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Sustainable Beckmann Rearrangement using Bead-Milling Technology: The Route to Paracetamol

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To address the growing demand for more sustainable and greener chemistry, mechanochemical methodologies are emerging as key players. However, to date there has been little data highlighting the benefits of these rising mechanochemical technologies with regard to process scale-up activities or implementation in commercial production scale. Herein, we report the first application of bead-mill technology (Dyno®-mill) for the sustainable mechanochemical synthesis of Acetaminophen, known under the brand name Paracetamol. Using the Beckmann rearrangement, the optimized solvent-free methodology delivered a final product on a scale of several tens of grams. In comparison to current production solvent-based process, the proposed process achieves a higher yield while also allowing the removal of solvents in the chemical reaction, hereby reducing one of the extensive drivers to waste generation. The mechanochemical approach was compared to solvent-based process using a combination of green metrics and EcoScale score. The mechanochemical synthesis of paracetamol scores the highest for all the metrics over currently used solution-based processes.

Introduction

Although the first documented application of mechanochemistry, a method that use mechanical force, like grinding and milling, to drive chemical reactions, was document as early as 314 B.C. by Theophrastus of Eresos,[1] the term "mechanochemistry" (MC) *per se* was only officially articulated in 1919, in the "Textbook of General Chemistry" by Wilhelm Ostwald.[2] It took another six decades for the definition established by G. Heinicke, to materialize the outline of this new subdiscipline of chemistry.[3] More recently, before the turn of the century, IUPAC defined a mechanochemical reaction as a "*chemical reaction that is induced by the direct absorption of mechanical energy*".[4] Solvent-free, or with extremely low amount of solvent for liquid assisted grinding (LAG) methods ($0 \leq \eta \leq 1$ μL/mg),[5] mechanochemistry is a powerful methodology that increase the reaction energy-efficiency with respect to conventional methods.[6] Solvents are one of the extensive drivers to waste generation,[7] therefore, the possibility to conduct syntheses in neat conditions, intrinsically addresses the growing demand for greener and more sustainable chemistry. Several examples demonstrate that mechanochemistry provides better green metrics compared to the corresponding solution-based processes[8a–c] and reduces CO_2 emissions and costs, also confirmed by Life Cycle Assessment (LCA) studies[9] applied to the mechanochemical continuous flow preparation of the World Health Organisation (WHO) essential medicine nitrofurantoin,[10] a mass-produced antibiotic listed among the top 200 drugs sold in 2021.[11] As a result, mechanochemistry is a very attractive approach to also improve the economic benefit of a process[12] and its safety, eliminating the use of toxic or hazardous solvent, a desirable milestone for R&D industrial settings.[13] As such, these features are critical attributes contributing to foster the development of sustainability policies aligned with the 17 sustainable development goals (SDGs) edited by the United Nations in 2015.[14] In 2020, major chemical societies (GDCh and ACS) highlighted seven of the seventeen interlinked SDGs where the chemical industry can play a central role[15] especially through the growing implementation of green chemistry practices and engineering innovation.[16] Within this framework, mechanochemical processes were already identifies by the International Union of Pure and Applied Chemistry (IUPAC) among the technologies to potentially make our Planet more sustainable,[17] and comply with several of the 12 Green Chemistry principles.[12,18] However, the implementation of mechanochemistry (both in batch and continuous) in manufacturing processes for covalent bond forming reactions has not reached yet the industrial era. The biggest challenge is especially in the manufacturing of Active Pharmaceutical Ingredients (APIs),[19a–d] needing to solicit inquisitiveness in developing green-by-design chemical processes during early-stage development activities in laboratories, KiloLab or pilot plant of chemical companies.[20] Such an approach does not include only green metrics[8a–b,21] or life-cycle assessment (LCA)[9] but also by implementing emerging technologies such as mechanochemistry, currently underserved in chemical indus-

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tries. Without this inescapable, canonical, transition the chemical industry will remain under continuous/increasing pressure to develop environmentally responsible processes.[12]

Since the seminal contributions describing the preparation of the metallo-drug bismuth subsalicylate (Peptobismol),[22] and the WHO essential medicine Phenytoin,[10,23] the preparation of API by mechanochemical processes is witnessing a growing interest (Figure 1).

