Effect of Reaction Parameters on the Synthesis of 5-Arylidene Barbituric Acid Derivatives in Ball Mills

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S Supporting Information

ABSTRACT: The influence of crucial reaction parameters on Knoevenagel condensation in planetary ball mills was investigated. Rotation frequency (ν_{rot}), milling ball diameter (d_{MB}), milling ball filling degree (Φ_{MB}), and beaker size had obvious influences on yield. It was found that higher ν_{rot} lower d_{MB} , milling beakers with larger diameter, and a Φ_{MB} of ~0.3 are advantageous for the reaction. Furthermore, the influence of the type of mill was investigated, including reactions performed in different planetary and mixer ball mills, in a stirred media mill, and with a mortar mill. Comparisons with the other solvent-free synthetic routes showed that ball milling is an effective way of performing the reaction with low energy intensity.

INTRODUCTION

The use of mechanical stress for the accomplishment of mechanochemical reactions is now an established field of research represented by a huge number of reactions in different fields of organic, inorganic, and organometallic chemistry and materials science.¹ In all cases, mechanical stress is provided to the reactants, whereby the energy input can be realized in different ways. The easiest but imprecise way is to use a mortar and pestle.² Results that are more reliable can be obtained with different types of ball mills, such as planetary (PBMs) or mixer ball mills (MBMs). The results of organic reactions in ball mills are subject to several influencing parameters, especially the influence of rotation frequency (ν_{rot}) , milling time (t), and number of milling balls (n_{MB}) .³ Although a large number of synthesis protocols have been published, parameters such as the milling ball diameter $(d_{\rm MB})^{3c,d,4}$ and beaker size⁵ have received less attention. Furthermore, comparative studies on reactions in different types of mills are rare.^{2,6} However, the kind of mill utilized can strongly influence the outcome of a reaction. For example, Schneider et al. investigated the Suzuki-Miyaura reaction in two types of PBMs and one MBM.² The reaction proceeded well in the PBMs at 300 min⁻¹, whereas in the MBM at the same frequency only low yields were observed. Wang and co-workers investigated pinacol couplings in an MBM and a mortar mill (MM).^{6a} Although mechanical energy is supplied in both mill types, higher yields of the pinacol coupling product were obtained in an MM.

We have recently investigated the influence of several reaction parameters on the yield of a Knoevenagel condensation of vanillin (1a) and barbituric acid (2a) (Scheme 1) in a planetary ball mill aiming to close this knowledge gap,⁵ including questions regarding the influence of beaker size, geometry, and the way the mechanical energy is provided. To this end, Knoevenagel condensation was performed using various tools for allocating mechanical stress.

Scheme 1. Generic Reaction Scheme of the Knoevenagel Condensation



To investigate the influence of different milling and grinding apparatuses, three different types of PBMs, an MBM, a stirred media mill (SMM), an MM, and a mortar and pestle were used. The main differences between the PBMs are the diameter of the main disc $(d_{\rm MD})$, the speed ratio (r), the maximal $\nu_{\rm rot,max}$, the maximal volume of the milling beaker $(V_{\rm MV,max})$, and the number of milling beakers $(n_{\rm MV})$ that can be applied (Table 1). PBM P7 offers the application of two milling beakers, and in PBM P5 four milling beakers can be utilized, in contrast to PBM P6 in which only one milling beaker can be installed. The used MBM offers two positions for milling beakers whereby their maximal volume is limited to 50 mL. The maximal oscillation frequency ($\nu_{\rm osc,max}$) is 1800 min⁻¹ ($\triangleq f = 30$ Hz).

Several reaction parameters were investigated and will be discussed for the different types of ball mills. The reactions performed by milling were compared to other solvent-free

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Table 1. Specifications of the Planetary (PBM) and Mixer Ball Mills (MBM) Utilized

type of ball mill	$d_{ m MD}$ [mm]	r ^a	$[\min^{\nu_{\max}}]$	V _{MV,max} [mL]	n _{MV}
PBM P5	250	1:-2.19	400	500	4
PBM P6	121.6	1:-1.82	650	500	1
PBM P7	140	1:-2	1100 ^b	80	2
MBM MM400			1800	50	2

^{*a*}Defined as the ratio of the rotation speed of the pot to the revolution speed of the main disk. ^{*b*}The maximal value of $\nu_{\rm rot}$ is dependent on $d_{\rm MB}$.

methods, whereas gentle grinding processes were supported by means of classical or microwave-assisted heating.

RESULTS AND DISCUSSION

Reaction in PBM Pulverisette 6 (PBM P6). The influence of several reaction parameters on the yield of the Knoevenagel condensation of **1a** with **2a** was investigated in PBM P6. The primary parameters chosen for this study are the rotation frequency ($\nu_{\rm rot}$), milling ball filling degree ($\Phi_{\rm MB}$), milling ball diameter ($d_{\rm MB}$), and the size of the milling beakers.

 $\Phi_{\rm MB}$ was defined as the volumetric ratio of the overall milling ball volume $(V_{\rm MB})$ to the total volume of the milling beaker $(V_{\rm MV})$.

$$\Phi_{\rm MB} = \frac{\sum V_{\rm MB}}{V_{\rm MV}} \tag{1}$$

Influence of the Rotation Frequency (ν_{rot}). The first parameter that was investigated in PBM P6 was the rotation frequency. This parameter directly influences the kinetic energy of the milling balls and consequently the stress energy that is transferred to the substrate. Furthermore, the temperature in the milling beaker is increased due to friction.⁸ This is why ν_{rot} was described to be the most important factor other than reaction time for reactions in ball mills.^{3d} In general, higher ν_{rot} leads to higher yields, which has been confirmed for several organic reactions.^{3d,e,6b,9} The results for the model reaction of 1a and 2a are presented in Figure 1. Whereas full conversion was not observed within 60 min at 450 min⁻¹, increasing ν_{rot} led to a gradual decrease in the milling time to achieve quantitative yields ($t_{97\%}$), hereafter defined as the time when the yield is $\geq 97\%$), and full conversion could be already achieved at 550 min⁻¹ after 30 min with 20 mm milling balls. The



Figure 1. Influence of ν_{rot} on $t_{97\%}$. Conditions: PBM P6, 250 mL steel beaker, ZrO₂-balls, $\Phi_{MB} = 0.25$, $d_{MB} = 20$ mm, 100 mmol **1a**, and 100 mmol **2a**. Milling time $t_{97\%} =$ time to reach yield $\geq 97\%$. At 450 min⁻¹, full conversion was not observed after 60 min.

minimum reaction time was observed at 650 min⁻¹. For experiments with 20 mm milling balls, $t_{97\%}$ was decreased by a factor of 4 when ν_{rot} was increased from 450 to 650 min⁻¹.

