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.
Supporting Information

Investigations of Thermally-Controlled Mechanochemical Milling Reactions
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Section 1. Materials and methods

CAUTION: Special precaution must be taken while heating the acyl azide compounds due to their explosive nature. In the temperature range we used, the acyl azides were stable and we have not experienced a single incident, but please take special care not to heat these compounds above 90 °C, and without toluene or similar liquid.

All chemicals were obtained from usual suppliers (Merck, Acros, Alfa Aesar) and were used as received. Toluene and THF were distilled from sodium before use. Compounds PNBA (p-nitrobenzoyl azide) and PMBA (p-methoxybenzoyl azide) were prepared using previously published procedures.\(^1\) Compound 

DU (1,1'-(1,4-phenylene)bis(3-(4-nitrophenyl)urea))\(^2\) and MA (N-(4-aminophenyl)-4-nitrobenzamide)\(^3\) were previously prepared and characterized, and analyses of herein prepared MA and DU products were compared to published results.

Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm).

NMR spectra were recorded on a Bruker Ascend 400 spectrometer in DMSO-d6. The following abbreviations were used to describe peak splitting patterns s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constants (\(J\)) were reported in Hertz (Hz). Chemical shifts are reported in ppm and referenced to tetramethylsilane TMS reference in proton spectra, and solvent signal (DMSO central peak at 39.52) in carbon spectra.

Attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR) were performed on Perkin Elmer Two spectrometer equipped with UATR diamond cell module in the range of 4000-450 cm\(^{-1}\) and with 4 cm\(^{-1}\) resolution. Data were processed using P-E Spectrum software (version 10.5.3.738, 2016).

HRMS spectra were recorded on Bruker autoflex MALDI-TOF spectrometer.

Power-consumption measurement. Power consumption for the common mechanochemical procedure and the heated milling procedure was assessed by using EMOS P5821 power consumption meter. Each procedure was measured twice.
Section 2. Mechanochemical syntheses

CAUTION: Special precaution must be taken while heating the acyl azide compounds due to their explosive nature. In the temperature range we used, the acyl azides were stable and we have not experienced a single incident, but please take special care not to heat these compounds above 90 °C, and without toluene or similar liquid added to the reaction mixture.

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.

Mechanochemical synthesis of MA (N-(4-aminophenyl)-4-nitrobenzamide). MA (orange-brown powder) was synthesized according to the previously reported literature procedure.¹

Mechanochemical synthesis of DA ((1,1'-(1,4-phenylene)bis(3-(4-nitrophenyl)amide)). PDA (28 mg, 0.25 mmol) and PNBA (100 mg, 0.5 mmol) were each positioned in the separate parts of the aluminum milling vessel, and the additive (toluene, 30-35 µL) was added to the PNBA side. The vessel was filled with argon gas. The temperature of the reactor vessel was raised to 40 °C, and the milling was commenced. After four hours milling, the reaction mixture was allowed to cool down to room temperature, and the white solid was isolated yielding 102 mg (96%) of product.

¹H NMR (400 MHz, DMSO-d6) δ/ppm 10.59 (s, 2H), 8.38 (d, 4H, J = 8.6 Hz), 8.19 (d, 4H, J = 8.6 Hz), 7.79 (s, 4H)
¹³C NMR (100 MHz, DMSO-d6) δ/ppm 163.66 (s), 149.13 (s), 140.59 (s), 129.17 (d), 123.55 (d), 120.80 (d)
IR (ATR) v / cm⁻¹ 3317, 1642, 1605, 1535, 1401, 1326, 1261, 855, 871, 821, 702, 669, 531
HRMS (MALDI-TOF) m/z [M + H⁺]− calculated for (C₂₀H₁₄N₄O₆) − 407.0992, found 407.0989.

