA remains stable upon prolonged milling (Figure S23).

However, keeping the temperature of the milling reactor vessel at 40 °C (Figure S8b) resulted in full conversion to symmetrical DA after 4 hours of thermally-assisted milling (Figure 3 and ESI, Section 6). No traces of urea or isocyanate were observed in the milling product, showing that this additional energy input does not trigger Curtius rearrangement. However, raising temperature to 80 °C while milling resulted in the first evidence of the urea product. Encouraged by this result, we pre-heated the reactor vessel containing both reactants to 70-90 °C for 1 hour before starting milling at the same temperature. This procedure yielded almost pure symmetrical diurea (DU) product in excellent yield (Figures 3 and S8, SI).

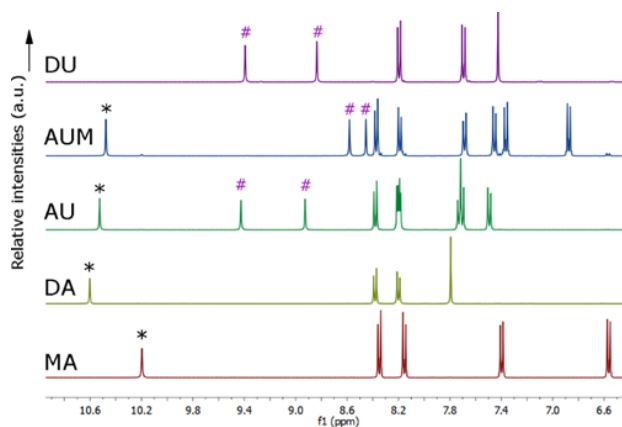


Figure 3. ^1H NMR spectra of the five formed products. The black asterisk denotes proton signals of the amide groups, and purple hash sign denotes protons corresponding to urea N–H.

Such simplicity in controlling the type of covalent bond to be formed in the milling process, and the type of the compound to be synthesised, is particularly emphasised when comparing the solution procedures for the preparation of the same compounds. They all involved several synthetic steps, and were not successful for some compounds, such as DA, despite testing several different multi-day procedures (please see below, section Solution syntheses of amide and urea derivatives, and SI, Section 3).

After we concluded that the conventional milling resulted in a mixture of MA and PNBA, we became interested in developing the one-pot controllable synthesis of a compound with amide and urea functionalities on the sides of the central amine. Reported solution syntheses for these amide-urea compounds are scarce and include several steps.^{57,58} Here, we milled the reaction mixture for 30 minutes, rapidly raised its temperature to 80 °C in 4 minutes, and continued milling at that temperature for an additional 60 minutes. In situ monitoring by Raman spectroscopy^{59,60} confirmed the crucial role of heating on this two-step reaction (Figure 4). The formation of MA is finished after the initial 6 minutes milling, and the temperature of the vessel (ca. 23 °C) and the reaction mixture composition remains stable until the temperature is raised at 30-minute mark. Immediately upon the temperature of the vessel reaching 80 °C (light blue spectrum denoted with an asterisk), Raman spectra reveal the formation of AU, characterized by bands at 1326 cm^{-1} and 1601 cm^{-1} , which concludes after additional 60 minutes milling (Figure 4). NMR confirmed the light-brown product to be the targeted AU (Figures 1c and 3). Raising the temperature leads to Curtius rearrangement of the remaining PNBA forming more reactive isocyanate, which in reaction with MA formed the final AU product in excellent yield.

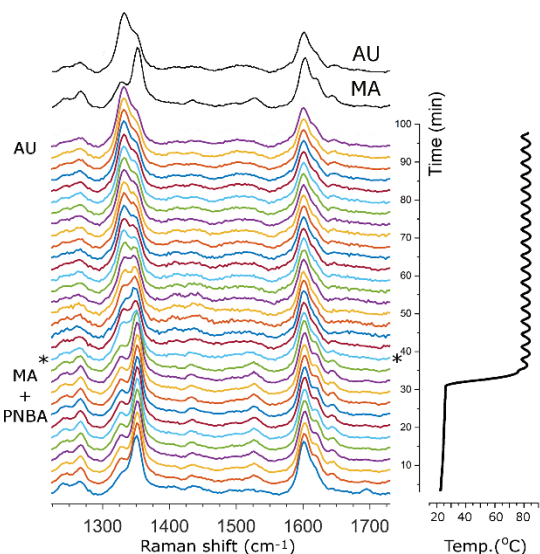


Figure 4. Tandem in situ Raman and temperature monitoring of mechanochemical LAG synthesis of amide-urea compound AU with DMF additive in PMMA reactor vessel. DMF was used instead of toluene as an additive for monitoring purposes since the toluene reacts with PMMA vessel at elevated temperatures. The low thermal conductivity of PMMA caused higher deviation from target temperature (± 5 °C), as the outer layers nearer aluminium sleeve overheat before the PID system receives feedback from the thermocouple and interrupts the heating cycle.