Influence of Milling Ball Diameter (d_{MB}). Milling balls are available in a large number of different diameters ranging from 0.20 to 30 mm. The question is what size is best for organic reactions in ball mills. The size of the milling balls is directly correlated to the energy input, as larger milling balls refer to a larger mass of single balls, leading to higher kinetic and stress energy.¹⁰ If the number of milling balls is constant, using smaller milling balls leads to decreased impact energy, and lower yields are observed.^{3c,d} However, at a constant milling ball filling degree ($\Phi_{
m MB}$), a smaller $d_{
m MB}$ is equivalent to a larger number of milling balls $(n_{\rm MB})$. This leads to an increased chance for collision of the milling balls expressed by an increased number of stress events and, in the end, a higher yield.¹¹ The results in Figure 2a show that at a constant milling ball filling degree, smaller milling balls accelerate the reaction. Quantitative yields for 30 mm milling balls were achieved after 40 min; this milling time could be reduced to 25 and 20 min using 20 and 10 mm milling balls, respectively. The results confirm that smaller milling balls are favorable over larger milling balls and should be used for this type of reaction. In Figure 2b, the dependence of the stress frequency (SF) and stress energy (SE) from $d_{\rm MB}$ is shown. SF is defined as the number of stress events per second, and SE is the energy that is supplied at each stress event.¹² Larger milling balls lead to higher SE but concurrently decrease the SF. In this case, the increase in SE was less than the decrease in SF (e.g., the SF for 30 mm milling balls is \sim 70-times lower than that of 10 mm milling balls, whereas the SE is only 45-times higher). This suggests that the stress energy of a single collision plays a minor role, and that the process is mainly affected by the stress frequency.

Influence of the Milling Ball Filling Degree (Φ_{MB}). As mentioned earlier, aside from the application of smaller milling balls, the stress frequency can be increased by using a larger number of milling balls. The milling ball filling degree represents the volume of the milling balls relative to the beaker volume. This important parameter influences not only the stress frequency but also the trajectories of the milling balls to affect the yield and the amount of heat dissipated by friction. $^{3a,c,1\acute{0},13}$ Fang et al. investigated the influence of Φ_{MB} on temperature in a lysis mill and observed that the temperature was maximum when 60% of the tube was filled with milling balls.¹⁴ Visualized in Figure 3a, the results showed that $\Phi_{\rm MB}$ is an important parameter in Knoevenagel condensation in PBMs. Independent of the $d_{\rm MB}$, a minimum for the milling time of approximately $0.25 \leq \Phi_{\rm MB} \leq 0.3$ was observed in which a broader minimum could be identified for the 10 mm balls. $\Phi_{\rm MB}$ that was either higher or lower than this range led to decreased yields, and the milling time had to be increased to reach similar conversion levels. If Φ_{MB} was less than optimal, the energy provided was reduced due to a lower number of milling balls. This led to a reduced stress frequency, and as the amount of substrate was constant, less energy was transferred to the substrate (Figure 3b). On the other hand, ball movement is hindered at high Φ_{MB} values, meaning that the milling balls have less acceleration and therefore the energy input is reduced.¹⁵ The manufacturer advises that in 250 mL milling beakers the recommended number of milling balls are 50×10 mm, 15×20 mm, and 6×30 mm balls, corresponding to $\Phi_{\rm MB}$ of 0.1, 0.25, and 0.34, respectively.¹⁶ For the 20 and 30



Figure 2. Influence of $d_{\rm MB}$ on the yield of the model reaction (a) and the stress conditions (b). Conditions: PBM P6, 250 mL steel beaker, $\rm ZrO_2$ -balls, $\nu_{\rm rot} = 650 \, \rm min^{-1}$, $\Phi_{\rm MB} = 0.42$ for $d_{\rm MB} = 10$ and 20 mm, $\Phi_{\rm MB} = 0.45$ for $d_{\rm MB} = 30$ mm, 100 mmol 1a, and 100 mmol 2a.



Figure 3. Influence of Φ_{MB} on $t_{97\%}$ (a) and the stress conditions (b). Conditions: PBM P6, 250 mL steel beaker, ZrO₂-balls, $\nu_{rot} = 650 \text{ min}^{-1}$, 100 mmol 1a, and 100 mmol 2a. $d_{MB} = 10 \text{ mm}$ in (b).

mm milling balls, these values are in accordance with the observed minimums. For the 10 mm milling balls, the manufacturers advice does not match with the optimal value found here for the model reaction and would result in reduced yields.

Influence of Beaker Size. Although a large number of organic reactions have been performed in PBMs, the influence of the beaker volume has not been investigated.^{2,17} However, the geometry of the milling beakers influences the energy input as shown by Mio and co-workers in milling experiments of gibbsite powder.¹⁸ To investigate the influence of the beaker size and geometry on the Knoevenagel condensation, we performed the model reaction in five different milling beakers in which the volume ($V_{\rm MV}$), inner diameter ($d_{\rm MV}$), and height ($h_{\rm MV}$) of the beaker were varied. As can be seen in Table 2, with increasing beaker volume, $t_{97\%}$ decreases significantly with a

Table 2. Influence of Beaker Size on Time to Reach Quantitative Conversion $(t_{97\%})^a$

$V_{\rm MV}$ [mL]	d _{MV} [mm]	h _{MV} [mm]	<i>t</i> _{97%} [min]	n_{1a} and n_{2a} [mmol]	${h_{ m MV}}/{d_{ m MV}}$	SE [10 ⁻⁴ J]	SF [s ⁻¹]
80	65	24	>60	32	0.37	1.00	73252
250	75	69	30	100	0.92	1.69	227012
330	75	80	30	132	1.07	1.75	312022
330	100	45	25	132	0.45	2.29	279640
500	100	69	18	200	0.69	2.26	452894