In this respect, mechanochemical methods for the preparation of marketed APIs exploiting molecular rearrangements,[20c,24] a powerful and very efficient strategy to increase molecular complexity, are still underdeveloped. Since the seminal article on the mechanochemical preparation of phenytoin by Biltz method, involving a pinacolic rearrangement,[23] only two examples were reported later on. Indeed, the mechanochemical synthesis of the anticonvulsant

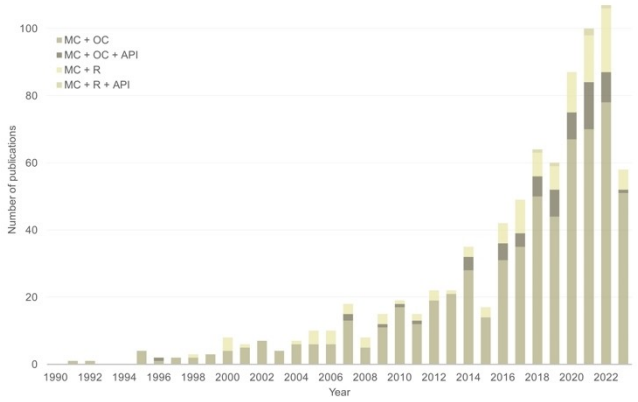


Figure 1. SciFinder^n data generated by combining keywords such as mechanochemistry (MC), organic chemistry (OC), active pharmaceutical ingredient (API) and rearrangement (R).

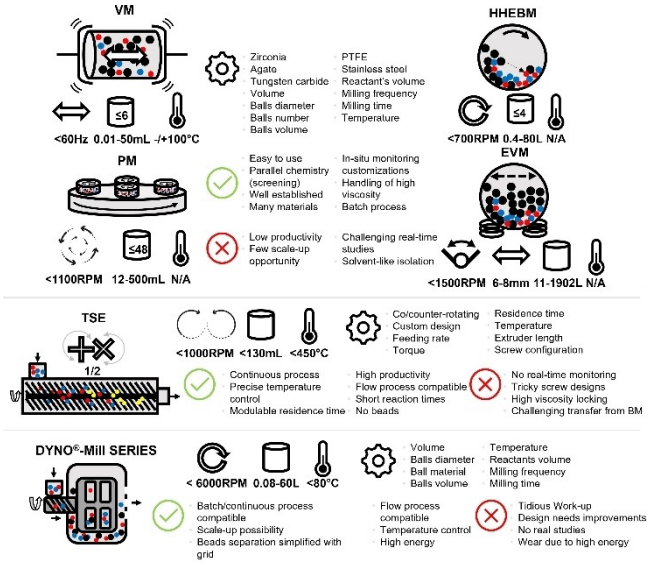


Figure 2. Advantages and limitations of commonly used mechanochemical devices for mg to multi/kilogram scale synthesis. *Legend:* vibratory mixer-mill (VM), planetary ball-mill (PM), eccentric vibration mills (EVM), horizontal high-energy ball mill (HHEBM), twin-screw extruder (TSE), and Dyno®-mill (DM).

Ethotoin and the painkiller paracetamol, prepared by mechanochemical Lossen[24a] and Beckmann[20c,24b] rearrangements respectively (at different scales, in batch[24a–b] and/or in continuous[20c]) were also described. The pharmaceutical cocrystal *rac*-Ibuprofene:nicotinamide was also prepared in Kg-scale in a vibrating eccentric mill (EVM, Figure 2).[25]

Access to paracetamol began at the end of the 19th century with the work of Hoechst A.G. for the synthesis of Antipyrine® and Amidopyrine®. The first synthetic drugs offering to the pharmaceutical industry substantial benefits with an annual production of 17 tons.[26] However, these compounds also bring to light side effects of drugs which indirectly doped the progress in pharmacokinetics and metabolic studies. Thus, in 1948, process improvements allow to isolate the Paracetamol in its pure form thus allowing to show his activity and full potential against pain and fever.[27] Paracetamol is the first line drug part of the analgesic and antipyretic for pain relief and fever reduction that is not part of the non-steroidal anti-inflammatory drugs (NSAIDs). It is currently used in the composition of more than 80 specific pharmaceutical formulations often in combination with NSAIDs or weak opioids. Regarding economic metrics of Paracetamol production an increase has been observed for the past few years and the global paracetamol market is predicted to continue to grow with a compound annual growth rate (CAGR) of 5.22% for the period from 2023 to 2028.[28] In this context, the use of mechanochemical processes to make its manufacturing more sustainable, is appealing. Paracetamol can be produced by various multi-step methodology combining *e.g.* acetylation, nitration, reduction, Beckmann rearrangement, hydrogenation, Bamberger rearrangement.[29] However, two main chemical routes are used at production scale: i) the classical route which consist of nitration, reduction by H_2 in presence of Raney-Ni and acylation in presence of acetic anhydride[30] (Scheme S1, ESI) or ii) Hoechst-Celanese process that incorporate a Friedelcraft acylation, an oxime formation, followed by a Beckmann rearrangement (Scheme S2, ESI).[31] It is on this second strategy, which is elegant and powerful, that we based our mechanochemical project.

