Supporting Information

for

Mechanochemical carbon-carbon bond formation that proceeds via a cocrystal intermediate

by

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S1 Materials and methods

Laboratory *in situ* **Raman monitoring** was performed using portable Raman system with a PD-LD (now Necsel) BlueBox laser source with the excitation wavelength of 785 nm equipped with B&W-Tek fiber optic Raman BAC102 probe and coupled with OceanOptics Maya2000Pro spectrometer. The probe was positioned under a reaction vessel on a moving stand and laser was focused 1 mm inside of the vessel.¹ Time-resolved *in situ* Raman spectra were collected in an automated fashion using an in-house code in MATLAB. Subtraction of vessel contribution to Raman spectra was described elsewhere.² After monitoring was finished, samples were taken out and analyzed by PXRD and FTIR-ATR. Spectral resolution of Raman spectra was 4 cm⁻¹.

Analysis of Raman spectra. Spectral range of $150 - 1986 \text{ cm}^{-1}$ was baseline corrected using piecewise asymmetric least squares^{3,4} and subsequently normalized with l^2 norm. The intensity of the peaks was derived by first selecting a suitable range of the Raman spectra and fitting peaks using nonlinear least squares approach implemented with *fit* function using Trust-region algorithm in MATLAB and Gaussian functions of the form:

$$f(x) = A * \exp(-((x - x_0)/c)^2) + O$$

where A is intensity, x_0 is peak position, c is peak width and O is linear offset. Standard deviations were estimated with the bootstrapping method where every spectrum was resampled 800 times.

Tandem *in situ* **monitoring** experiment was performed at ESRF beamline ID15A as previously described.^{2,5} Experimental hutch was air-conditioned at 22 °C, the Raman laser probe approached the reaction vessel from below and laser focus and X-ray beam path were positioned to coincide on at same part of the reaction mixture, X-ray radiation wavelength of 0.177 Å was selected using a multilayer monochromator, diffraction data were recorded on a Dectris Pilatus 3X CdTe 2M detector positioned 1057 mm from the sample, radial integration of the raw diffraction images was performed using an in-house script in MATLAB, exposure time for each pattern was 9.0 s Time resolution between consecutive diffraction patterns was ca. 10 s and time resolution of Raman spectra was 10 s.

Laboratory powder X-ray diffraction (PXRD) patterns were collected on an Aeris Panalytical diffractometer using Ni-filtered copper radiation in the Bragg-Brentano geometry with the sample prepared in a thin layer on a silicon zero-background holder.

Single crystal X-ray diffraction Diffraction measurements were conducted on a small orange crystal $(0.01 \times 0.01 \times 0.06mm)$ using an Oxford Diffraction Xcalibur Nova R (microfocus Cu tube) at 126 K. Data reduction was performed using the CrysAlisPRO program package.⁶ The structure was solved and refined using Olex2 v1.02⁷ and SHELXL.⁸ The non-H atoms were treated anisotropically, while the H atoms were placed in calculated positions and refined as riding on their respective non-H atoms. The structure contains water molecule in disorder. CCDC 1869002 contains the supplementary crystallographic data.

Fourier-transform infrared attenuated total reflectance (FTIR-ATR) measurements were performed on a Perkin-Elmer Spectrum Two instrument equipped with a diamond crystal Quest ATR Accessory, from 4400 cm⁻¹ to 500 cm⁻¹, with resolution 1 cm⁻¹.

Solution-state NMR spectra were recorded on a Bruker Ascend 400 spectrometer in DMSOd₆ at 298 K. Chemical shifts are reported in ppm and referenced to solvent signal.

Solid-state NMR analysis. ¹³C NMR and ¹⁵N NMR cross-polarization magic angle spinning (CP-MAS) NMR spectra were obtained on an Agilent Technologies VNMRS 600 MHz NMR spectrometer equipped with a 3.2 mm NB Double Resonance HX MAS Solids Probe. Larmor frequencies of carbon and nitrogen nuclei were 150.76 and 60.76 MHz, respectively. The ¹³C NMR and ¹⁵N NMR CP-MAS NMR spectra were externally referenced using hexamethylbenzene (HMB) and ammonium sulfate (≈ 355.7 ppm with reference to nitromethane at ≈ 0.0 ppm), respectively. Samples were spun at the magic angle with 16 kHz during ¹³C measurement and with 10 kHz during ¹⁵N measurement. For more precise assignment of ¹³C spectra, we applied Lee–Goldburg CP-MAS NMR spectroscopy. ¹H - ¹³C Lee–Goldburg CP-MAS NMR measurements correlate only the nearest ¹H and ¹³C nuclei and thus enable easier and more reliable assignment than the more common and robust (RAMP) CP-MAS measurements. In Lee–Goldburg CP-MAS measurements, ¹H magnetization is locked along the effective magnetic field, which is inclined at the magic angle with respect to the static magnetic field. In this way during the CP, block ¹H-¹H homonuclear dipolar interactions are efficiently suppressed. In our experiment a moderate proton radio-frequency power corresponding to a ¹H nutation frequency of 68 kHz was used for the Lee–Goldburg CP.