^aConditions: PBM P6, steel beaker, ZrO₂-balls, $\Phi_{\rm MB}$ = 0.30, $\Phi_{\rm GS}$ = 0.30, $d_{\rm MB}$ = 10 mm, and $\nu_{\rm rot}$ = 550 min⁻¹.

constant $\Phi_{\rm MB}$ and grinding stock filling degree $\Phi_{\rm GS}$, which is defined as the ratio of the bulk volume of the substrates and $V_{\rm MV}$.⁵ While no quantitative yields could be achieved in an 80 mL beaker after 1 h, full conversion was achieved after 30 and 18 min in 250 and 500 mL beakers, respectively. Thus, $V_{\rm MV}$ is not the only parameter of importance, $d_{\rm MV}$ and $h_{\rm MV}$ also influence yield. By keeping $d_{\rm MV}$ constant and changing $h_{\rm MV}$, we found that taller beakers led to slightly better results. Varying $d_{\rm MV}$ at a constant $h_{\rm MV}$ showed that $t_{97\%}$ decreases from 30 to 18 min when the diameter was increased from 75 to 100 mm.

An explanation of the results is that changes in diameter and/ or height lead to changes in the number of milling balls and therefore to changes in the SF (eqs 2 and 3).^{11a} In addition, the energy input can be influenced by the curvature of the base of the beaker, which differs among the equipment examined.⁸

$$n_{\rm MB} \propto d_{\rm MV}^2$$
 and $n_{\rm MB} \propto h_{\rm MV}$ (2)

$$SF \propto n_{\rm MB}$$
 (3)

The kinetic energy of the milling balls is dependent on $d_{\rm MV}$. $E_{\rm kin}$ is given by the mass of a single milling ball $(m_{\rm MB})$, the revolution radius (R), and the square of the angular velocity of the revolution (Ω) .^{10,18}

$$E_{\rm kin} = \frac{1}{2}m_{\rm MB}v^2 = m_{\rm MB}R\Omega^2 d_{\rm MB} \tag{4}$$

$$E_{\rm kin} \propto SE$$
 (5)

Therefore, if $d_{\rm MV}$ changes, $E_{\rm kin}$ and ultimately the stress energy (SE) will be influenced. Furthermore, discrete element method (DEM) simulations show that milling beakers with the

same volume but larger diameters have bulk changes in their packing and higher velocities (see Supporting Information). Figure 4 illustrates the dependence of the specific power on the



Figure 4. Dependence of specific power on the geometry of the milling beaker. Conditions: PBM P6, steel beakers of different geometries (see Table 2), ZrO_2 -balls, $\Phi_{MB} = 0.30$, $d_{MB} = 10$ mm, and $\nu_{rot} = 550 \text{ min}^{-1}$.

 $h_{\rm MV}/d_{\rm MV}$ ratio. The highest specific power is seen at 0.7 and leads to the shortest reaction times. At a constant diameter and different heights, the higher power is calculated for larger values of $h_{\rm MV}$ due to a higher SF. The SE is roughly the same when $d_{\rm MV}$ is equal.

Scope of the Reaction. The investigated model reaction was successfully performed in PBMs with quantitative yields. Thus, further cleanup is not necessary as the reaction proceeds without side products. Figure 5 illustrates this finding by comparing the ¹H NMR spectra of a commercially available sample and the product obtained by ball milling in a PBM.



Figure 5. Comparison of ¹H NMR spectra of a commercial and ball mill product 3a. (A) Sample obtained by ball milling and (B) the commercial sample.

To enlarge the scope of reaction, we performed the Knoevenagel condensation with several solid aldehydes and barbituric acid (2a) with its 1,3-dimethyl derivative (2b) as the CH acidic compound (Scheme 1). As one can see in Table 3, quantitative yields were achieved in almost all cases. Only the reactions of 2a with 1d or 1e had lower yields at 82 and 85%, respectively.

Reactions in PBM P5 and P7. To investigate the influence of the type of mill, the model reaction was performed in PBM P5 and P7. The following results show the influence of $\nu_{rov} d_{MB}$, and Φ_{MB} for reactions in PBM P7. In general, similar behaviour as in PBM P6 was observed.⁵ Figure 6 shows that the milling time can be reduced by a factor 12 if ν_{rot} is increased from 600 to 1000 min⁻¹. Furthermore, as in PBM P6, smaller milling

Table 3. Substrate Screening of the Model Reaction^a

entry	substrate 1	substrate 2	product 3	yield [%]
1	1a	2a	3a	>97
2	1b	2a	3b	>97
3	1c	2a	3c	>97
4	1d	2a	3d	82
5	1e	2a	3e	85
6	1f	2a	3f	>97
7	1a	2b	3g	>97
8	1b	2b	3h	>97
9	1c	2b	3i	>97
10	1d	2b	3j	>97
11	1e	2b	3k	>97
12	1f	2b	31	>97
				-

^{*a*}Conditions: PBM P6, 250 mL steel beaker, ZrO2-balls, $\Phi_{\rm MB} = 0.30$, $d_{\rm MB} = 10$ mm, $\nu_{\rm rot} = 650$ min⁻¹, t = 20 min, 100 mmol **1**, and 100 mmol **2**.

balls tended to be advantageous relative to larger ones. Visualized in Figure 6a, the milling time to achieve quantitative yields at a constant $\nu_{\rm rot}$ was always lower for 2 than 5 mm balls, except at 1000 min⁻¹ where the reaction was completed within 10 min in both cases due to the high energy input. Regarding $\Phi_{\rm MB}$ (Figure 6b), the results also indicate an optimum similar to that in PBM P6, but the optimal value was slightly shifted to a lower $\Phi_{\rm MB}$ of ~0.2.