Along this line and in view of a growing exploitation of mechanochemical process for drug manufacturing, the investigation of process methodologies for large scale synthesis, and comparative studies relying on the use of different mechanochemical devices is of crucial importance. Several mechanochemical devices, providing different types of mechanochemical stresses, operating in continuous or in batch, enabled sustainable organic syntheses (Figure 2).[8a,9,18]

Notwithstanding, bead milling technology in a Dyno®-mill (DM), also known as agitator bead mill, usually applied for horizontal wet milling processes, was never explored for mechanochemical transformations, both in dry or in liquid assisted grinding (LAG) conditions (Figure 3 and supporting information). The mixture of solid can be fed, through the hopper, into the grinding chamber by a screw conveyor (semi- or continuous mode) or through the outlet lid by removing the sieve plate (batch mode). The patented Dyno-Accelerator (DA) throw the grinding media and chemicals which collide,

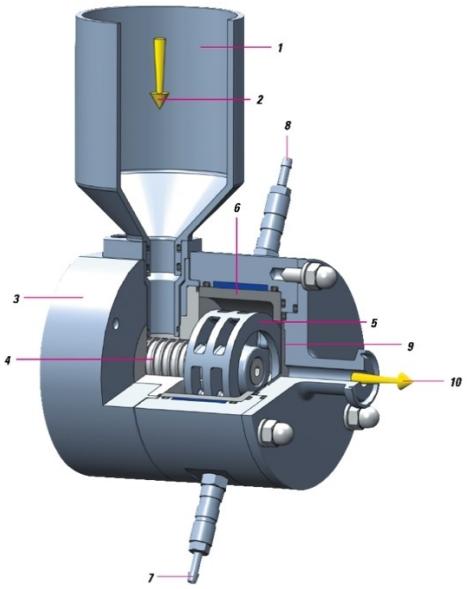


Figure 3. Working principle of horizontal bead mill (Dyno®-Mill). *Legend*: 1. Feed hopper; 2. Product inlet; 3. Seal housing for lip seal or double mechanical seal; 4. Screw conveyor; 5. Dyno-Accelerator; 6. Coolable grinding container; 7. Cooling inlet, 8. Cooling outlet; 9. Grinding media separator or sieve plate; 10. Lid outlet (Image reproduced by kind permission of WILLY A. BACHOFEN AG Switzerland ©).

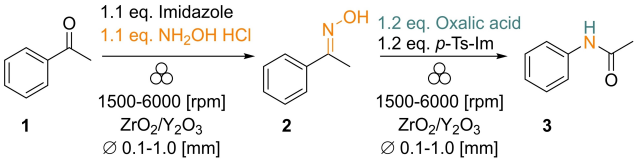
providing high energy input, through share, impact, shock, and ensures mechanochemical reaction. In batch configuration, the grinding balls and chemicals are retained in the milling chamber by replacing the sieve by a screen plate. Bead-mills are extensively used in process fields *e.g.* manufacture of paints/lacquers, grinding of minerals, processing of chemicals, food, and drugs, disintegration yeast, cyanobacteria, and microalgae for the release of intracellular product. Their efficiency depends on equipment parameters such as chamber and agitator geometry, as well as process parameters like concentration of the reaction medium, agitator speed, flow rate, mode of operation (recirculation or continuous mode), bead filling ratio, type, and diameter. In bead mills equipment, the product particles are stressed either by two-sided contact (compression) or by one-sided contact (impact). The large quantity of beads aims to maximize the occurring transferred energy per stress event and the number of stress events per unit of time. Thus, the overall performance is driven by the probability of the chemicals to be mechanically processed by the milling beads, respectively by the probability of the particles to be trapped in an active grinding zone by a grinding bead with sufficient energy to induce the reaction.[32]

Herein, the bead milling technology in a Dyno®-mill was used for the mechanochemical Beckmann rearrangement (BKR) reaction, finalized to the preparation of the WHO essential medicine paracetamol.[10] To benchmark the sustainability of this approach, comparative green metrics calculations were done for the bead milling process and compared with the current Beckmann rearrangement production process in solution use at commercial scale.[31]