Mechanochemical synthesis of DU ((1,1'-(1,4-phenylene)bis(3-(4-nitrophenyl)urea)). PDA (28 mg, 0.25 mmol) and PNBA (110 mg, 0.57 mmol) were each positioned in the separate parts of the milling vessel, and the additive (toluene, 40 µL) was added to the PNBA side. The vessel was filled with argon gas. The reactor vessel was heated to 90 °C and kept at that temperature without milling for an hour, after which the milling was started. The reaction mixture was milled for an additional 60 minutes, and the pale yellow product 112 mg (98%) was isolated. ¹H NMR spectrum was in accordance with previously published procedure.²

Mechanochemical synthesis of AU ((4-nitro-N-(4-(3-(4-nitrophenyl)ureido)phenyl)benzamide)). PDA (28 mg, 0.25 mmol) and PNBA (110 mg, 0.57 mmol) were each positioned in the separate parts of the milling vessel, and the additive (toluene, 40 µL) was added to the PNBA side. The vessel was filled with argon gas. The reactor vessel was milled at 30 Hz (2x 1.4 g balls) for 30 minutes before the temperature was raised to 80 °C, and the milling was continued at this stable temperature for further 60 minutes. The ochre product was isolated and analyzed (105 mg, 95% isolated yield).

¹H NMR (400 MHz, DMSO-d6) δ/ppm 10.52 (s, 1H), 9.42 (s, 1H), 8.92 (s, 1H), 8.37 (d, 2H, J = 9.2 Hz), 8.22-8.16 (m, 4H), 7.72 (d, 2H, J = 9.0 Hz), 7.69 (d, 2H, J = 9.4 Hz), 7.49 (d, 2H, J = 9.2 Hz)
Mechanochemical synthesis of AUM (4-nitro-N-(4-(3-(4-nitrophenyl)ureido)phenyl)benzamide). PDA (28 mg, 0.25 mmol) was positioned to one side of the reactor vessel. PNBA (50 mg, 0.25 mmol) and p-methoxybenzoyl azide (44.2 mg, 0.25 mmol) were both positioned to the other part of the milling vessel, and the additive (toluene, 40 µL) was added to the mixture of azides. The vessel was filled with argon gas. The reaction mixture was milled for 30 minutes after which the temperature of the reactor was raised to 70-90 °C and the milling was continued for additional 60-120 minutes. Crude product was triturated with ethanol yielding 101 mg (95%) of pure AUM.

Mechanochemical Knoevenagel condensation. The masses and the milling media were chosen according to the published procedure. Barbituric acid (128 mg, 1 mmol) was positioned to one side of the reactor vessel. Vanillin (152 mg, 1 mmol) was positioned to the other part of the milling vessel, to prevent the reactants to mix before the milling started. The vessel was filled with argon gas. The reaction mixture was milled for 20-45 minutes at a selected temperature (25 °C, 50 °C, 75°C and 100 °C, respectively). The isolated products were subjected to 1H NMR (Figure S22) and PXRD analyses (Figure 4, manuscript).

Mechanochemical MOF-74 synthesis. For this experiment, we modified the published procedure by introducing lighter milling media (balls of 1.4 g instead of 3.5 g balls used for a standard mechanochemical MOF-74 synthesis). 220 mg of H$_2$DHTA (1.1 mmol) and 180.7 mg of ZnO (2.2 mmol) were placed in separate parts of the reactor. 250 µL of water was added to the ZnO side. The temperature of the milling vessel was raised to 75 °C, and the milling (30 Hz, two stainless steel balls each weighing 1.4 g) was conducted for 5 minutes (1st experiment) and 8 minutes (2nd experiment). The pale yellow product was immediately isolated and analyzed by PXRD (Figure S23).
Section 3. Solution synthesis

Solution synthesis of **MA.** *p*-Phenylenediamine (224 mg, 2.1 mmol) and *p*-nitrobenzoyl azide (400 mg, 2.1 mmol) were dissolved in 20 mL of ethanol, and the resulting mixture was stirred at room temperature for 4 hours. The precipitated product was filtered and washed with ethanol yielding 240 mg (44 %) of pure MA. Proton spectrum was in accordance with previously published data.

**DA** was not accessible from solution syntheses using *p*-phenylenediamine and *p*-nitrobenzoyl azide reactants after numerous attempts, several different solvents used (DMSO, toluene, ethanol, THF) and multi-days are stirring or moderate heating.