The maximal $\nu_{\rm rot}$ in PBM P5 is limited to 400 min⁻¹, which is considerably below the $\nu_{\rm rot}$ in PBM P6 in which no quantitative yields were obtained within 60 min at 450 min⁻¹. Observing the influence of the rotation frequency in PBM P5, we found that at $\nu_{\rm rot} = 300 \text{ min}^{-1}$ after a milling time of 60 min, a yield of 15% could be achieved (Figure 7). At 350 min⁻¹, quantitative yield was observed after 60 min, and at 400 min⁻¹, the reaction was completed after 30 min of milling time.

Comparison of Different Types of Ball Mills. Upon the three investigated PBMs being compared, it is evident that the reaction is transferable from one type of PBM to another. Similar results for $t_{97\%}$ were achieved, especially when $\nu_{\rm rot}$ was adjusted to the milling system. Figure 8 compares the results at different values of $\nu_{\rm rot}$. In PBM P5, quantitative yields were achieved after 30 min at 400 min⁻¹. This corresponds to results at 550 min⁻¹ in P6 and 800 min⁻¹ in PBM P7. Scholl et al. reported similar results for the synthesis of Ti₅Si₃ in PBMs P5 and P6.6e The reason that comparable results can be obtained at lower $\nu_{\rm rot}$ in P5 is the higher diameter of the main disc leading to increased energy input. Furthermore, the speed ratio (r) is different and may influence the energy input as well. Whereas Mio et al. reported that the specific impact energy and ball motion depend on r, Rosenkranz and co-workers did not observe a change in ball motion.^{7,13} The reaction in PBM P7 requires a comparably higher $\nu_{\rm rot}$ due to the lower kinetic energy based on the smaller inner diameter of the milling beakers. Similar results and trends were observed with respect to the influence of the investigated parameters $\nu_{\rm rot}$, $d_{\rm MB}$, and $\Phi_{\rm MB}$.

Reactions in a Mixer Ball Mill (MBM). In MBMs, ball movement is caused by horizontal or vertical oscillation of the milling beakers, and therefore the trajectories of the milling balls are different from those in PBMs (Figure 9). The energy is mainly provided by impact and friction when the milling balls collide into one another and with the cap of the milling beaker.



Figure 6. Influence of $\nu_{rov} d_{MB}$ (a), and Φ_{MB} (b) on $t_{97\%}$ in PBM P7. Conditions: PBM P7, 45 mL steel beaker, and ZrO_2 -balls with (a) $\Phi_{MB} = 0.26$ and (b) $\nu_{rot} = 800 \text{ min}^{-1}$, $d_{MB} = 10 \text{ mm}$, 20 mmol **1a**, and 20 mmol **2a**.



Figure 7. Influence of $\nu_{\rm rot}$ on the model reaction in PBM P5. Conditions: PBM P5, 250 mL steel beakers, ZrO₂-balls, $\Phi_{\rm MB} = 0.29$, $d_{\rm MB} = 10$ mm, 100 mmol **1a**, and 100 mmol **2a**.



Figure 8. Dependence of $t_{97\%}$ on $\nu_{\rm rot}$ in three different PBMs. Conditions for PBM P5 and P6: 250 mL steel beakers, ZrO_2 -balls, $\Phi_{\rm MB} = 0.29$, $d_{\rm MB} = 10$ mm, 100 mmol **1a**, and 100 mmol **2a**. For PBM P7: 45 mL steel beakers, ZrO_2 -balls, $\Phi_{\rm MB} = 0.21$, $d_{\rm MB} = 10$ mm, 20 mmol **1a**, and 20 mmol **2a**.

For reactions in MBMs, the same parameters as in PBMs are important. The influence of the oscillation frequency (ν_{osc}) was discussed for several reactions in the literature, indicating that higher frequencies are beneficial as shown for PBMs.^{2,3b,f} However, the influence of other parameters, such as $d_{\rm MB}$ and $\Phi_{\rm MB}$, have rarely been analyzed for reactions in MBMs.^{3b,19} To investigate the influence of reaction parameters on the model reaction, we performed a Knoevenagel condensation of **1a** with **2a** in an MBM MM400 at 30 Hz with horizontal oscillation.

Figure 10 shows the influences of $d_{\rm MB}$ and milling time. Higher yields were observed at extended milling times. Regarding $d_{\rm MB}$ at a constant $\Phi_{\rm MB}$, 5 mm milling balls led to high yields within 30 min, and quantitative yields were observed after 35 min of milling. In contrast, 10 mm milling balls yielded the condensation product in quantitative amounts after 40 min,



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Figure 9. Schematic movement and construction of an MBM milling beaker.



Figure 10. Influence of t and $d_{\rm MB}$ on yield in an MBM. Conditions: MBM MM400, 35 mL steel beaker, ZrO₂-balls, $\Phi_{\rm MB}$ = 0.30, $\nu_{\rm osc}$ = 30 Hz, 14 mmol 1a, and 14 mmol 2a.

and the yield increased slower with milling time. Analagous to the reactions observed in PBMs, smaller milling balls accelerated the reaction in the MBMs due to an increased number of stress events.

In PBMs, the milling ball filling degree was revealed to be a crucial parameter that strongly influenced the outcome of the reaction. Therefore, reactions with different $\Phi_{\rm MB}$ were performed in MBMs. As seen in Figure 11, at $\Phi_{\rm MB} = 0.06$, only low yields were achieved, and no full conversion was observed after 60 min. Upon $\Phi_{\rm MB}$ being increased to 0.18, the reaction was highly accelerated and quantitative yields could be achieved within 40 min. At $\Phi_{\rm MB} = 0.3$, $t_{97\%}$ could be further reduced, indicating that in the area of $\Phi_{\rm MB} = 0.06-0.3$ higher values for $\Phi_{\rm MB}$ are preferable. Handling of $\Phi_{\rm MB} > 0.3$ was difficult due to the geometry of the milling beakers (Figure 9).



Figure 11. Influence of $\Phi_{\rm MB}$ in an MBM. Conditions: MBM MM400, 35 mL steel beaker, $\rm ZrO_2$ -balls, $d_{\rm MB}$ = 10 mm, $\nu_{\rm osc}$ = 30 Hz, 14 mmol 1a, and 14 mmol 2a.