This approach was further exploited for selective one-pot preparation of non-symmetric amide-urea derivatives (Figure 1b). To this end, an equimolar mixture of PDA, PNBA and *p*-methoxybenzoyl azide (PMBA) was initially milled at room temperature for 20 minutes, then the temperature was raised to 70 °C, and the milling was continued for further 120 minutes (Figure S8d). The same result was also observed when the temperature of the reactor was increased to 80 °C and 90 °C, respectively. NMR revealed that before the heating step, the mixture contains pure MA and PMBA (Figure S24). This finding indicates that the *p*-substituent on the acyl azide governs the reactivity of acyl azides towards the initial nucleophilic substitution with an amine. This reaction mixture, containing MA and PMBA, reacts to pure AUM upon heating, when the PMBA rearranges to isocyanate (Figures 1b and S24).

In general, all five amide/urea compounds prepared by thermally-controlled milling were isolated in excellent yields and high-purity (ESI, NMR spectra of crude products) demonstrating a considerable level of selectivity for developed mechanochemical procedures.

Solution syntheses of amide and urea derivatives

For comparison, we also developed optimized solution procedures (for exact details, please see ESI, Section 3). Pure MA was formed in 44 % yield from ethanol after stirring the mixture of PNBA and PDA at RT for 4 hours. DA was not accessible after five days stirring in dried tetrahydrofuran (THF) or DMSO and even when the temperature was raised to 50 °C. In other solvents, MA would precipitate from the reaction mixture, thus preventing further reaction. To prepare AU, isolated MA was

refluxed in THF with separately prepared *p*-nitrophenyl isocyanate yielding AU in 80 % yield over two steps, and also AUM in 73 % yield from separately prepared *p*-methoxyphenyl isocyanate. Attempts to prepare the isocyanate in situ resulted in the incomplete reaction due to the precipitation of reaction mixture. DU was formed in the reaction of PDA and separately prepared *p*-nitrophenyl isocyanate in THF in 87 % yield over two steps. All reactions yielding urea derivatives were stirred under reflux for several hours to ensure the completion of the reaction. In general, aside from higher solvent consumption and longer reaction time, solution synthesis of these compounds could not be conducted as a one-pot process or by using only one solvent, and generally had lower yields. The probable reason for this behaviour is low solubility of intermediate compounds such as MA, requiring additional synthetic steps and solvents for reaction to come to completion, whereas the solubility issues did not limit the mechanochemical reactions.

Mechanistic study of high-temperature mechanochemical Knoevenagel condensation

We tested the effect of different temperatures on mechanism and rates of model C–C bond-forming organic reaction, mechanochemical Knoevenagel condensation between vanillin (van, melting point 83 °C) and barbituric acid (barb, melting point 245 °C).^{61,62,25} This reaction was considered as a model reaction for organic mechanochemistry; it was used for estimating the energetics of milling,⁶³ and for scaling the mechanochemical reactions to flow processing.^{64,65} Knoevenagel condensation between van and barb was recently milled at higher temperatures where it was shown by solution NMR spectroscopy how this reaction could be significantly accelerated by increasing the temperature to 75 °C.⁴⁸ In this paper, and other contributions dealing with the mechanochemical reaction between van and barb, the focus was on the efficiency of the condensation reaction, usually demonstrated by solution NMR of the final product. However, application of solid-state analytical methods resulted in interesting discoveries for this system; for example, it was discovered only very recently how rheological changes occur during milling of barb and van.⁶⁵ Further, advanced in situ monitoring techniques revealed this condensation reaction to having a unique and complex mechanism in mechanochemical organic chemistry,⁶⁶ where barb and van self-assemble after 2 hours dry milling into a cocrystal with reacting groups in a beneficial arrangement for C–C bond to form.⁶⁶ Prolonged milling of the in situ formed cocrystal (for further 11–13 hours) results in the reaction between the aldehyde and –CH₂ group of barb, yielding an amorphous form of the Knoevenagel product (form **I**) which remains stable for further 40 hours of milling. During monitoring, we identified three different solid forms of Knoevenagel product in total, a form without Bragg reflections which we called “amorphous”, form **I**, and two crystalline forms, **II** and **III**, respectively, each with a unique Raman spectrum. **II** and **III** formed exclusively in the presence of liquid additives.

