Supporting Information

Quantitative Determination of Activation Energies in Mechanochemical Reactions
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A Materials and Methods

**Experimental detail.** Ibuprofen (ibu), $C_{13}H_{18}O_2$, (99%, Alfa Aesar, Germany) and nicotinamide (na), $C_6H_6N_2O$, (≥ 99.5%, Sigma Aldrich, Germany) were purchased commercially and were used without further purification. Grinding was performed for all reactions (LAG and neat grinding) at 50 Hz for 40 min in a conventional ball mill (Pulverisette 23, Fritsch, Germany). In a typical experiment, the coolable stainless-steel jar subpart of a 10 mL vessel was pre-tempered with two steel balls of 10 mm diameter and 4 g in mass. Afterwards, the pre-tempered reactants were added in a stoichiometric ratio of 1:1 into the vessel for a total load of 1 g (0.6281 g ibuprofen and 0.3719 g nicotinamide). The vessel was directly sealed with a Makrolon top part. The nitrogen stream was turned on 30 s before milling in order to reach the required temperature quickly after starting the milling process. The temperature of the jar was controlled in the range of ± 1 K by adjusting the nitrogen stream. The experiments were conducted at the following temperatures: 282 K, 286 K, 290 K, 294 K, 298 K, and 302 K. Each experiment was repeated six times.

**Raman Spectroscopy.** Raman measurements were performed using a Raman RXN1™ Analyser (Kaiser Optical Systems, France). The spectra were collected using a contactless probe head (working distance 6.0 cm, spot size 1.0 mm). Raman spectra were recorded with an acquisition time of 5 s and 5 accumulations (NIR excitation radiation at $\lambda = 785$ nm and an irradiation of 6.6 W/cm$^2$).

**Powder X-ray diffraction (PXRD).** The milling synthesis of the ibu:na cocrystal was verified by PXRD (Figure S1). All PXRD experiments were carried out using a D8 diffractometer (Bruker AXS, Karlsruhe, Germany) in transmission geometry (Cu-K$_{\alpha}$ radiation, $\lambda = 1.54056$ Å).
B X-ray powder diffraction patterns and crystal structure of compounds

Fig. S1 XRD patterns of the ibu:na cocrystal (black) and the respective reactants ibu (red) and na (blue).

Fig. S2 Crystal structure of the ibu:na cocrystal along the a-axis.

Fig. S3 Crystal structure of the ibu:na cocrystal along the b-axis.
Fig. S4 Crystal structure of the reactant ibu along the a- and the b-axis.

Fig. S5 Crystal structure of the reactant ibu along the c-axis.
Fig. S6 Crystal structure of the reactant Na along the a- and the b-axis.

Fig. S7 Crystal structure of the reactant Na along the c-axis.
C Raman data of compounds

**Fig. S8** Raman spectra of the ibu:na cocrystal and the reactants ibu and na.

**Fig. S9** Zoomed Raman spectra of the ibu:na cocrystal and the reactants ibu and na.
Fig. S10  a) Raman spectra of the empty grinding jar, the ibu:na cocrystal and the reactants ibu and na with the grinding jar background. b) Zoomed Raman spectra.
D Temperature-dependent data

**Fig. S11** Time-dependent and background corrected Raman spectra of the ibu:na synthesis. Milling synthesis was performed at 50 Hz for 40 min at 286 K.
Table S1: Temperature-dependent rate constants obtained at different Raman signals. sd. = standard deviation.

<table>
<thead>
<tr>
<th>T [K]</th>
<th>784 cm(^{-1})</th>
<th>820 cm(^{-1})</th>
<th>1042 cm(^{-1})</th>
<th>1391 cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k [min(^{-1})]</td>
<td>sd.</td>
<td>k [min(^{-1})]</td>
<td>sd.</td>
</tr>
<tr>
<td>282</td>
<td>0.073</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>286</td>
<td>0.086</td>
<td>0.008</td>
<td>0.027</td>
<td>0.005</td>
</tr>
<tr>
<td>290</td>
<td>0.103</td>
<td>0.007</td>
<td>0.029</td>
<td>0.002</td>
</tr>
<tr>
<td>294</td>
<td>0.106</td>
<td>0.017</td>
<td>0.030</td>
<td>0.002</td>
</tr>
<tr>
<td>298</td>
<td>0.113</td>
<td>0.007</td>
<td>0.032</td>
<td>0.004</td>
</tr>
<tr>
<td>302</td>
<td>0.129</td>
<td>0.027</td>
<td>0.034</td>
<td>0.009</td>
</tr>
</tbody>
</table>

E Arrhenius equations

\[
k = A e^{-\frac{E_a}{(RT)}}
\]

\[
\ln(k) =-\frac{E_a}{R}\left(\frac{1}{T}\right) + \ln(A)
\]

Fig. S12 Arrhenius plots according to the temperature-dependent rate constants determined based on the Raman signal at 784 cm\(^{-1}\), 820 cm\(^{-1}\), 1042 cm\(^{-1}\), and 1391 cm\(^{-1}\).