Results and Discussion

Process Development

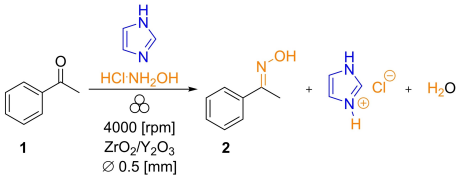
Based on the previous findings[24b] for the sustainable and eco-efficient mechanochemical BKR to access paracetamol at lab-scale in batch, DM was herein used as tool for investigating the scalability of the mechanochemical BKR in batch.



As a benchmark, the preparation of acetanilide (**3**) was investigated. The two-step synthesis consisted in a condensation reaction between acetophenone (**1**) and hydroxylamine hydrochloride leading to the corresponding acetophenone oxime (**2**) (*step 1*), followed by its rearrangement to the corresponding amide (**3**) (*step 2*). Each reaction step was investigated separately. In the first sets of tests, it was necessary to verify the chemical resistance of DN spare parts, in particular the elastomers used for the seals of the grinding chamber. Accordingly, both solubility and compatibility tests were conducted with various elastomer (Viton™, EPDM, Karlrez®, for additional data see supporting information Table S1 and S2).

Then, the mechanochemical synthesis of acetophenone oxime (**2**) was investigated at 4000 rpm (66% of the maximum speed of dyno-accelerator set arbitrarily) using the same stoichiometric ratio of reagents as previously reported,[24b] leading to 86% NMR yield in 45 min (Table 1, Entry 1). The increase of the number of equivalents of imidazole and hydroxylamine hydrochloride from 1.1 to 1.2, led to oxime intermediate **2** with 92% yield in 35 min (Table 2, Entry 2). A

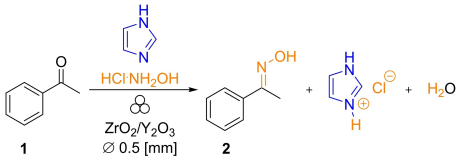
Table 1. Solvent-free synthesis of oxime **2** in a bead mill.



Entry[a]	Equivalents[b]	Time [min]	Yield [%][c]
1	1.1	45	86
2	1.2	35	92
3	1.2	10	93
4	1.2	5	87

[a] Reactions performed the dyno®-mill with 0.5 mm Zirconia beads stabilized with Yttria at 4000 rpm. Chemicals and beads filling are respectively 30 and 50 v/v% of DM volume chamber (0.080 L). The reaction scale was 250 mmol; [b] Number of equivalents of imidazole, and hydroxylamine hydrochloride compared to acetophenone (**1**); [c] Yield corrected by the assay which was defined by ^{1}H qNMR in d_6-DMSO with 1,4-dimethoxybenzene as reference.

Table 2. Dyno®-Mill Research Lab parameters optimization for the oxime **2** neat synthesis.



Entry	Rotor speed [rpm]	Beads filling [v/v%][a]	Chemicals filling [v/v%][b]	Yield [%][c]
1	2000	50	30	90
2	4000	50	30	91
3	6000	50	30	89
4	4000	25	30	87
5	4000	0	30	90
6	4000	0	60	87
7	4000	0	75	95
8[d]	4000	0	75	96

[a] Reactions were performed in the dyno®-mill. The reaction scale was 250 mmol; [b] Trials were performed with equimolar amounts of imidazole and hydroxylamine hydrochloride (1.2 equiv.) with respect to acetophenone (**1**), during 10 min; [c] Yield corrected by the assay which was defined by ^{1}H qNMR in d_6-DMSO with 1,4-dimethoxybenzene as reference; [d] Reaction performed with equimolar amounts (1.05 equivalents) of imidazole, and hydroxylamine hydrochloride with respect to acetophenone (**1**), during 20 min.

stepwise decrease of the reaction time down to 10 min had not impact on the recovered yields (Table 1, Entries 3–5), with a drop in yield observed for shorted reaction time (Entry 6).