Here, we aimed to study how raising the temperature of the reaction mixture influences the mechanism and the rate of the Knoevenagel condensation (Figures 5 and 6). We modified our thermally-controlled reactor vessel by introducing a sapphire window into the wall (Figure S29) to monitor the milling reaction under increased temperatures directly and compare it with

the in situ data collected for milling of barb and van at room temperature (Figures 5 and Figure 6). It was shown here that milling at stable 50 °C resulted in the rapid formation of (barb)(van) cocrystal after 25 minutes milling (Figure 5a). After 40 minutes, weak signals of **I** start to show, but cocrystal remains the dominant component of the mixture after an hour milling. PXRD and NMR analyses confirmed these observations (Figure S27). The formation of cocrystal intermediate at 50 °C is accelerated when compared to milling at room temperature, where it starts to form upon an hour milling, and finishes after almost two hours of uninterrupted milling.⁶⁶

Raising the temperature to 75 °C results in a change of reaction mechanism (Figure 6a), where **III**, a phase not attainable after more than 50 hours of conventional milling,⁶⁶ forms rapidly and directly from the reactants. The formation of **III** is visible after 7 minutes milling, and the reaction finishes in the following 15 minutes (Figure 5b). No evidence of cocrystal intermediate or any other solid phase of the product is evident from the in situ Raman data, but the lack of Raman signals in the initial stages of milling, before the **III** forms, indicate that the reaction mixture got stuck on the vessel walls, i.e. it changed its rheological properties.

We have chosen 50 °C and 75 °C to match previous studies on the kinetics of Knoevenagel condensation,^{48,65} taking care for reaction to be conducted below the melting point of vanillin. Hutschings et al. assessed different reaction parameters in reaction, such as temperature, the volume of water additive, and frequency, and they concluded that the unusual sigmoidal kinetics observed is a combination of chemical and mechanical factors.⁶⁵ Authors used mixer mill with a large stainless steel ball (13.6 g weight) and have observed the rheological changes of the reaction mixture during milling, which transformed into a cohesive rubber-like film around the milling ball. Most importantly, this cohesive state was directly connected to an increase in reaction rate. Authors reported here that the temperature of the interior of the milling vessel during milling increased to 60–70 °C and the temperature of the ball to 80 °C. The properties and exact composition of the rubbery phase were not possible to determine, as it would transform into powder almost immediately upon the opening of the vessel for sampling. The discovery of this cohesive phase and also of the cocrystal intermediate⁶⁶ in such a well-established system emphasize the need for a deep and interdisciplinary study of mechanochemical milling reactions if we want to understand them better. A similar change in rheology could be a reason for sticking the reaction mixture and loss of the signal observed in the initial phase of our experiments conducted at 75 °C (Figure 5b). Also, solid-state transformations and syntheses of organic systems involve eutectic or molten phases,⁶⁷ so the sticking of the sample that occurs in the initial ten minutes milling at 75 °C could also indicate the conducting condensation reaction.

