

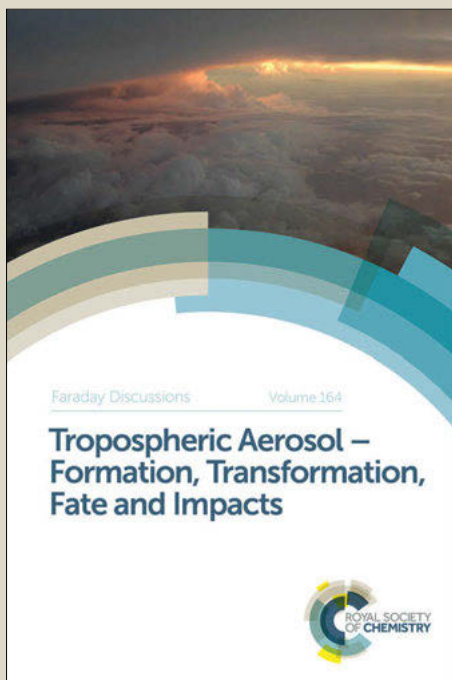
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ARTICLE TYPE

Scale-up of organic reactions in ball mills: Process intensification with regard to energy efficiency and economy of scale

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The scale-up of the Knoevenagel-condensation between Vanillin and Barbituric acid carried out in planetary ball mills is investigated from an engineering perspective. Generally, the reaction proceeded in the solid state without intermediate melting and afforded selectively only one product. The reaction has been used as a model to analyze the influence and relationship of different parameters related to operation in planetary ball mills. From the viewpoint of technological parameters the milling ball diameter, d_{MB} , the filling degree with respect to the milling balls' packing, $\Phi_{MB,packing}$, and the filling degree of the substrates with respect to the void volume of the milling balls' packing, Φ_{GS} , have been investigated at different reaction scales. It was found that milling balls with small d_{MB} lead to higher yields within shorter reaction time, $t_{reaction}$, or lower rotation frequency, rpm . Thus, the lower limit is set considering the technology which is available for the separation of the milling balls from the product after the reaction. Regarding $\Phi_{MB,packing}$ results indicate that the optimal value is roughly 50% of the total milling beakers' volume, $V_{B,total}$, independently from reaction scale or reaction conditions. Thus, 30% of $V_{B,total}$ are taken by the milling balls. Increase of the initial batch sizes changes Φ_{GS} significantly. However, within the investigated parameter range no negative influence on the yield was observed. Up to 50% of $V_{B,total}$ can be taken over by the substrates in addition to 30% for the total milling ball volume. Scale-up factors of 15 and 11 were realized considering the amount of substrates and the reactor volume, respectively. Beside technological parameters, variables which influence the process itself, $t_{reaction}$ and rpm , were investigated also. Variation of those allowed to fine-tune the reaction conditions in order to maximize the yield and minimize the energy intensity.

Introduction

Mechano-chemical reactions in general and specifically those carried out in ball mills have attracted serious attention throughout many fields of inorganic, organometallic, and organic synthesis as well as materials science.¹⁻⁸ Mechano-chemical reactions are characterized by a specific stress load which initiates directly (or indirectly) the breaking and making of chemical bonds.⁹ If the mechanical stress should be subjected to solid materials in order to initiate chemical reactions by the release of frictional energy two principal methods exist: manual grinding using mortar and pestle and ball milling using laboratory equipment like planetary (PBM).¹ Manual grinding is the easiest and thus the most cost-effective way to initiate reactivity between solids on the mechanical pathway. However, it has been shown that those reaction protocols lack on the necessary robustness, reliability, and process controllability.¹⁰ This is due to the fact that the applied force is directly linked to the physiological prerequisites of the experimenter, which becomes critical if the reaction time is long. Thus, accomplishment of the reactions by different persons may lead to different results, except for reactions with a low activation barrier or a high thermodynamic