Part of the volume is located in the cap of the beaker. The results of the reaction with $\Phi_{MB} = 0.45$ showed that because of the reduced space for acceleration only low yields could be achieved.

In MBMs and PBMs, $t_{97\%}$ is in the same range for both types of ball mills (see Figure 1). A transfer from PBM to MBM is possible, and similar $d_{\rm MB}$ and $\Phi_{\rm MB}$ effects are observed. In contrast to the horizontal MBM shown above, MBMs can also be operated with vertical oscillating milling beakers. In a vertical MBM Pulverisette 23 (15 mL steel beaker, 5 steel balls, $d_{\rm MB}$ = 10 mm), the condensation reaction of **1a** and **2a** was examined at three operating frequencies. With $\nu_{\rm osc}$ = 50 s⁻¹, a yield of 80% was observed after a milling time of 60 min. For reactions executed at 40 and 30 s⁻¹, low yields of 10 and 8%, respectively, were detected.

Reaction in a Stirred Media Mill (SMM). Stirred media mills are used for a broad scope of applications, especially for fine and ultrafine grinding of materials. This type of mill consists of a stationary grinding chamber and a rotating agitator that hits and accelerates the milling balls.²⁰ Two reactions were performed with different setups. In the first experiment, the stirrer speed was set to 500 min⁻¹, but after 1 h of milling, only low yields were observed. Therefore, in the second experiment, the stirrer speed was increased in two steps to 1000 min^{-1} (5 min at 500 min⁻¹, 5 min at 750 min⁻¹, and then continuous milling at 1000 min^{-1}). In both cases, handling of the mixture was difficult as the substrates partially stuck at the wall of the grinding chamber over the course of the reaction, causing the mixing efficiency to be reduced. However, high yields were observed after 30 min (Figure 12). The successful transfer of the reaction from a PBM to a stirred media mill is an important



Figure 12. Reaction of **1a** and **2a** in an SMM. Conditions: 500 mL steel beaker, steel balls, $d_{\rm MB} = 2$ mm, $\Phi_{\rm MB} = 0.60$, 200 mmol **1a**, and 200 mmol **2a**. Squares: stirrer speed = 500 min⁻¹. Circles: stirrer speed = 5 min at 500 min⁻¹, 5 min at 750 min⁻¹, and then 1000 min⁻¹.

step for scaling up because SMMs can be equipped with grinding chambers with volumes of several liters.

Reaction in a Mortar Mill (MM). Manual grinding by mortar and pestle is a common way to deliver mechanical energy to substrates and has been used for miscellaneous organic reactions.²¹ However, this method has some disadvantages, including safety aspects due to the open reaction system and problems regarding scaling up the reaction. A significant disadvantage is that the energy input is strongly dependent on the strength and endurance of the experimenter such that reproducibility and long reaction times are problematic. The energy provided by mortar and pestle is generated by friction and, in contrast to ball mills, impact is not a factor.

Performing the Knoevenagel reaction with mortar and pestle showed only 11% conversion after 1 h of grinding. In additional to the low yield, hand grinding for such long times is not very practical. A way of avoiding some of the disadvantages of using mortar and pestle is the application of a mortar mill (MM).^{6a} This automated version of hand grinding with a mortar and pestle affords more reproducible results; the acting force can be adjusted and is operator independent. As shown in Table 4, in

Table 4. Comparison of Hand and MM Grinding^a

	n_{1a} and n_{2a} [mmol]	grinding time [min]	yield [%]
manual grinding	10	60	11
MM	50	60	19
		120	33
MM	100	60	9
		120	13

^{*a*}Conditions: MM Pulverisette 2, mortar and pestle made of ZrO₂, 200 N tangential force, and 100 N downforce.

an MM Pulverisette 2, 19% of product could be gained after 60 min, which could be increased to 33% after 120 min. By doubling the initial amount of substrate, the yields decreased to 9 and 13% after 60 and 120 min, respectively. The advantage of an MM compared to manual grinding with mortar and pestle is evident. Higher yields could be achieved, and at the same yield, the reaction could be scaled up by a factor of 10. However, compared to reactions in PBMs and MBMs, no quantitative conversion could be obtained in the examined time range; reaction times had to be considerable longer to achieve comparable yields. Thus, the energy provided is apparently not enough to reach full conversion.

Grinding Reactions Supported by Thermal Heating and Microwave Irradiation. Grinding reactions supported by thermal heating (thermal-assisted grinding = TAG) were performed in a water bath at 45 and 75 °C using a rotary evaporator as the reactor. Mixing of the reactants was ensured by rotating a round-bottom flask containing 2 mm glass milling balls at 100 min^{-1,22} An additional reaction was performed in a Rotaprep microwave reactor (microwave-assisted grinding = MAG) with a rotating vessel and 220 g glass balls. In this case, 5 mL of water was added to the reaction mixture because the reaction mixture could not be heated by microwave irradiation without it. Samples were taken after 5 and 10 min of irradiation at 800 W at a constant temperature of 75 °C.

The results are summarized in Table 5. The reaction in a water bath at 45 $^{\circ}$ C only yielded 5% after 1 h. Increasing the temperature to 75 $^{\circ}$ C led to a strong increase in the yield to 75%. Reactions initiated by microwave heating led to an inhomogeneous product, probably due to inhomogeneous

Table 5. Grinding Reactions Supported by Thermal Heating (TAG) and Microwave Irradiation (MAG)

	temperature [°C]	time [min]	yield [%]
TAG ^a	45	15	1
		30	4
		60	5
TAG^{a}	75	15	37
		30	38
		60	75
MAG^{b}	75	5	82
		10	90

^{*a*}Conditions: rotary evaporator with water bath, 250 mL roundbottom flask, 75 g glass balls, $\nu_{\rm rot} = 100 \text{ min}^{-1}$, $d_{\rm MB} = 2 \text{ mm}$, 40 mmol **1a**, and 40 mmol **2a** ($\Phi_{\rm MB} = 0.098$, $\Phi_{\rm GS} = 0.12$). ^{*b*}Conditions: Rotaprep microwave reactor, 2000 mL vessel, 220 g glass balls, $d_{\rm MB} = 2$ mm, 800 W, $\nu_{\rm rot} = 25 \text{ min}^{-1}$, 100 mmol **1a**, and 100 mmol **2a** ($\Phi_{\rm MB} =$ 0.035, $\Phi_{\rm GS} = 0.04$).

water distribution (see Supporting Information). Nevertheless, yields of 90% could be achieved after 10 min.