Thermal analysis. Differential scanning calorimetry (DSC) analysis was performed on a Mettler Toledo DSC823e measuring module. Each sample (3 to 5 mg) was placed in a pierced aluminium crucible and then heated at a rate of 5 °C min⁻¹ from 25 °C to 350 °C with an inert stream of nitrogen flowing at 50 mL min⁻¹.

Thermal stability of polymorphs were detected from TGA experiments (Discovery TGA, TA Instruments). Around 5–10 mg of each sample was put in platinum HT pan type. All samples were heated at the rate of 5.0 °C/min up to 250 °C. Experiments were performed in an inert N₂ atmosphere.

Crystal structure determination from powder diffraction data. The crystal structure of the barb:van cocrystal was solved from and refined against powder diffraction data. The powder diffraction pattern was collected on an Aeris Panalytical diffractometer using Ni-filtered copper radiation in the Bragg-Brentano geometry with the sample prepared on a silicon holder. The diffraction pattern was indexed with a monoclinic unit cell (a = 10.53644(31) Å, b = 18.23475(57) Å, c = 6.97824(22) Å, $\beta = 111.6043(22)^{\circ}$, V = 1246.537(63) Å³) while likely systematic absences indicated the the $P2_1/c$ space group. This unit cell volume corresponds well to four formula units comprised from one barb and one van molecule in the unit cell and thus one barb and one van molecule in the asymmetric unit. The crystal structure was solved by global optimization in direct space taking the barb and van molecules as separate rigid bodies. When an approximate crystal structure model was found, torsions were also included in the optimization. The best structure model obtained was introduced into Rietveld refinement using geometry restraints on bond distances and angles as well as planarity restraints set to the expected values. All calculations were performed using the program Topas (Bruker-AXS, Karlsruhe, Germany). The cif file for the barb:van cocrystal was deposited with the Cambridge crystallographic data center (CCDC) under the number 1818969. These data can be retrieved free of charge from the CCDC upon request.

Ab initio calculations. Density functional theory calculations (DFT), including nudget elastic

band calculations (NEB) with climbing image method⁹ were performed with ATK-DFT code^{10–12} using PBE exchange-correlation functional¹³ with Grimme D2 dispersion corrections¹⁴ and SG15 pseudopotentials¹⁵. Results of NEB calculations show minimum energy path between fixed initial and final configuration. We obtained initial configuration for solid state calculation by relaxing XRD configuration. Final configuration we obtained by first forcing formation of C=C bond and then relaxing all coordinates. For NEB calculation in vacuum, we took reacting barb and van molecules from solid state calculation and removed all others. Result of NEB calculation in crystal is shown in Fig. 3, and in vacuum in Fig. S1. Minimum energy path to form C=C bond involves rotating barb around nitrogen-nitrogen axis and rocking its two hydrogens that participate in the reaction (see also supplementary movies). Barb rotation is easy (energetically cheap) in vacuum, while it is very limited due to surrounding molecules (and energetically expensive) in unit cell of the crystal. In vacuum, since barb rotation is cheap, more than 80% of energy barrier is due to one hydrogen atom jump from barb to van, after which reaction goes without further barrier. In unit cell of the crystal, on the other hand, barb cannot rotate and large hydrogen rocking-like movement is necessary to bring hydrogen in as good as possible position to jump to van. This movement takes 150 kJ/mol, almost half of the total barrier. We could not afford to consider larger cells due to already large computational cost, but it is clear that larger cell would result in a smaller total barrier for reaction as surrounding molecules could relax. The lowest limit for barrier is set by calculation in vacuum. Vibrational modes that correspond to barb rotation have $\omega \approx 30$ cm⁻¹ (see movie) and those that correspond to hydrogens rocking mode have $\omega \approx 100 \text{ cm}^{-1}$ (see movie). Since these modes are thermally excited, especially barb rotation, reaction will proceed with smaller energy requirements.