driving force. From chemical engineering point of view ball mills should be applied since those offer the possibility to control the reaction time, energy density, and other parameters.^{1, 11} Two different types of ball mills are applicable for organic synthesis at the laboratory scale: PBMs and vibration or mixer ball mills (MBMs). In case of PBMs the grinding media (in the present case milling balls) are accelerated due to rotation of the milling chamber which itself is mounted on a sun disc rotating in the opposite direction. The resulting trajectories of the milling balls result in frictional forces (gliding) and impact processes between the balls, the chamber, and of course the mill charge between them. The kinetic energy is transformed and dissipated as thermal energy and allows the initiation of chemical reactions resulting in phenomena like *reactive milling*, *mechano-chemical reactions*, or *mechanically-assisted reactions*.^{1, 2, 12} In case of MBMs the milling chambers are accelerated horizontally or in horizontal and vertical plane following a circular arc or the surface of a spherical cap, respectively. Independently from the mill type it is possible to control the energy entry by control of the process conditions.¹³ Despite the advantages of lab-scale PBMs (but also MBMs) over the utilization of mortar and pestle there are some serious disadvantages or knowledge-gaps in comparison to traditional methods of energy entry like thermal heating or advanced

technologies like microwave-assisted synthesis. Lab-scale ball mills generally have no possibility for cooling or heating, which makes an energy management and heat recycling complicated or even impossible. From engineering viewpoint the lack of controllability (regarding the input power) is critical: the regulation by torque sensors mounted to the rotation axis is impossible due to constructive limitations. Thus, important parameters which are necessary for a scale-up are not as easy to achieve as in stirred media ball mills (SBMs). Only a few scaled-up examples in the field of organic synthesis in ball mills have been published up today.^{14, 15} Those that have been published are rather an alignment of different reactions showing the general possibility that scale-up is possible, than a systematic investigation of scale-up parameters and process conditions.

Within the present study the authors want to show not only that a scale-up including a technology switch from PBM to SBM is possible, but they also want to understand the mechanisms and principles in order to establish a scale-up protocol with suitable parameter sets. The study is dedicated to multi-ball milling systems with the same principle of milling ball movement: rotation. Thus, the present study does not include scale-up in MBMs and the present report will only consider the first step of the program: a scale-up within the system of PBMs. Those experiments would not be possible with MBMs due to the volumetric restrictions of the milling beakers' volume in case of lab-scale apparatus⁷.

Generally, processes in ball mills are characterized by different parameters, regardless from the type of process, *i.e.* a mechanochemical or a mechanically-assisted reaction or particle comminution, and the type of ball mill. In contrast to particle refinement solely, the balance volume for reactions in ball mills has to be enlarged taking into account chemical parameters of the specific reactions.^{1, 11, 16} The large number of influencing variables can be categorized into:

- i. chemical parameters,
- ii. technological parameters, and
- iii. process parameters.

Chemical parameters summarize all those variables which are directly linked to the chemical transformations taking place in the chamber of the ball mill, which includes i) the type of chemical reaction, ii) the presence of catalysts or additives, iii) the reagent ratio, or iv) the presence of low amounts of liquid(s) in case of

liquid-assisted grinding, LAG.¹⁷⁻²²

With respect to **technological variables**, the importance of i) the type of ball mill, ii) the milling material, iii) the number and iv) size of milling balls as well as v) the filling degree of the milling beakers for the accomplishment of chemical reactions should be considered. This set of parameters describes the technology which is used for the comminution.

Process parameters are useful for controlling the energy entry during the process. Thus, i) operating frequency *rpm*, ii) reaction time t_{reaction} , and iii) temperature T are the main values which should be considered. Whereas *rpm* is directly correlated to the kinetic energy of the grinding media and thus, to the energy which can be dissipated as heat to the mill charge, t_{reaction} and T assign for the progression of a chemical reaction and are linked to the reaction kinetics.

In order to scale-up reactions in ball mills all those parameters have to be considered. In the following chapters the influence of main parameters on the outcome of a model reaction will be discussed.

Experimental Part

General information

All chemicals were purchased from Sigma Aldrich or Alfa Aesar and used as received. The reactions were accomplished in a Fritsch Pulverisette P7 premium line and a Fritsch Pulverisette P6 classic line planetary ball mill (Fritsch GmbH, Idar-Oberstein, Germany) using 45 ml (**P7-45**) and 250 (**P6-250**) or 500 ml milling beakers (**P6-500**) made from stainless or tempered steel, respectively (Table 1). The milling balls applied were made from magnesia-stabilized zirconia at varied diameter, d_{MB} , and milling ball number, n_{MB} . Both d_{MB} and n_{MB} determine the milling ball filling degree, $\Phi_{\text{MB,packing}}$. This parameter is defined as the volumetric ratio of the milling balls' packing volume (including the void volume between the milling balls) to the total volume of the milling beaker, $V_{\text{B,total}}$ (Eq. 1).

$$\Phi_{\text{MB,packing}} = \frac{V_{\text{MB,packing}}}{V_{\text{B,total}}} \quad (1)$$

Table 1 Experimental parameters (for the relationship between individual parameters see Electronic Supporting Information).