The reaction outcome was also optimized in terms of other processing parameters, such as the rotor speed (also called accelerator, 1500 to 6000 rpm), the size of the beads (Ø 0.1–1.0 mm) and their filling degree inside the reactor (0–60 v/v%), the filling degree of chemicals (15–75 v/v%) and the nature of the grinding media (ZrO_2/Y_2O_3 and $ZrSiO_4$). When keeping the beads and chemicals filling level constant (Table 2, Entries 1–3), or decreasing the bead filling level (Table 2, Entry 4), and modifying the speed of the accelerator only, no difference in yield was observed. The reaction still proceeded even in the absence of beads (Table 2, Entry 5) leading to comparable NMR yields, suggesting the energy carry-over by the accelerator is sufficient alone to promote the reaction, involving a liquid reagent (acetophenone).

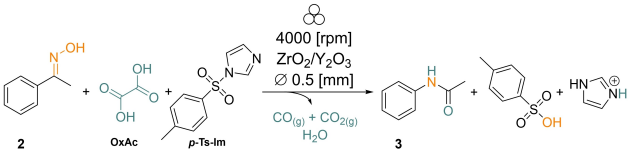
This is a major advantage especially in view of large-scale synthesis, simplifying the product recovery from the reactor, with no need of to separate the beads from the product. In this context, the downstream operations will be much easier, cost will drop significantly because there will be no need to carry out physical separation of the beads and the product (*e.g.*, decrease of operational cost) and the process is greener (*e.g.*, lower amount of solvent are necessary). The absence of beads allows to increase the filling level of chemicals up to 75 v/v%, giving access to a productivity per batch multiply by a factor of 2.5 (Table 2, Entry 6–7). Finally, by further reducing the number of equivalents of imidazole, and hydroxylamine hydrochloride (from 1.2 to 1.05), a similar reaction performance was possible (Table 2, Entry 8).

Starting from these findings, the preparation of acetanilide (**3**) was carried out in the same milling conditions. Therefore, acetophenone oxime (**2**) was reacted in the presence of equimolar amounts (1.2 equiv) of oxalic acid (OxAc) and *p*-tosyl imidazole (*p*-Ts–Im). In agreement with previously reported data,[24b] very low conversion of the acetophenone oxime (**2**) was observed in the absence of OxAc (Table 3, Entry 1). Oxalic acid being necessary for the reaction, acetanilide **3** was isolated in 36% ^{1}H qNMR yield (Table 3, Entry 2) after 120 min in the absence of milling, reaching 92% in only 30 min when the beads filling was 50 v/v % (Table 3, Entry 3), clearly indicating that the BKR (step 2) required higher mechanochemical energy inputs than the condensation reaction (step 1) to proceed. To this end, operational parameters such as: i) the speed of the accelerator (Table 4), ii) the influence of zirconia-based milling beads having different density and hardness, different sizes, and iii) the reactor filling degree, were investigated.

Therefore, similarly to step 1, it was shown that an increase in the accelerator speed (from 2000 to 6000 rpm), led to a 14% increase of the reaction yield (Table 4, Entries 1–2), with comparable results at 4000 rpm milling speed (Table 4, Entry 3). In sight of the 3% yield differences between 4000 and 6000 rpm, the process optimization was continued while keeping the rotor speed at 4000 rpm in order to reduce energy consumption and for a better life span of the equipment. The yield dropped to 84 and 45% respectively, by decreasing the number equivalent of OxAc and *p*-Ts–Im (Table 4, Entry 4) or by decreasing the reactor filling degree (Entry 5), probably due to the reduced probability of collisions among the particles into the reactor.

To verify the influence of milling beads hardness and density on the outcome of the reaction, both mechanochemical steps were also investigated in the presence of two different zirconium-based milling beads having the same diameter (Ø

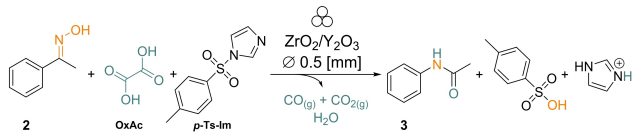
Table 3. Optimization of BKR of acetanilide.



Entry[a–c]	OxAc [eq.]	Beads filling [v/v%]	Time [min]	Yield [%][d]
1	–[e]	50	120	traces[f]
2	1.2	0	120	36
3	1.2	50	30	92

[a] The reactions were performed in the dyno®-mill with 0.5 mm Zirconia beads stabilized with Yttria at 4000 rpm. The reaction scale was 45 mmol; [b] Chemical's filling is 30 v/v% of DM volume chamber; [c] 1.2 equivalents of oxalic acid (OxAc) and 1.2 equivalents of *p*-tosyl imidazole (*p*-Ts–Im) compared to oxime intermediate (**2**); [d] Yield corrected by the assay define by ^{1}H qNMR in d_6-DMSO with 1,4-dimethoxybenzene as reference; [e] Trial carried-out without oxalic acid; [f] Only traces of desired product were observed by ^{1}H NMR.