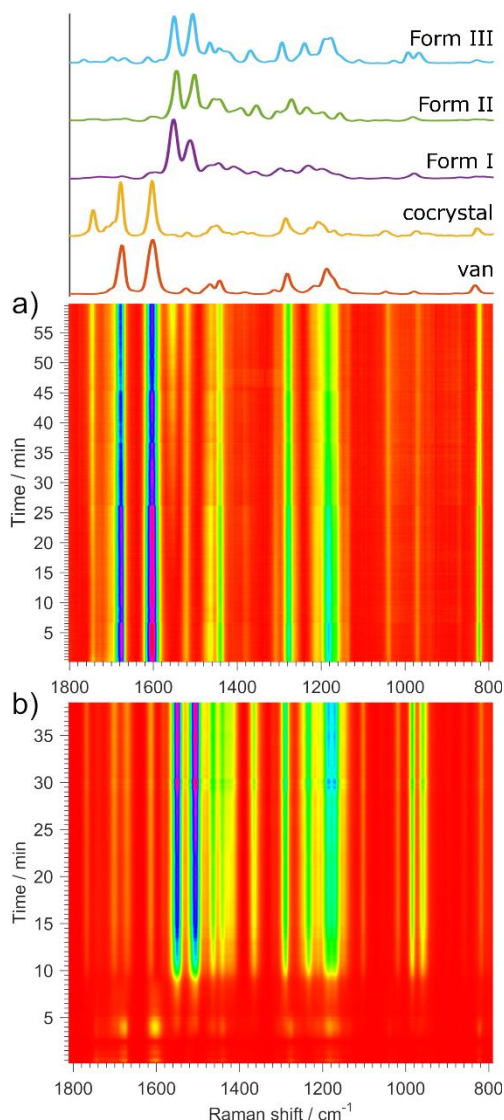


Figure 5. In situ Raman monitoring of dry milling of van and barb (1:1 molar ratio) at a) 50 °C; and b) 75 °C. The ex situ spectra of reactants and products are given on top. In reaction at 75 °C, the reaction mixture gets sticky before the product (**III**) with C-C bond forms.

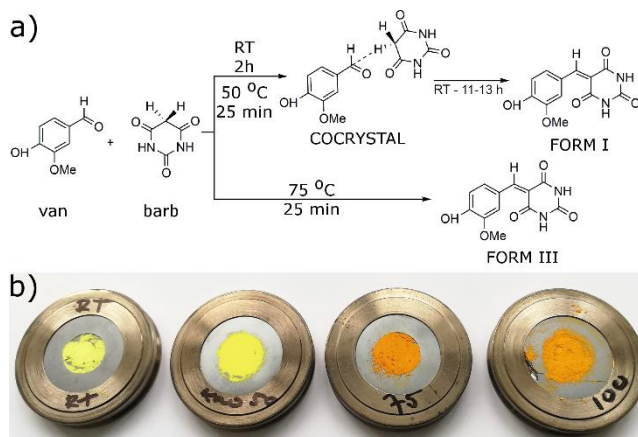


Figure 6. a) Dry milling of the barb and van in mixer mill proceeds through a cocrystal intermediate to gain form **I** at room temperature and 50 °C, respectively, whereas the milling at 75 °C affords form **III** rapidly and directly from reactants; b) products of thermally-controlled milling. KNO label denotes the product of neat grinding experiments at variable temperatures. The product with a C=C double bond has an orange color.

Thermally-controlled mechanochemical synthesis of aldimine compounds

Milling the amines with aldehydes afford another type of covalent bond C=N (imine), through nucleophilic attack of amine on the carbonyl of an aldehyde with the elimination of one water molecule. This condensation reaction is extensively used for the preparation of aldimines, sometimes also known as Schiff bases, modular compounds widely used as ligands, receptors, and sensors. Mechanochemical synthesis proved highly suitable for preparation of these compounds,^{68,69} and even complex and highly-crystalline covalent-organic frameworks⁷⁰ based on C=N bonds were successfully prepared by grinding.^{71,72}

We were interested here in studying how the milling at elevated temperatures reflects on rates and efficiency in double-imine condensation of the van with PDA (Figure 7). Milling the PDA and van (1:2 ratio) at ambient temperature resulted in a bright orange-red product without Bragg reflections after 60 minutes milling (Figures 7b and 7c). NMR analysis showed the red solid to be a mixture of van, monosubstituted van(PDA) Schiff base, and disubstituted (van)₂(PDA) Schiff base (Fig S28). Performing the milling for 60 minutes at 75 °C resulted in a pale yellow crystalline powder. NMR analysis showed the yellow product to be the pure disubstituted (van)₂(PDA) Schiff base (Figure S28). High luminescence prevented the monitoring of the thermally-controlled reaction by in situ Raman spectroscopy, but the yellow colour of the product is visible in transparent PMMA jars after 5 minutes milling. The formation of disubstituted (van)₂(PDA) Schiff base is also confirmed by PXRD (Figure S29).