	Symbol [Unit]	P7-45-	P6-250-	P6-500-
Revolution Speed of disk	rpm [min^{-1}]	750 - 850	450 - 650	450 - 650
Gear ratio	k [-]	-2	-1.82	-1.82
Rotational speed of beaker	$2rpm$ [min^{-1}]	1500 - 1700	819 - 1183	819 - 1183
Milling ball diameter	d_{MB} [mm]	2, 5, 10	10, 20, 30	10, 20, 30
Total volume of milling beaker ^a	$V_{\text{B,total}}$ [ml]	45	250	500
Milling ball filling degree	$\Phi_{\text{MB,packing}}$ [-]	0.3 - 0.8	0.18 - 0.8	0.3 - 0.8
Amount of starting material ^{i b}	$n_{\text{initial},i}$ [mmol]	20	100 - 200	200 , 300

^a Material for $V_{\text{B,total}} = 45$ and 500 ml: stainless steel. Material for $V_{\text{B,total}} = 250$ ml: tempered steel. ^b Bold-face numbers indicate the standard reaction conditions.

Experimental procedure

The milling beakers were equipped with the respective number of milling balls. Afterwards equimolar amounts of Vanillin and Barbituric acid were added in the given order. Milling was

accomplished at the respective frequency, *rpm*, and milling time, t_{reaction} , according to parameter values shown in Table 1 and assigned in the Figures and Table of the following sections. The nomenclature of the respective experiments is as follows: type of ball mill-beaker volume ($V_{\text{B,total}}$)-batch size ($n_{\text{initial},i}$). For instance,

P7-45-20 is related to experiments in the PBM P7 classic line with 45 ml beakers and a batch size of 20 mmol related to one starting material. The relationship between $\Phi_{\text{MB,packing}}$, d_{MB} , and n_{MB} for the individual experimental conditions can be found in the Electronic Supporting Information.

Analytical procedure

After the milling process samples of the crude reaction product (100 mg) were placed on top of a thin layer of silica gel and were extracted with ethyl acetate (5 ml). The organic extract was analyzed with GC-FID using a 7890A-GC (Agilent Technologies) with the following measurement conditions: HP5 column (30 m lengths, 0.32 mm diameter, 0.25 mm film thickness); H_2 (12 psi); temperature program: 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: 280 °C; detector temperature: 300 °C.

Results and Discussion

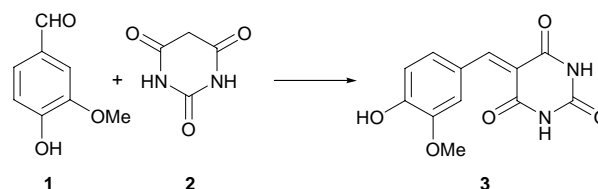
One long-term goal of the project is to close the gap between lab-scale applications of ball mills, *i.e.* planetary ball mills (PBMs), and stirred media ball mills (SBMs) for utilization at technical scale. Thus, a volumetric scale-up factor of 220 should be realized starting with $V_{\text{B,total}} = 0.045$ (PBM) to 101 (SBM) whereas in the present case experiments in two different PBMs will be reported carried out in milling beakers with $V_{\text{B,total}} = 45$ (P7) to 500 ml (P6; volumetric scale-up factor = 11). This affords some experimental prerequisites which narrowed down the number of model reactions to a few examples. The following criteria should be fulfilled by the model reaction.