Figure S1: Minimum energy path for reaction of one molecule of barb and one molecule of van in vacuum. A dashed line is cubic spline interpolation and is a guide to the eye.

S2 Ex situ PXRD analysis



Figure S2: PXRD data for the cocrystal and forms I and II heated to 150 $^{\circ}$ C. Form III remains stable upon heating.

S3 Laboratory Raman in situ monitoring



Figure S3: *In situ* monitoring of solid barbituric acid and vanillin *via* Raman spectroscopy for 50 hours. Formation of cocrystal starts around 70 min into milling followed by formation of the Knoevenagel condensation product **I** that remains stable even up to 50 h milling time.



Figure S4: *In situ* monitoring of LAG of solid barbituric acid and vanillin *via* Raman spectroscopy with 20 μ L of acetonitrile. Cocrystal phase formed about 3 minutes into milling. Transformation from **I** to form **II** takes place after 15 hours and subsequently to form **III** after 24 hours of milling.



Figure S5: *In situ* monitoring of LAG of solid barbituric acid and vanillin *via* Raman spectroscopy with 20 μ L of nitromethane. Similar as in LAG with acetonitrile cocrystal is formed after around 3 minutes. Transformation from form **I** to form **II** takes place around 15 hours and subsequently to form **III** after 20 hours of milling.



Figure S6: *In situ* monitoring of LAG of solid barbituric acid and vanillin *via* Raman spectroscopy with 20 μ L of ethanol. In LAG with 20 μ L of ethanol the formation of form **III** proceeds directly from cocrystal phase.



Figure S7: In situ monitoring of LAG of solid barbituric acid and vanillin via Raman spectroscopy with addition of 20 μ L of dipea. In the beginning of the experiment part of the material sticked to the walls of the jar and only signals from barbituric acid was observed. As milling proceeded material became more homogeneous. No cocrystal formation can be observed and condensation product I formed directly from the reactants.

S4 NMR analysis

Solution NMR analysis



Figure S8: a) ¹H NMR spectrum of barbituric acid in DMSO-d₆ (400 MHz). b) ¹³C DEPT-Q NMR spectrum of barbituric acid in DMSO-d₆ (101 MHz). ¹H NMR (DMSO-d₆, 400 MHz, δ /ppm): 11.10 (s, 2H, H_a), 3.46 (s, 2H, H_b); ¹³C NMR (DMSO-d₆, 101 MHz, δ /ppm): 167.79 (C2), 151.67 (C3), 39.44 (C1).



Figure S9: a) HSQC and b) HMBC spectra of barbituric acid in DMSO-d₆ (400 MHz).



Figure S10: a) ¹H NMR spectrum of vanillin in DMSO-d₆ (400 MHz). b) ¹³C DEPT-Q NMR spectrum of vanillin in DMSO-d₆ (101 MHz). ¹H NMR (DMSO-d₆, 400 MHz, δ /ppm): 10.24 (s, 1H, H_d), 9.77 (s, 1H, H_a), 7.42 (dd, 1H, J = 8.07 Hz, H_f), 7.39 (d, 1H, J = 1.88 Hz, H_b), 6.96 (d, 1H, J = 8.07 Hz, H_e), 3.84 (s, 3H, H_c); ¹³C NMR (DMSO-d₆, 101 MHz, δ /ppm): 191.00 (C1), 153.03 (C5), 148.16 (C4), 128.71 (C2), 126.08 (C7), 115.39 (C6), 110.67 (C3), 55.58 (C8).



Figure S11: a) COSY b) HSQC and c) HMBC spectra of vanillin in DMSO-d₆ (400 MHz).



Figure S12: a)¹H NMR spectrum of form III in DMSO-d₆ (400 MHz). b) ¹³C DEPT-Q NMR spectrum of form III in DMSO-d₆ (101 MHz). ¹H NMR (DMSO-d₆, 400 MHz, δ / ppm): 11.25 (s, 1H, H_b), 11.13 (s, 1H, H_a), 10.55 (s, 1H, H_f), 8.47 (s, 1H, H_h), 8.22 (s, 1H, H_c), 7.86 (d, 1H, J =8.38 Hz, H_d), 6.90 (d, 1H, J =8.38 Hz, H_e), 3.83 (s, 3H, H_g); ¹³C NMR (DMSO-d₆, 101 MHz, δ /ppm): 164.18 (C3), 162.49 (C2), 155.89 (C5), 153.06 (C9), 150.22 (C1), 146.96 (C10), 132.53 (C7), 124.20 (C6), 118.01 (C11), 115.32 (C8), 113.98 (C4), 55.51 (C12).