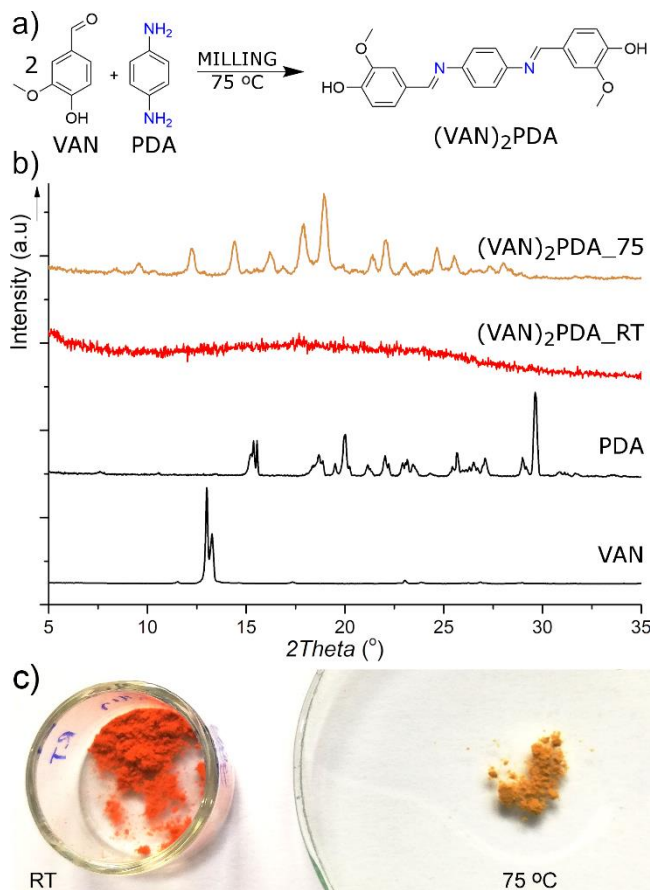


Figure 7. a) Mechanochemical synthesis of disubstituted Schiff base of vanillin and PDA; b) PXRD patterns for products collected after 60 minutes milling at 75 °C (yellow pattern) and RT (red pattern); and c) products isolated after 60 minutes of milling the van and PDA (2:1) at RT (left) and 75 °C (right).

Thermally-controlled milling in the synthesis of MOF-74 metal-organic framework

The proposed strategy is not limited to organic C–N, C=N, and C–C covalent reactions. We explored here thermally-controlled mechanosynthesis of an archetypal metal-organic framework (MOF) MOF-74, widely investigated due to modularity, catalytic activity, and open-metal sites.^{73,74,75} Zn-MOF-74 was prepared by 70-90 minutes milling of zinc oxide (ZnO, melting point 1975 °C) and 2,5-dihydroxyterephthalic acid (H₄dhta, melting point 300 °C),⁴⁵ using 3.5 or 4 g ball at 30 Hz oscillation rate. Such harsh milling can strain the product crystallites and may affect the overall stability of the product. For example, mechanochemistry is now widely used for the amorphization of crystalline MOFs,^{76,77,78} and the preparation of rare phases of MOFs, such as kat-phase of another popular MOF, ZIF-8, available exclusively from the amorphization of ZIF-8 and recrystallization of the amorphous matrix by continued ball milling.⁷⁹ In thermally-controlled LAG(H₂O) at 75 °C, the reaction concludes after 8 minutes milling, yielding pure and highly-crystalline Zn-MOF-74 despite using smaller milling media (2 x 1.4 g stainless steel balls) which was inefficient for conventional preparation of MOF-74 even after 24 hours milling.⁴⁵ The reaction mechanism at 75 °C remains the same as in milling without

external heating (Figure 8), involving a formation of Zn(H₂O)₂(H₂dhta) intermediate, clearly visible in PXRD after 5 minutes milling. This intermediate, formed by reaction of zinc oxide with carboxylic groups on H₄dhta ligand, reacts with remaining ZnO into MOF-74 after additional milling. Herein, both reactants have high melting points but reactivity of ZnO is significantly increased when the temperature is raised by 50 °C from conventional milling conditions.

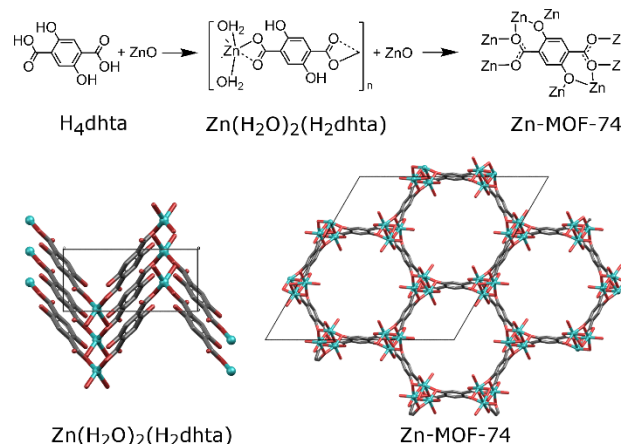


Figure 8. Mechanochemical synthesis of Zn-MOF-74 is a two-step process, involving closed [Zn(H₂O)(H₂dhta)]_n intermediate.