Solution synthesis of **DU.** *p*-Nitrobenzoyl azide (211 mg, 1.1 mmol) was refluxed in 5 mL of dry toluene under argon for two hours. The solvent was evaporated, and crude isocyanate was dissolved in 5 mL of THF and added to a stirred solution of *p*-phenylenediamine (PDA, 56 mg, 0.52 mmol) in 10 mL of dry THF. The mixture was refluxed for 3 hours under argon and cooled to room temperature. Formed product was filtered, washed with THF, and dried on air. The reaction yielded 211 mg (87 % over two steps) of pure **DU.** Proton spectra are in accordance with previously published data.

Solution synthesis of **AU.** In 5 mL of dry toluene *p*-nitrobenzoyl azide (86 mg, 0.45 mmol) was refluxed under argon for two hours. The solvent was evaporated, and crude isocyanate was added as a solution in 5 mL of THF to a stirred solution of MA (104 mg, 0.4 mmol) in 6 mL of dry THF (some heating is required for full dissolution). The mixture was refluxed for 3 hours under argon, and the product was filtered after cooling the solution to room temperature. The product was washed with THF and dried on air. The reaction yielded 152 mg (80 % over two steps) of pure **AU.**

Solution synthesis of **AUM** (4-nitro-N-(4-(3-(4-nitrophenyl)ureido)phenyl)benzamide). In 5 mL of dry toluene *p*-methoxybenzoyl azide (80 mg, 0.48 mmol) was refluxed under argon for two hours. The solvent was evaporated, and the crude isocyanate was added as solution in 5 mL of THF to a stirred solution of MA (104 mg, 0.4 mmol) in 6 mL of dry THF (some heating is required for full dissolution). The mixture was refluxed for 3 hours under argon, cooled to room temperature and the product was filtered, washed with THF and dried on air. The reaction yielded 143 mg (73 % over two steps) of pure AUM.
Section 4. The construction of a thermally-controlled milling reactor vessel

*Description of a system for milling at a controlled temperature.* The milling was conducted in 14 mL milling vessel (named milling chamber or milling inner vessel) encased in 2 mm thick aluminum sleeve with 75 W heater and thermocouple embedded into the inner vessel. The aluminum sleeve is insulated by a thermally-insulating silicate layer and encased in outer shield for better insulation during the oscillations induced by mechnochemical reactor (Fig. S1). The power cords are flexible high-temperature wires available in any electronics store. The total length of the reactor is 65 mm. The reactor vessel was adapted to fit into the insulated hands of the IST-636 (InSolido Technologies, Croatia) mixer mill (Fig. S2). The temperature was controlled over an in house developed PID auto-adaptive system, using an Omega Engineering thermal controller and 20 A solid-state relay (Figs. S3-S5), ensuring fast response in heat pulses, and adaptation to ever-changing temperature conditions inside of the vessel depending on the impact of the milling media, reaction mixture composition, reaction enthalpy, and also on radiation and convection processes.

The heater control system consists of:
1. Omega CN8DPT-145-24-E/P PID Thermal Controller
2. driver unit based on the STP55N MOSFET transistor
3. ports for USB and RS-232 communication for device control and data collection
4. Power Supply Module MeanWell RSP-320-24

All listed units are integrated into a metal housing with corresponding USB terminals for RS-232, 220V power input, K-type thermocouple input, heater output, and LEDs for the heater operation signaling. The Omega CN8DPT-145-24-E/P thermal controller front panel is visible at the front panel of the box. A display with actual temperature (big digits) and default temperature (small digits) is visible on the front panel of the thermal controller.

*Work Principle:* Thermal Controller has the function of registering the signal from the thermal sensor (k-type thermocouple), comparing the actual temperature with setpoint temperature, and through the factory-installed PID heater control algorithm. The Omega CN8DPT-145-24-E/P uses a PID algorithm that enables adaptive behavior of the temperature control system with regard to the properties of the heater; it’s environment and the sample itself.