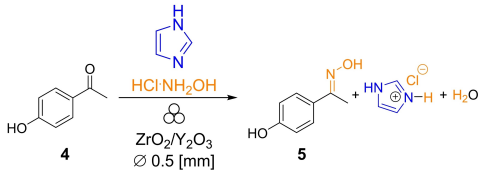
Table 4. Optimization of solvent-free BKR with bead mill for the synthesis Acetanilide **3**.



Entry[a,b]	Rotor speed [rpm]	Chemicals filling [v/v%]	Equivalent[c]	Yield [%][d]
1	2000	30	1.2	83
2	6000	30	1.2	97
3	4000	30	1.2	94
4	4000	30	1.0	82
5[e]	4000	15	1.2	45

[a] The reactions were performed in the DM at 4000 rpm, using 0.5 mm zirconia beads stabilized with yttria during 30 min. The reaction scale was 45 mmol; [b] Beads filling degree is 50 v/v% of DM volume chamber (0.080 L); [c] Number of equivalents of oxalic acid (OxAc), *p*-tosyl imidazole (*p*-Ts–Im) compared to oxime intermediate (**2**); [d] Yield corrected by the assay define by ^{1}H qNMR in d_6-DMSO with 1,4-dimethoxybenzene as reference; [e] Reaction time was 60 min.

Table 5. Bead mill synthesis of 4′-hydroxyacetophenone oxime.



Entry[a]	Rotor speed [rpm]	Equivalents[b]	Time [min]	Yield [%][c]
1[d]	6000	1.05	30	88
2	4000	1.05	30	96
3	4000	1.01	30	85
4	4000	1.01	60	90

[a] Reactions were performed in the dyno®-mill using 80 v/v% filling rate with a 1:1 ratio of beads (106.7 g, 29 ml) and reactants (39.9 g, 31 ml). The reaction scale was 140 mmol; [b] Number of equivalents of imidazole, and hydroxylamine hydrochloride compared to *p*-hydroxyacetophenone (**4**); [c] Yield corrected by the assay which was defined by ^{1}H qNMR in d_6-DMSO with 1,4-dimethoxybenzene as reference; [d] Without beads and 70 v/v% filling rate with chemicals.

0.5 mm): ZrO_2/Y_2O_3 and $ZrSiO_4$. Zirconia (ZrO_2) beads stabilized with yttria (Y_2O_3) show great mechanical properties with a Mohs scale hardness of 9 and a bulk density of 3.7 g/cm^3, while zirconium orthosilicate, ($ZrSiO_4$) beads possessing a Mohs scale hardness of 7.2 and a bulk density of 2.4 g/cm^3. As expected, for both reaction steps, a drop in yield was observed when using less hard and less dense zirconium orthosilicate beads. The yield of acetophenone oxime (**2**) dropped from 92 to 86% (step 1), while for BKR (step 2) to acetanilide (**3**), the yield decreased from 97% to 90%. Along the same trend, when reducing the bead size (Ø 0.1 mm) the BKR did not occur, due to a less efficient energy transfer which do not allow the reaction to proceed.

In the optimized conditions for both steps (Table 2, Entry 8 and Table 4, Entry 2), an overall yield of 93% was obtained for the synthesis of 6.3 g of acetanilide (**3**) in 105 min, which compares to 91% obtained for the telescoped (one-pot) methodology in batch previously reported at lab-scale allow to obtain 130 mg in 60 min.[24b]