Influence of Reaction Temperature. The results of the reactions in the water bath strongly indicate that the reaction is temperature dependent. During ball milling, the reaction temperature raises due to friction and heat dissipation.⁸ In PBMs, direct control of the temperature is impossible. Only by pausing the milling cycle for a considerable amount of time to allow the milling vessels to cool down is an imprecise control of heat flux possible. Therefore, the influence of the temperature during ball milling was investigated. The reactions were performed in an MBM with custom-made double-walled stainless steel vessels (8 mL) that allow for temperature adjustment by circulating a heated fluid through the system.²³ Reactions were performed with optimal conditions, as found in MBM with standard stainless steel beakers (Table 6). The

Table 6. Influence of the Reaction Temperature on Knoevenagel Condensation in an MBM^a

thermostat temperature [°C]	internal beaker temperature [°C]	yield after 5 min [%]	yield after 20 min [%]
40	38.7	4^b	9
50	48.6	12^b	16
60	57.5	11	30
70	67.0	37	82
75	73.1	76	97
80	78.0	88	97

^{*a*}Conditions: MBM MM301, 8 mL double-walled steel beaker, ZrO₂-balls, $\Phi_{\rm MB}$ = 0.3, $d_{\rm MB}$ = 5 mm, $\nu_{\rm osc}$ = 30 Hz, 3.2 mmol 1a, and 3.2 mmol 2a. ^{*b*}After 10 min.

results can be found in Table 6. At 40 $^{\circ}$ C, only 4 and 9% yields could be achieved after 10 and 20 min, respectively. If the temperature of the milling beakers was increased, the yields were improved, and at 80 $^{\circ}$ C (below the melting points of the single substrates), quantitative yields could be achieved after 20 min. Even at 70 $^{\circ}$ C, a yield of 82% was observed. In all cases, the yields are higher than for reactions performed in a water bath with intense mixing by glass balls at comparable temperatures (Table 5). This result indicates that the reaction is not solely accelerated by temperature increase due to friction, and that ball milling has a real effect. This can be attributed to intense mixing of the reactants, the constant generation of

"fresh" surfaces by particle size reduction, and direct energy input by impact and friction.^{1d,24}

Comparison of Methods. Table 7 offers a comparison of the investigated methods, in which it is seen that reactions in ball mills lead to the highest yields in short reaction times. The reactions with a mortar and pestle and MM do not yield quantitative product even after reaction times of 1 and 2 h. Better results could be achieved by TAG and MAG. The reaction time for the TAG-process was 60 min, whereas the microwave-assisted reaction was as fast as reactions in PBMs P6 and P7 at optimized conditions. Aside from the reaction vield. the energy intensity is also of interest.^{2,25} The lowest E value was calculated for the MAG-process. However, one has to consider that in this case the addition of water was necessary. Comparing the reactions in ball mills, reactions in PBMs were slightly less energy intensive than reactions in an MBM. The highest energy intensities were observed for the reaction in an MM and by TAG. These reactions required 16-fold more energy than that of the reaction in PBM P6.

Regarding the scale of the reaction, the lowest amount of substrate could be treated using a mortar and pestle as well as in MBMs. To scale up the reaction, PBMs and SMMs are the best choices. Figure 13 illustrates the scale of the reactions in the investigated PBMs. Scaling up was achieved by utilizing a larger volume and number of milling beakers (e.g., PBM P5). Thus, scaling up from PBM P7 with one 45 mL beaker (Figure 13, P7 (45; 1)) to PBM P5 with four 250 mL beakers (250; 4) was successful by a scaling factor of 20. For the reactions in PBM P6 with 250 and 500 mL beakers, the initial amounts of 100 and 200 mmol could be doubled without a negative effect on the yield or $t_{97\%}$.⁵ Similarly, the grinding stock filling degree $\Phi_{\rm GS}$ could be increased from 0.3 to 0.6. Thus, further scaling in P5 with a scaling factor of 80 should be possible by utilizing 500 mL beakers.

CONCLUSIONS

The Knoevenagel condensation proceeded quantitatively in different kinds of PBMs as well as in an MBM at a comparable time upon adjusting ν . The reaction could be scaled up in PBMs by a factor of 20. Inducing mechanical energy by grinding with a mortar and pestle or in an MM resulted in quite lower yields. Under microwave irradiation, high yields could be achieved, but the addition of water was essential. Also, good yields were achieved under solvent-free conditions with TAG using a water bath, but the reaction time was much longer than that of ball milling. In comparison to the other investigated methods, the results confirm that ball milling is a powerful technique for organic reactions that is fast, solvent-free, and requires low energy intensity.

The influence of crucial parameters was investigated for different types of ball mills. It was shown that the rotation frequency ($\nu_{\rm rot}$), the milling ball filling degree ($\Phi_{\rm MB}$), the milling ball diameter ($d_{\rm MB}$), and the beaker size all have a strong influence on the yield. On the basis of these results, some general strategies and conclusions for performing organic reactions in planetary ball mills can be drawn. The application of smaller milling balls is preferable over larger ones, and a milling ball filling degree of 0.3 is optimal. Under these conditions, the rotation frequency and the grinding stock filling degree can be optimized, allowing for subsequent scaling up by increasing the number of beakers.