Once a second, the CN8DPT controller analyzes the temperature change and turns the heater on or off to achieve a stable temperature. The Omega CN8DPT does not have sufficient power at its outputs, and therefore, output signal should be sent to unit 2 (driver unit). The signal is first sent to the MOSFET driver (UCC27324) that raises the voltage to the level which is required to turn on the MOSFET transistor. When the MOSFET gets this signal, it closes the circuit that includes the heater, i.e., it behaves like a switch. When there is no signal, the MOSFET switches off, and the heater goes off. The power supply for the entire system provides the Meanwell Power Supply Module RSP-320-24 (24V /13.4A).

The device can be controlled via RS-232 port or USB port, and it is possible to collect data from both protocols.

In this way, the controller was able to “learn” about the object it heats through PID algorithms, enabling the application of the specific heating program to reactor vessel oscillating at 30-36 Hz with
less than 1 % deviation in some cases, when thermally conductive inner chamber transduces the temperature to thermocouple quickly, and the PID systems is able to respond rapidly to the change in temperature. The maximum temperature tested during milling was 250 °C (Figure S6), but we believe this setup may be applied for even higher temperatures when using suitable side-insulators. We used LogOS software (InSolido Technologies, Zagreb, Croatia) for temperature control and logging, but alternatively, the PLATINUM software by Omega Engineering can be used for the same purpose.

Figure S1. The construction of a thermally-controlled reactor vessel. The inner chamber (14 mL inner volume, 2 mm thick wall) where the milling is performed can be made of different materials, such as polytetrafluoroethylene (PTFE), poly(methyl methacrylate)PMMA, aluminum, stainless steel, and zirconia. For our experiments, we used mostly inner chamber made of PTFE or stainless steel. PMMA was used when we needed chamber transparent to Raman laser, but this can be avoided with the inclusion of a sapphire window into the chamber (Fig. S31). Thermocouple for PID control is embedded into the wall of the inner chamber.
Figure S2. Mounting of thermally-controlled milling reactor vessel onto the mixer mill. The reactor vessel can be adapted to fit different mixer mills.
Figure S3. Thermal controller: electronics and wiring.

1 - Omega CN8DPT-145-24-E/P2 thermal controller
2 - MOSFET based heater driver board
3 - MeanWell RSP-320-24 power supply (24VDC)
4 - Mains power inlet (110V/220V) with fuse and power switch
5 - Heater output terminals
6 - RS-232 /0 sub-9 connector
7 - K-type thermocouple connector
1a - 110V/220V power inlet
1b - SSR output (to MOSFET driver board)
1c - thermocouple input
1d - RS-232 input/output
2a - STP55N MOSFET transistor
2b - UCC27324 MOSFET driver
2c - 12V regulator 7812 (powering MOSFET driver)
2d - main power input/output connectors
2e - SSR signal input (from SSR output of thermal controller)
2f - heater power outputs (to back panel heater output terminals)
2g - 24V power inlet (from MeanWell RSP-320-24 power supply)
Figure S4. Schematic representation of circuitry on power and heater driver board.
Figure S5: Schematic representation of internal wiring on power and heater driver board.

Omega CN3OPT-140-24/E/E thermal controller (front panel)

POWER & HEATER SOURCE MODULE

Reactord heater controller

TITLE: Internal wiring schematic

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Section 5. Thermal data

Figure S6. Thermal data for milling experiment (30 Hz oscillation, 2x1.4 g balls, stainless steel inner reactor chamber) performed at 250 °C targeted temperature. The maximum deviation is 2.2 °C, or 0.9 %
Figure S7. The acceleration of milling vessel (shown as G-force) during the left-right swing operation of IST-636 mixer mill at 30 Hz, measured by ADXL377 - High-G Triple-Axis Accelerometer (Adafruit, NYC, USA).
Figure S8. Thermal data for mechanochemical syntheses of a) MA, showing the increase in temperature to ca. 25 °C after the formation of MA is finished and remains stable before the next synthetic step; b) DA, milled for 240 minutes in aluminum vessel at 40 °C; c) DU, preheated at 90 °C for 60 minutes before the milling was started and continued for 60 minutes; and d) AUM, again showing the formation of MA, followed by heating the PTFE vessel for further 130 minutes to give AUM product. Higher temperature deviations for some experiments result from heating inertia in PID controller induced by poor temperature conductivity of 2.5 mm thick PTFE walls of the inner reaction capsule, where the layers nearer to the heater overheat before the inner layers achieve the target temperature and sensor sends the feedback signal to the controller. The heat from the outer layers then cause small overheating of the inner layers, causing maximum deviation of ±5 °C for some experiments.
Section 6. NMR and IR spectra

Figure S9. $^1$H NMR spectrum of DA in DMSO-$d_6$.