- The starting material(s) should be available in the necessary *quantity* at reasonable *costs* and suitable *purity*.
- The application of *hazardous substances* and the formation of gases during processing should be avoided.
- The materials should be air-stable allowing processing and storage under *standard atmosphere*.
- To avoid three-phase systems with possible changes in viscosity and plasticity of the mill charge *dry media milling* should be accomplished.
- The melting points of the starting material(s), the product(s) and intermediate(s) should be ≥ 70 °C to avoid formation of eutectics which would influence the morphology of the mill charge.
- The reaction should have a *high selectivity* and quantitative conversion ($\leq 97\%$) should be reachable within $10 \leq t_{\text{reaction}} \leq 45$ min (using a PBM with $V_{\text{B,total}} = 45$ ml).
- In order to control and monitor the reaction progress *fast and robust analytical methods* should be applied. Any promoting effect during work-up or sample preparation should be excluded.
- The grinding chambers or its interior should be made from *stainless steel*.
- To avoid chemical interactions with the substrate(s), milling balls should be made from *magnesia-stabilized zirconia* (MSZ).

Decision criteria i)-vi) relate to the class of chemical parameters. Especially the availability considering costs and purity as well as possible hazards during handling and operation influence the

suitability of existing protocols for organic, ball mill-assisted reactions. Several candidates, for instance metal-catalyzed, cycloaddition, or condensation reactions, were evaluated as model reactions.^{1, 2, 7} *Kaupp* published several examples which may be considered as model reactions, although there are often limitations regarding the melting points and / or the utilization / liberation of gaseous reactants.^{14, 15} Both limitations exclude an application of PBMs as reactors, thus an internal scale-up prior to technological switch to SBM is not possible.

However, two suitable candidates were short-listed: i) imine formation starting from anilines and benzaldehydes and ii) Knoevenagel condensation of benzaldehydes with CH-acidic compounds.²³⁻²⁷ Both fulfill most of the criteria, whereas it is well known that many condensation reactions yielding imines proceed already upon co-crystallization, which is an indicator for a low activation barrier and high reaction rate even in the solid state.^{14, 28-31} Furthermore, analytics is complicated due to high solid state reactivity and spontaneous product formation in solution. Thus the Knoevenagel reaction between Vanillin (**1**) and Barbituric acid (**2**) yielding 5-(4-hydroxy-3-methoxybenzylidene)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **3** (Scheme 1) was chosen as the two-component model reaction.^{24, 32-35} All criteria with respect to chemical parameters are fulfilled and processing in both types of intended ball mills – PBM and SBM – will be possible.



Scheme 1 Model reaction for systematic scale-up studies.

Evaluation of a rapid, robust, and reliable analytic method in order to control and monitor the reaction progress is a second prerequisite for the investigation of other parameters. With respect to applicability solid-state analytic techniques like ATR-FTIR, solid-state NMR, or (P)XRD are the methods of choice since work-up incorporating solvents can be omitted. Unfortunately the methods lack of possibilities for quantification of the substrates and / or the product. For instance, with ATR-FTIR only semi-quantitative information can be obtained from signals assigning the presence of the CHO-group in **1**. Solution-based methods like ^1H and ^{13}C NMR confirm the identity of the product and the absence of any side products or isomers. A post reaction in deuterated solvents like $\text{DMSO-}d_6$ or CDCl_3 was not observed. However, high throughput analysis as well as quantification with the required precision is difficult. Since the product formation is accompanied by coloration of the solid product mixture UV-VIS measurements in DMF as solvent were performed. Those allow precise quantification, but a high amount of DMF (100 ml per sample) is required for sample preparation. Solid-liquid extraction of a small representative sample with 5 ml EtOAc allowed the selective separation of unconverted **1** from **2** and **3**, which was analyzed chromatographically (GC-FID). Since no side and consecutive products were detectable ($> 99\%$ selectivity) conversion and yield were calculated from those measurements based on a calibration for **1**.

General considerations

According to the criteria summarized above restrictions follow for some technological parameters in order to reduce the parameter space. The type of ball mill is a PBM in every case (Table 1).^{13, 36} The basic effect leading to the specific trajectories of the milling balls is the rotation around their central axis and rotation in the opposite direction around the central axis of the sun disk where the beakers are mounted on. Thus the movement type, *i.e.* rotation, is in principle identical to the conditions in an SBM. The PBMs used herein are different in their size mainly determined by the distance of the two axes and the gear ratio of the two resulting rotations (Table 1). Secondly, stainless ($V_{B, total} = 45$ and 500 ml) / tempered steel ($V_{B, total} = 250$ ml) was chosen as material for the milling beakers and milling balls were made from MSZ. All experiments have been carried out at room temperature and milling was accomplished without cycled or reversed operation mode. The following parameters were varied and their influence will be discussed:

- rotation frequency, rpm [min^{-1}] (process parameter),
- milling ball diameter, d_{MB} [mm] (technological parameter),
- milling ball filling degree, $\Phi_{MB, packing}$ [-] (Eq. 1; technological parameter),
- milling beaker volume, $V_{B, total}$ [ml] (technological parameter), and
- the grinding stock filling degrees, Φ_{GS} [-] (Eqs. 6-8; technological parameter).