Table 7. Comparison of Investigated Methods

method	$n_{1a} \text{ and } n_{2a} $ [mmol]	time [min]	conditions ^a	yield [%]	energy intensity [kWh mol ⁻¹]
PBM P7	2×20	10	$\nu_{\rm rot}$ = 1000 min ⁻¹ , $d_{\rm MB}$ = 5 mm, $V_{\rm MV}$ = 45 mL, $\Phi_{\rm MB}$ = 0.26, $\Phi_{\rm GS}$ = 0.3	>97	1.89
PBM P6	100	12	$\nu_{\rm rot}$ = 650 min ⁻¹ , $d_{\rm MB}$ = 10 mm, $V_{\rm MV}$ = 250 mL, $\Phi_{\rm MB}$ = 0.26, $\Phi_{\rm GS}$ = 0.3	>97	1.03
PBM P5	4×100	30	$\nu_{\rm rot}$ = 400 min ⁻¹ , $d_{\rm MB}$ = 10 mm, $V_{\rm MV}$ = 250 mL, $\Phi_{\rm MB}$ = 0.29, $\Phi_{\rm GS}$ = 0.3	>97	nd
MBM MM400	2×14	35	$\nu_{\rm osc}$ = 30 s ⁻¹ , $d_{\rm MB}$ = 10 mm, $V_{\rm MV}$ = 35 mL, $\Phi_{\rm MB}$ = 0.3, $\Phi_{\rm GS}$ = 0.3	>97	2.33
MBM P23	6	60	$\nu_{\rm osc}$ = 50 s ⁻¹ , $d_{\rm MB}$ = 10 mm, $V_{\rm MV}$ = 15 mL, $\Phi_{\rm MB}$ = 0.26, $\Phi_{\rm GS}$ = 0.3	80	3.96
SMM	200	40	$\nu_{\rm rot}$ = 1000 min ⁻¹ , $d_{\rm MB}$ = 2 mm, $V_{\rm MV}$ = 500 mL, $\Phi_{\rm MB}$ = 0.6, $\Phi_{\rm GS}$ = 0.3	>97	nd
mortar and pestle	10	60		11	
MM	50	120	200 N siteforce, 100 N downforce	33	16.06
MAG	100	10	75 °C, 800 W, 5 mL H ₂ O, V = 2000 mL, $\nu_{\rm rot}$ = 25 min ⁻¹ , $\Phi_{\rm MB}$ = 0.035, $\Phi_{\rm GS}$ = 0.04	90	0.14
TAG	40	60	75 °C, $\nu_{\rm rot}$ = 100 min ⁻¹ , V = 250 mL, $\Phi_{\rm MB}$ = 0.098, $\Phi_{\rm GS}$ = 0.12	75	16.77

 ${}^{a}\nu_{\rm rot}/\nu_{\rm osc}$ = rotation/oscillation frequency, $d_{\rm MB}$ = milling ball diameter, $V_{\rm MV}$ = milling beaker volume, $\Phi_{\rm MB}$ = milling ball filling degree, and $\Phi_{\rm GS}$ = grinding stock filling degree.



Figure 13. Realization of scaling up reactions in PBMs. Values in italics are theoretical.

EXPERIMENTAL SECTION

All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used as received. The reactions were accomplished in a Fritsch Pulverisette P6 classic line, a Fritsch Pulverisette P7 premium line, and a Fritsch Pulverisette P5 planetary ball mill (Fritsch GmbH, Idar-Oberstein, Germany). If not otherwise stated, milling beakers made of stainless or tempered steel were used with a volume of 250 mL for reactions in PBM P6 and PBM P5 and of 45 mL for PBM P7. Reactions in MBMs were accomplished in a MM400 mixer ball mill (Retsch, GmbH) with 35 mL steel beakers and in Pulverisette 23 (Fritsch GmbH) with 15 mL steel beakers. The milling balls of various diameters ($d_{\rm MB}$) and amounts ($n_{\rm MB}$) were made of magnesiastabilized zirconia. Both, $d_{\rm MB}$ and $n_{\rm MB}$ determine the milling ball filling degree ($\Phi_{\rm MB}$).

The reactions in MM were performed in a mortar mill Pulverisette 2 (Fritsch GmbH). Experiments with mortar and pestle were carried out using devices made of porcelain. A PE 075 agitator bead mill (Netzsch GmbH) was used for the reactions in the stirred media mill. Reactions with classical heating were performed with a rotary evaporator Laborota 4001 (Heidolph Instruments GmbH and Co. KG). Experiments under microwave irradiation were performed with a Rotaprep microwave system (MLS GmbH).

For determining the conversion, we extracted samples of the crude reaction product (100 mg) with ethyl acetate (5 mL) and filtered them over a thin layer of silica gel. The organic extract

was analyzed by a gas chromatography flame ionization detector (GC-FID) using a 7890A-GC (Agilent Technologies) with the following measurement conditions: HP5 column (30 m length, 0.32 mm diameter, 0.25 mm film thickness); H₂ (12 psi); temperature program of 80 °C (hold for 1 min), 15 K min⁻¹ up to 200 °C, 30 K min⁻¹ up to 280 °C (hold for 1 min); injector temperature of 280 °C; detector temperature of 300 °C. NMR spectra were recorded with a Bruker Avance 250 or 400 MHz system at room temperature in DMSO- d_6 .

For measuring the line power consumption, an Energy Check 3000 (Voltcraft) was used. The energy intensity was calculated according to eq 6^2

$$E = \frac{E_{\text{line power}}}{\text{yield } \times \text{ batch size}}$$
(6)

where $E_{\text{line power}}$ is measured in kWh and the batch size is in mols.

The simulations of the stress conditions were carried out with EDEM 2.5 (DEM Solutions) based on the discrete element method. The milling balls and the rotating geometry are modelled as discrete elements, and in each time step, the resulting velocities and accelerations as well as contact forces are computed. The powder is recognized due to an adjustment of friction and damping coefficients.¹³

Energy is transferred to the substrate by stress during collision events between either two colliding milling balls or a ball and the beaker. The maximum amount of energy that is transferred is determined by the kinetic energy and thus by the relative velocity in the normal direction and the mass of the colliding elements.^{11b,13}

$$SE_{ball-ball-collision} = 0.25 m_{MB} v_{rel,normal}^2$$
 (7)

$$SE_{ball-beaker-collision} = 0.50 m_{MB} v_{rel,normal}^2$$
(8)

By the stress energy distributions, mean \overline{SE} values were formed for an export interval of 0.3 s at steady state.

$$\overline{SE} = \frac{\sum_{j=1}^{n} SE_j}{\text{number of collisions}}$$
(9)

The absolute values of stress frequency (SF) as collisions per second were directly exported from the simulation. By the mean stress energy \overline{SE} and the stress frequency, the upper limit of transferred power is defined as

$$Power = \overline{SE} \times SF \tag{10}$$

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Experimental Procedure for Reactions in PBMs and an MBM. The milling beakers were equipped with the respective number of milling balls. After, equimolar amounts of **1a** and **2a** were added in the given order. Milling was accomplished at the respective frequency, ν_{rot} or ν_{osc} and listed milling time.