A moderate increase in reaction mixture temperature (15-50 °C) having such a substantial effect on the selectivity and reactivity of the milling synthesis of organic or coordination compounds further challenge^{27,39} the existence of localized hot-spots or similar phenomena in mechanochemical reactions involving soft materials, which is still sometimes considered as a primary driving force behind the unique reactivity of mechanochemical process.^{3,80} The application of heating to the milling process also results in significant overall energy saving. Twenty minutes milling at 75 °C spends in total 0.026 kW/h, while the conventional Knoevenagel process, which requires at least 13 hours milling at RT, consumes a minimum of 0.598 kW/h (for more details, please check ESI).

Table 1. Comparison of different synthetic procedures for the preparation of compounds targeted in this study.^a

	Solution			Conventional Milling			High Temp. Milling		
	θ (°C)	t (h)	η (%)	θ (°C)	t (h)	η (%)	θ (°C)	t (h)	η (%)
MA	RT	4	44	25	20-30 min	100	-	-	-
DA	-	-	-	25	-	-	40	4	96
DU	110	5	87	25	-	-	90+90	1+1	98
AU	110	5	80	25	-	-	RT+80	1.5	95
AUM	110	5	73	25	-	-	RT+70	1+3	95
KNO	80	2 ⁸¹	78	25	13 ⁶⁶	100	75	15 min	100
MOF	105	20	51	25	24 ⁴⁵	-	75	5-8 min	100

a-We have taken in account only the milling reactions performed in similar manner to this study (30 Hz, mixer mill, 2 stainless steel balls of 1.4 g each). The yields correspond to the isolated yields.

Conclusion

In summary, thermally-controlled milling significantly accelerates the mechanochemical reactions, reduces the energy costs and need for extreme milling conditions, and has a strong and profound influence on mechanisms and the outcome of milling reaction. Most notably, it expands the mechanochemical reactivity and selectivity to a level not achievable by conventional milling or solution procedures. The proposed methodology is advantageous for the mechanochemical formation of C–C, C=N, and C–N bonds affording various imines, amides and ureas, some of which are not available by milling at ambient conditions. The vast potential of milling under controlled heating regimes was demonstrated here on the one-pot selective and controllable synthesis of four different compounds containing amide and urea functionalities from the same acyl azide and diamine, without the need for protecting the amine group or any additional synthetic steps other than modulating the temperature of the milling reactor. The procedure is not limited to organic chemistry; thermally-controlled milling proved beneficial for the rapid and efficient formation of highly crystalline MOF-74. While the mechanism for the high-temperature formation of MOF-74 remains the same as in the room temperature milling, the mechanism of Knoevenagel condensation changes on elevated temperatures, avoiding the self-assembly of the cocrystal intermediate and affording a solid form of product not available from conventional dry milling. The results presented accentuate the need for better control and understanding of mechanochemical procedures for their broader applicability and show how the application of external stimuli through specific heating programs can elevate mechanochemistry to a new level of chemical reactivity.

ASSOCIATED CONTENT

Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>, and includes additional PXRD, FTIR-ATR, Raman and particle size distribution data.

KEYWORDS:

Thermally-controlled mechanochemistry, advanced mechanochemical reactivity, sustainable organic synthesis, amide, urea, MOF-74

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Funding Sources

This work was supported by Croatian Science Foundation through Grant No. 4744 and the European Social Fund through Grant Met4Pharm R.C.2.2.08-0024

Notes

Krunoslav Užarević is a share-holder in InSolido Technologies (Croatia).

‡ Martina Tireli did all the work while employed at Ruđer Bošković Institute.

ACKNOWLEDGMENT

We are grateful to Ivan Halasz for critically reading the paper, Stipe Lukin for help with graphical material, Vitomir Stanišić for constructing the reactor vessel and Ivan Kulcsár for help with energy-consumption measurements and photograph.

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Mechanochemical milling under controllable heating regimes enables chemical reactions not attainable by conventional mechanochemical or solution procedures, and also reduces the time and energy costs of the production process.