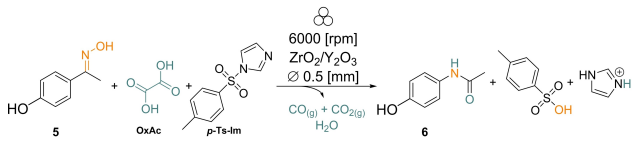
Application to Acetaminophen Synthesis

Aiming to translate our findings to the preparation of paracetamol (acetaminophen), solid *p*-hydroxyacetophenone **4** was used in the first step, instead of liquid acetophenone. A lower molecular mobility is therefore expected in contrast with a liquid-solid reaction. As such a first run at 6000 rpm without beads and 70 v/v% chemicals filling of the vessel's volume (near maximum since 20 v/v% is occupied by accelerator) was conducted. The corresponding *p*-hydroxyacetophenone oxime **5** was obtained in a slightly lower yield (88% *vs.* 96%) compared to the reaction conducted from acetophenone (Table 5, Entry 1 *vs.* Table 2 entry 8). By reducing the rotor speed to 4000 rpm and by adding 40 v/v% of zirconia (ZrO_2/Y_2O_3, Ø 0.5 mm) beads, the conversion was full, the yield increased to 96% with an assay higher than 96 wt% (Table 5, Entry 2), with the remaining 4 wt% corresponding to water. Under these milling conditions, more than 30 g of the desired *p*-hydroxyacetophenone oxime **5** were obtained in only 30 min. By decreasing the number of equivalents of imidazole, and hydroxylamine hydrochloride, to 1.01 the yield dropped, even if the reaction time was increased (Table 5, Entries 3–4).

Optimized conditions for the mechanochemical Beckmann rearrangement of acetanilide **3** were used as starting point to perform the synthesis of acetaminophen **6** (paracetamol) from the corresponding *p*-hydroxyacetophenone oxime **5**, in a 88% yield after only 30 min (Table 6, Entry 1). No improvements were observed by increasing the reaction time to 45 min (Entry 2) or by decreasing the number of equivalents of OxAc and *p*-Ts–Im (Entries 3–4), suggesting a very fast reaction at the beginning which then slow down. This hypothesis was confirmed by repeating the synthesis under the same reaction conditions, but increasing the reaction time by 50%. As a result, the conversion was slightly higher, leading to 93% yield (Entry 5), reaching 95% yield by increasing up to 2.0 equivalents both OxAc and *p*-Ts–Im (Entry 6). However, the benefit is not significant enough to be considered of an added value in terms of sustainability.

The BKR to paracetamol **6** led an overall 89% yield over two steps to prepare 7.45 g in 75 min, compared to the same process, leading to 84% yield in a one-pot fashion for 127 mg in $>$60 min.[24b] To control if the product is compliant with current control quality specifications, the synthesized material was checked for levels of residual metals by Microwave Plasma-Atomic Emission Spectrometer (MP-AES), while polymorphous forms were checked by Fourier-Transform Infrared spectroscopy (FT-IR).

Table 6. Bead mill synthesis of acetaminophen **6**.



Entry[a]	Equivalent[b]	Time	Yield [%][c]
1	1.2	30	88
2	1.2	45	90
3	1.0	15	88
4	1.0	30	88
5	1.0	45	93
6	2.0	45	95

[a] Reactions performed in a dyno®-mill. The filling rate was 80 v/v%, with a 0.6 ratio of reactants and beads. The reaction scale was 56 mmol; [b] Number of equivalents of oxalic acid (OxAc) and *p*-tosylimidazole (*p*-Ts–Im) compared to oxime intermediate (**5**); [c] Yield corrected by the assay which was defined by ^{1}H qNMR in d_6-DMSO with 1,4-dimethoxybenzene as reference.

Therefore, MP-AES analyses on isolated acetaminophen **6** showed the presence of 1.1 ± 0.1 ppm of yttrium and 5.3 ± 0.3 ppm of zirconium. Given that no relevant data for oral exposure on zirconium and yttria are available to the best of the author's knowledge, the Permitted Daily Exposure (PDE) for both metals could not be calculated according to the U.S Food & Drug Administration (FDA) Q3D(R2) elemental impurities guidance for industry.[33] However, in comparison to class 2 elements, that are generally considered as route-dependent human toxicants, and have relatively high (class 2 A) or reduced (class 2B) probability of occurrence in the drug, elements specifications limits are between 5–30 ppm. The large-scale synthesis of paracetamol **6** in a DM, presents yttria values below these thresholds, and zirconium at the same level than cobalt (Co), the more restricted class 2 metal.

Moreover, FT-IR analyses conformed that the isolated polymorphic form of acetaminophen **6** was the monoclinic I form, which is the most stable and desired polymorph compared to orthorhombic (II) and unstable form (III) (see supporting information).[34] Based on these findings, the gram-scale mechanochemical preparation of acetaminophene **6** in a DM is compliant with two of the desirable quality specifications, as per the current guidelines.

Green Metrics

In order to assess the performance of BKR in a DM for preparing Acetaminophen **6** (paracetamol), also from the point of view of its sustainability, green chemistry metrics[35] were calculated and compared with the current Beckmann rearrangement production process in solution use at commercial scale[31] (Tables S3–S7, ESI).