Figure S10. $^{13}$C NMR spectrum of DA in DMSO-$d_6$. 
Figure S11. ATR-FTIR spectrum of DA.
Figure S12. $^1$H NMR spectrum of AU in DMSO-d6

Figure S13. $^{13}$C NMR spectrum of AU in DMSO-d6
Figure S14. ATR-FTIR spectrum of AU.
Figure S15. $^1$H NMR spectrum of AUM in DMSO-$d_6$.

Figure S16. $^{13}$C NMR spectrum of AUM in DMSO-$d_6$. 
Figure S17. ATR-FTIR spectrum of AUM.
Figure S18. $^1$H NMR spectrum of crude DU from mechanochemical synthesis recorded in DMSO-$d_6$.

Figure S19. $^1$H NMR spectrum of crude AU from mechanochemical synthesis recorded in DMSO-$d_6$. 
Figure S20. $^1$H NMR spectrum of crude DA from mechanochemical synthesis recorded in DMSO-$d_6$.

Figure S21. $^1$H NMR spectrum of crude MA from mechanochemical synthesis recorded in DMSO-$d_6$. 
Figure S22. $^1$H NMR spectrum of crude AUM from mechanochemical synthesis recorded in DMSO-$d_6$.

Figure S23. $^1$H NMR spectrum after 24 hours of NG milling of PDA with two equivalents of PNBA recorded in DMSO-$d_6$. 
Figure S24. $^1$H NMR spectrum of a mixture of PMBA, PDA, and PNBA after milling and before heating, recorded in DMSO-$d_6$. The milling of the reaction mixture for 3 hours at ambient temperature yields pure MA and the remaining PMBA reactant. PNBA, containing electron withdrawing group, undergoes nucleophilic substitution with PDA upon milling at RT to form MA. PMBA, bearing electron-donating group does not react with PDA when the PNBA is present in the reaction mixture. In such reaction mixture, elevation of temperature induces in situ Curtius rearrangement of PMBA into an isocyanate, which reacts with MA to gain final amide-urea product AUM in excellent yield. AUM is characterized by p-NO2 amide and p-OC3 urea peripheral substituents,
Figure S25. Overlay of ATR-FTIR spectra of PDA and PNBA reactants and all products formed from them by mechanochemical procedures.
Section 7. Raman spectra

Figure S26. Overlay of Raman spectra of all products formed by mechanochemical procedures.
Section 8. Characterization of Knoevenagel condensation product

Figure S27. a) NMR spectra of crude reaction mixtures; mechanochemical Knoevenagel condensation of barbituric acid and vanillin on different temperatures; and b) PXRD of products of thermally-controlled Knoevenagel condensation; KNO represents the dry milling experiment of bar band van performed at different temperatures.
Section 9. Thermally controlled mechanochemical synthesis of (van)2(PDA) Schiff base

Figure S28. $^1$H NMR spectra of products obtained after milling the van:PDA (2:1) mixture at room temperature (blue) and at 75 °C (red). $^1$H NMR of van mixture is given at the bottom as black spectrum.