The last two parameters, $V_{B, total}$ and Φ_{GS} , relate also to the batch size, $n_{initial, i}$, as a chemical parameter. The parameter spaces for all variables are summarized in Table 1 and for the relationship between d_{MB} , n_{MB} , and $\Phi_{MB, packing}$ the reader is referred to the Electronic Supporting Information. In most cases the dependency of those parameters to the reaction time $t_{reaction}$ is discussed additionally. Furthermore, the net energy input will be considered in the investigations.

Influence of the rotation frequency

As first parameter the influence of the rotation frequency, rpm , on the yield of the model reaction was investigated for two different PBMs resulting in three different basic experimental conditions (Table 1). The results are summarized in Figure 1 and are arranged in a way that $n_{initial, i}$ increases from top to bottom. In all cases sigmoidal curves were found, whereas the time at which quantitative yield, $t_{97\%}$, is reached depends on rpm and the batch size, $n_{initial, i}$. Generally, the higher rpm the earlier a yield $\geq 97\%$ is reached independently from the type of ball mill. Despite the increasing value for $n_{initial, i}$ from top to bottom the reactions can be completed in less than 15 min. Especially, in the bottom case (P6-500-200) $t_{reaction} \leq 10$ min is sufficient for quantitative conversion operating at $rpm = 650$ min^{-1} . The promoting effect of the rotation frequency has been demonstrated for many reactions in ball mills and is related to an increase of the system's kinetic energy which is proportional to rpm^2 .^{1, 37} Beside $t_{reactions}$, it has been shown that the influence of rpm on a chemical reaction in ball mills is the most important one.³⁸ Several examples are described in literature indicating this mathematical correlation between *e.g.* yield or conversion and rpm a ball mill is operated with. Generally higher rpm result in an increase of those variables. Examples regarding organic synthesis are very

widespread resembling many fields of synthesis chemistry: for instance cross-coupling,^{10, 38} redox chemistry,³⁹⁻⁴² organocatalytic reactions,⁴³ condensation reactions,^{34, 44-46} polymer grafting,⁴⁷ or reactions of carbohydrates.⁴⁸