Experimental Procedure for Reactions in an SMM. The grinding chamber (500 mL) was equipped with 2 mm steel balls (1860 g). After, equimolar amounts of **1a** and **2a** were added in the given order. Milling was accomplished at the listed stirrer speed and milling time.

Experimental Procedure for Reactions in MM. Equimolar amounts of **1a** and **2a** were added in the mortar bowl made of zirconium oxide in the given order. The grinding pressure in the pestle axis (downforce) was adjusted to 100 N, and the grinding pressure against the wall of the mortar (siteforce) was adjusted to 200 N. The frequency of the mortar bowl was fixed to 50 s⁻¹. Milling was accomplished at the listed milling times.

Experimental Procedure for Reactions with Mortar and Pestle by Hand Grinding. Equimolar amounts of 1a and 2a were added in the mortar bowl in the given order. Grinding was accomplished at the listed milling time.

Thermal-Assisted Grinding (TAG). A 250 mL roundbottom glass flask was charged with 2 mm glass balls (75 g). After, equimolar amounts of **1a** and **2a** (40 mmol) were added in the given order. The water bath of a rotary evaporator was preheated to 75 °C, and the filled glass flask was fastened to the rotary evaporator. The rotation frequency was set to 100 min⁻¹, and the reaction was accomplished at the listed time.

Microwave-Assisted Grinding (MAG). A 2000 mL glass flask was charged with 2 mm glass balls (220 g). After, equimolar amounts of 1a and 2a (100 mmol) as well as 5 mL of water were added in the given order. The reaction was accomplished under reduced pressure (750 mbar) and with a rotation frequency of 25 min⁻¹. The reaction mixture was heated to 75 °C with a maximum power input of 800 W.

Spectral Data of Products Listed in Table 3 (¹H NMR, DMSO- d_6 , δ (ppm)). 5-(4-Hydroxy-3-methoxybenzylidene)barbituric Acid (3a).²⁶ 11.24 (s, 1 H), 11.11 (s, 1 H), 10.54 (s, 1 H), 8.46 (s, 1 H), 8.21 (s, 1 H), 7.78 (d, J = 8.1, 1 H), 6.89 (d, J = 8.3, 1 H), 3.81 (s, 3 H).

5-(4-Hydroxybenzylidene)barbituric Acid (**3b**).²⁷ 11.23 (s, 1 H), 11.10 (s, 1 H), 10.80 (s, 1 H), 8.31 (d, 2 H), 8.20 (s, 1 H), 6.86 (d, 2 H).

5-(3-Hydroxybenzylidene)barbituric Acid (**3c**).²⁷ 11.35 (s, 1 H), 11.19 (s, 1 H), 9.63 (s, 1 H), 8.16 (s, 1 H), 7.61–6.9 (m, 4 H).

5-(4-Nitrobenzylidene)barbituric Acid (**3d**).²⁸ 11.48 (s, 1 H), 11.30 (s, 1 H), 8.31 (s, 1 H), 8.23 (d, 2 H), 8.02 (d, *J* = 7.5, 2 H).

5-(3-Nitrobenzylidene)barbituric Acid (**3e**).²⁸ 11.46 (s, 1 H), 11.31 (s, 1 H), 8.90 (s, 1 H), 8.33 (s, 1 H), 8.29-8.21 (m, 2 H), 7.72 (t, J = 12.8, 1 H).

5-(4-Chlorobenzylidene)barbituric Acid (**3f**).²⁹ 11.38 (s, 1H), 11.23 (s, 1H), 8.23 (s, 1H), 8.05 (d, J = 8, 2 H), 7.51 (d, J = 8, 2H).

5-(4-Hydroxy-3-methoxybenzylidene)-1,3-dimethylbarbituric Acid (**3g**). FTATR-IR: 3157, 1664, 1636, 1603, 1587, 1538, 1497; mp 228–231 °C.³⁰

5-(4-Hydroxybenzylidene)-1,3-dimethylbarbituric Acid (**3h**).³¹ 10.82 (s, 1 H), 8.28 (m, 3 H), 6.87 (2 H), 3.91 (6 H).

5-(3-Hydroxybenzylidene)-1,3-dimethylbarbituric Acid (**3i**).³² 8.23 (s, 1 H), 7.56 (s, 1 H), 7.39 (d, J = 7.3, 1 H), 7.26 (t, J = 7.6, 1 H), 6.94 (d, J = 7.5, 1 H), 3.21 (s, 3 H), 3.17 (s, 3 H).

5-(4-Nitrobenzylidene)-1,3-dimethylbarbituric Acid (**3***j*).³³ 8.4 (s, 1 H), 8.25 (d, J = 8.6, 2 H), 7.97 (d, J = 8.6, 2 H), 3.23 (s, 3 H), 3.14 (s, 3 H).

5-(3-Nitrobenzylidene)-1,3-dimethylbarbituric Acid (**3k**).³⁴ 8.82 (s, 1 H), 8.42 (s, 1 H), 8.32 (d, J = 7.5, 1 H), 8.2 (d, J = 7.7, 1 H), 7,73 (t, J = 8, 1 H), 3.24 (s, 3H), 3.16 (s, 3H).

5-(4-Chlorobenzylidene)-1,3-dimethylbarbituric Acid (31).³⁵ 8.31 (s, 1 H), 8.04 (d, J = 8.4, 2 H), 7.53 (d, J = 8.45, 2 H), 3.22 (s, 3 H), 3.16 (s, 3 H).

ASSOCIATED CONTENT

S Supporting Information

Pictures of DEM simulations of the milling ball bulk relative to the diameter of the milling beaker, TAG, MAG, inhomogeneous product composition after MAG, and of the custom-made double-walled steel beaker. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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