Figure S29. PXRD of product of van:PDA (2:1) mixture milled for 5 minutes at 75 °C. The PXRd of the product corresponds to (van)2(PDA) Schiff base.
Section 10. Thermally-controlled mechanochemical synthesis of MOF-74

Figure S30. (a) PXRD data for products obtained by LAG (H$_2$O) of a mixture of ZnO and H$_4$DHTA at 75 °C. WOBHEB represents a pattern for MOF-74 calculated from single-crystal, and ODIPOH represents a calculated pattern for [Zn(H$_2$DHTA)(H$_2$O)$_2$]$_n$ intermediate. In a pattern collected after 5 minutes milling at 75 °C, visible traces of ZnO and the intermediate are denoted with asterisk and hash sign. (b) Enlarged section of 30-50 2Theta degrees, showing the absence of ZnO in the product obtained after 8 minutes milling. ZnO has a three strong peaks at 31.8, 34.5 and 36.3 which partially overlap with MOF-74. ZnO is however clearly distinguishable by a strong peak at 47.6 and visible in the product milled for 5 minutes. In the product milled for 8 minutes (red pattern) the peaks related to ZnO are not visible.
Figure S31. Modified thermally-controlled reactor vessel with embedded sapphire window for in situ Raman spectroscopy. The external shielding is removed for clarity reasons.
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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. At this point, it has been applied for the preparation or transformation of a broad range of materials, from supramolecular materials and pharmaceutical co-crystals, diverse organic and organometallic compounds, discrete or porous coordination compounds, all the way to hard inorganic materials, nanoparticles, and intermetallic compounds. Mechanochemistry is dubbed Chemistry 2.0, as it opened a pathway towards numerous compounds not attainable by any other synthetic procedures. Despite recent advances in understanding the impact of milling media on bulk reaction mixture and the energetics derived from kinetic and thermal energy in milling processes, fundamental knowledge about these basic reaction parameters is still largely lacking. The need for temperature control in the milling process has been emphasized as a central issue for mechanochemistry in several recent reviews, expecting it to overcome the activation energy barrier for some reactions and thus open a way towards a new level of chemical reactivity. 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. Only a few reports existing to date, however, show how milling at a sub-ambient or stable increased temperature of the milling vessel affects rate and selectivity 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-(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. 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,\(^\text{43}\) highly crystalline MOF-74 was available after a several minutes milling, showing almost 10-fold acceleration despite using much milder milling conditions.

**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 µL) 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,\(^\text{40,46,63}\) 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.\(^\text{40,69}\) 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 aluminium or steel, the deviations are

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**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.
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.29 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.31,32,33,34,35 Although it could be expected based on estimated energetics of milling,12 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 (η=0.25 µL/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.57,48 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 passivated 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 preheated the reactor ves-
sel 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).

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.\textsuperscript{7,8} 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\textsuperscript{50,60} 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\textsuperscript{-1} and 1601 cm\textsuperscript{-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 3](image-url)  
Figure 3. \textsuperscript{1}H 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.

![Figure 4](image-url)  
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-nitropheryl 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-nitropheryl 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).61,62,52 This reaction was considered as a model reaction for organic mechanochemistry; it was used for estimating the energies 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.66 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.67 Further, advanced in situ monitoring techniques revealed this condensation reaction to having a unique and complex mechanism in mechanochemical organic chemistry,68 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,64,65 taking care for reaction to be conducted below the melting point of vanillin. Hutchings 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 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 aldmines, 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, and even complex and highly-crystalline covalent-organic frameworks based on C=N bonds were successfully prepared by grinding.

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).
 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 mechanochemical synthesis of an archetypal metal-organic framework (MOF) MOF-74, widely investigated due to modularity, catalytic activity, and open-metal sites. Zn-MOF-74 was prepared by 70-90 minutes milling of zinc oxide (ZnO) having such a substantial effect on the selectivity and reactivity of the milling synthesis of organic or coordination compounds further challenge 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. 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.

| Solution | Conventional Milling | High Temp. Milling |
|----------|----------------------|--------------------|
|          | θ (%) | t (h) | η (%) | θ (%) | t (h) | η (%) |
| MA       | 26 | 10 | 95 | 26 | 10 | 95 |
| DA       | 25 | 10 | 95 | 25 | 10 | 95 |
| DU       | 25 | 10 | 95 | 25 | 10 | 95 |
| AU       | 25 | 10 | 95 | 25 | 10 | 95 |
| AUM      | 25 | 10 | 95 | 25 | 10 | 95 |
| KNO      | 25 | 10 | 95 | 25 | 10 | 95 |
| MOF      | 25 | 10 | 95 | 25 | 10 | 95 |
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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.