Figure S13: a) COSY b) HSQC and c) HMBC spectra of form III in DMSO-d $_6$ (400 MHz).



Figure S14: ¹H NMR spectra of a) cocrystal, b) form I, c) form II, and d) form III in DMSO- d_6 (400 MHz).

Solid-state NMR analysis



Figure S15: ¹H-¹³C CP-MAS spectra of a) barbituric acid, b) vanillin (600 MHz)



Figure S16: ¹H-¹³C CP-MAS spectra of a) cocrystal, b) form II (600 MHz)



Figure S17: ¹H-¹³C CP-MAS spectrum of form III (600 MHz)



Figure S18: ¹H MAS spectra of a) barbituric acid, b) vanillin, c) cocrystal, d) form II, e) form III (600 MHz)



Figure S19: ¹H-¹³C LG-CP-MAS of a) barbituric acid, b) vanillin, c) cocrystal, d) form II, e) form III



Figure S20: ¹H-¹⁵N CP-MAS spectra of a) cocrystal, b) form II, c) form III (600 MHz)

S5 FTIR-ATR and Raman analysis



Figure S21: FTIR-ATR spectra for starting compounds and cocrystal.



Figure S22: Raman spectra for starting compounds and cocrystal.



Figure S23: FTIR-ATR spectra of the Knoevenagel condensation products.



Figure S24: Raman and FTIR-ATR spectra of the Knoevenagel condensation product: a) form **I**, b) form **II**, c) form **III**.

S6 Thermal analysis



Figure S25: DTA and TGA data for form I



Figure S26: DTA and TGA data for form II



Figure S27: DTA and TGA data for form ${\bf III}$



Figure S28: DSC data for a) barbituric acid, b) vanillin, c) cocrystal d) form **I**, e) form **II**, f) form **III**

S7 Single crystal X-ray analysis



Figure S29: Rietveld fit of the experimental pattern (collected using $CuK\alpha$ radiation) of Form II with the crystal structure model of Form II obtained from a single crystal X-ray diffraction experiment. The calculated pattern was modeled assuming slight preferred orientation. Colour code: black-measured, blue-calculated, grey-difference. Tick marks represent calculated peak positions.

Molecular formula	C ₁₂ H ₁₁ N ₂ O _{5.5}
M _r	271.2
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ /n
a / Å	14.148(8)
b/Å	14.7902(14)
c / Å	12.1137(16)
α/ °	90
β/°	115.1137(16)
γ/ °	90
V / Å ³	2278.7(7)
Ζ	8
$\lambda(CuK_{\alpha})$ / Å, mirror monochromator	1.54184
Temperature / K	126.3(6)
Crystal dimension / mm ³	0.32 imes 0.21 imes 0.11
<i>hkl</i> range	-13, 15; -15,18; -17,16
Number of measured reflections	11607
Number of independent reflections	4672
Number of reflections with $I > 2\sigma(I)$	2342
Number of parameters	366
$R[F^2 > 4\sigma(F^2)]$	0.0784
$wR(F^2)$	0.1808
Goodness-of-fit, S	0.989

Table S1: Crystallographic data for II.

Molecular formula	$C_{12}H_{12}N_2O_6$
Formula weight / g mol $^{-1}$	280.24
Asymmetric unit formula	$C_{12}H_{12}N_2O_6$
Space group	P2 ₁ /c
<i>a</i> / Å	10.53644(31)
<i>b</i> / Å	18.23475(57)
<i>c</i> / Å	6.97824(15)
α / °	90
β/°	111.608(2)
γ/°	90
<i>V</i> / Å ³	1246.537(63)
Ζ	4
Temperature / K	295
Radiation type	CuK/α_1
R _p	0.023
R _{wp}	0.031
Gof	1.91
$R(F^2)$	0.01

Table S2: Crystallographic data for cocrystal.

S8 Co-crystallisation from solution



Figure S30: PXRD patterns for solids isolated from mother liquids containing dissolved barb and van in 1:1 molar ratio. All isolated products show PXRD patterns characteristic for reactants.

S9 Tandem in situ PXRD and Raman monitoring



Figure S31: Time-resolved PXRD patterns and Raman spectra from tandem *in situ* monitoring experiment of milling solid barbituric acid and vanillin in LAG experiment with 15 μ L EtOH.

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