One of the current processes for industrial production of Acetaminophen **6** in Good Manufacturing Practices (GMP) environment handle BKR as key chemical step. In this context, for a meaningful comparison, the present mechanochemical process is assessed against the improved Hoechst-Celanese process in solution (HCSP, Table S2, ESI).[36] As a result, better green metrics[8a] were obtained for the mechanochemical BKR in the DM compared to the process in solution (Figure 3 and Table S7, ESI). Indeed, the Atom Economy (AE)[37] raised from 0.24 (for the solution based-process) to 25.79%, the lower value in solution was due to the use of hydroxylammonium sulfate ($(NH_3OH)_2SO_4$) for preparing the oxime **5**, together with catalytic amount of potassium iodide (KI) and thionyl chloride ($SOCl_2$), used for in the second step (BKR). The *E*-Factor[38] is highly improved for the mechanochemical BKR to paracetamol **6** in the DM (19.05) compared to solution synthesis (41.75), through waste reduction (solvent only for downstream operations and reuse over more cycle). Process Mass Intensity (PMI)[39] and Reaction Mass Efficiency (RME)[40] metrics deliver the same trend with 50% cut for both metrics in favor of the DM process (42.75 *vs.* 19.78 for PMI and 41.05 *vs.* 22.92% for RME) (Figure 4, Table S7, ESI).

PMI can be considered as the most representative mass-based metrics since all the material involved in the process are deemed relative to the quantity of the targeted product. On top of these well accepted and used metrics an additional comparison of bead milling *vs.* solution process with the EcoScale[41] (Table S5–6, ESI) was also carried out. This semi-quantitative tool takes into consideration not only green characteristics but also the economical parameters, which other tools do not permit. In the same way than the other metrics, the EcoScale fully supports the mechanochemical methodology with a score of 71 *vs.* 23 for the solution-based process. Overall, very promising when considering the mechanochemical step itself, however when considering an industrial application, not only the upstream process must be considered but also the downstream, where there is still room for improvement related to the solvent use.

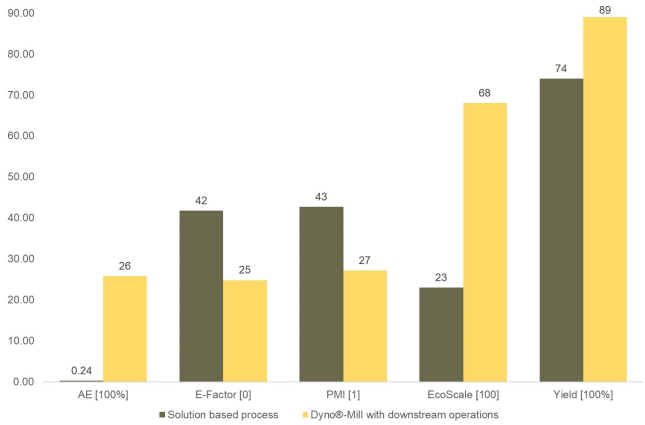


Figure 4. Comparative graphical plot of green chemistry metrics calculated for the preparation of Acetaminophen **6** known as Paracetamol.

Conclusions

BKR is a powerful chemical transformation giving access to a game-changing methodology when used in combination with mechanochemistry, leading to amide bond. The results delivered through this study give access to a green and cutting-edge process alternative with respect to current solution-based processes or other milling technologies in batch. The developed strategy is solvent-free during the chemical transformation stage, requires a reduced amount of solvent (EtOH, MTBE or AcOEt) in the downstream operations (solubilization, filtration, crystallization), does not require the use of toxic reagents, and with smooth reaction conditions, is consistent with the principles of sustainable development. This statement is strengthened through higher green metrics values and EcoScale score for mechanochemistry *vs.* solution-based process with data produced in scale-up trials on several tens of grams. The proposed bead-mill solvent-free mechanochemical approach was successfully applied to the synthesis of Acetaminophen **6**, commonly known as Paracetamol (overall yield of 89%). On top of standard metrics, residual amount of metal is bellow FDA guideline and the expected monoclinic I polymorphic form is delivered. Finally, the results achieved in the frame of this contribution highlight the potential of applying bead-mill based technologies for industrial production, in batch, semi-batch or continuous mode, as well as expends the tools operable for solid-solid state reaction.

Supporting Information

The Supporting Information is available free of charge at https://doi.org/10.1002/cssc.202301921. Experimental procedures, green metrics, ^{1}H, ^{13}C NMR, and spectral data of compounds.

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Conflict of Interests

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.
The authors declare no competing financial interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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