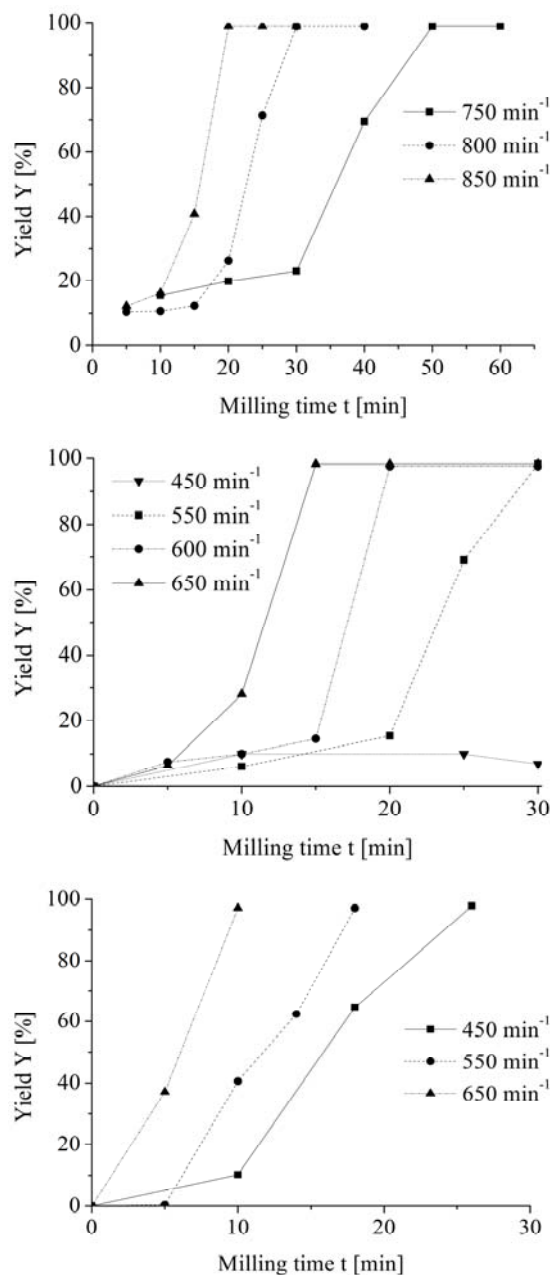


Figure 1 Influence of milling time, $t_{reaction}$, and rotation frequency, rpm , on the yield of the model reaction, Y (Scheme 1), for different ball mills and experimental conditions: **P7-45-20** (top; $d_{MB} = 10$ mm, $\Phi_{MB, packing} = 0.35$), **P6-250-100** (middle; $d_{MB} = 20$ mm, $\Phi_{MB, packing} = 0.45$), and **P6-500-200** (bottom; $d_{MB} = 10$ mm, $\Phi_{MB, packing} = 0.50$). For indication of the experimental conditions see Table 1 in the experimental section and the given explanations.

Although Figure 1 indicates that the correlation between rpm and yield can be generalized and seems to be independent from the batch size and the size of the utilized ball mill there remains one challenge. Based on rpm alone it is not possible to compare the results directly. Specifically the energetic conditions in the milling beaker depend on rpm and on the angular velocity, ω ,

which itself depends on rpm and the distance between the two rotating axes (comparison between **P7** and **P6**). Both ball mills have also different rpm_{max} which are 1100 and 650 min^{-1} , respectively. Additionally, rpm_{max} depends also on d_{MB} : the higher d_{MB} the lower is rpm_{max} in order to avoid abrasion and process instabilities due to high energy impacts of the milling balls (**P7**: $rpm_{max} = 850 min^{-1}$ for $d_{MB} = 10 mm$). Furthermore, the milling beaker size should be considered (comparison between **P6-250** and **P6-500**). Increasing $V_{B,total}$ results in an increasing inner diameter of the milling beaker, d_B , since its height is limited due to constructional restrictions. A higher d_B influences the centrifugal force applicable to the moving milling balls and therefore their kinetic energy is different. Those considerations allow to construe the findings regarding the striking independency of $t_{97\%}$ from $n_{initial,i}$. Despite the lower rpm in case of **P6** the higher distance between the rotational axes results in similar energetic conditions (compared to **P7**) allowing to convert the increased amount of starting materials in nearly the same time.

20 Influence of the milling ball diameter

In order to interpret the findings regarding the influence of d_{MB} on $t_{97\%}$ some preliminary considerations are necessary. From experiments and theoretical considerations in the field of wet comminution in SBMs a cubic proportionality between d_{MB} and the stress energy is indicated (Eq. 2).^{37, 49, 50}

$$E_{stress,feed} = d_{MB}^3 \cdot v_p^2 \cdot \rho_{MB} \cdot K^{-1} \text{ with } K = f(E_{Y,i}) \quad (2)$$

Thus, one might expect, the higher d_{MB} the higher is the stress energy transferred to the mill feed. However, this implication considers only one aspect: the energy which is transferable during one single collision. Most significant differences to the present case are the mill type, the type of milling (wet vs. dry milling), and the total filling degree of the milling reactor, Φ_{total} (Eq. 7; see later), and the fact that a chemical reaction takes place. Thus, a more general consideration has to be done regarding the influence of d_{MB} on the stress energy E . In general, the stress energy is considered as an energy distribution summing up all stress energies, SE , from all single stress events (Eq. 3).

$$E = \sum_{i=1}^{SN} SE_i = SF \cdot \overline{SE} \cdot t_{reaction} \quad (3)$$

The number of stress events, SN , itself is the product of $t_{reaction}$ and the stress frequency, SF .⁵¹ SF and SN correlate with n_{MB} which is inversely proportional to d_{MB} , assuming that the overall mass of the milling balls, $m_{MB,total}$, is constant. Thus, both parameters, d_{MB} and n_{MB} , influence the outcome of the individual comminution process or chemical reaction in ball mills. Since the parameters influence also the median of the stress energy distribution variation of both values may result in different yield, even if following the above mentioned prerequisite: $m_{MB,total} \approx$ constant.⁴⁰

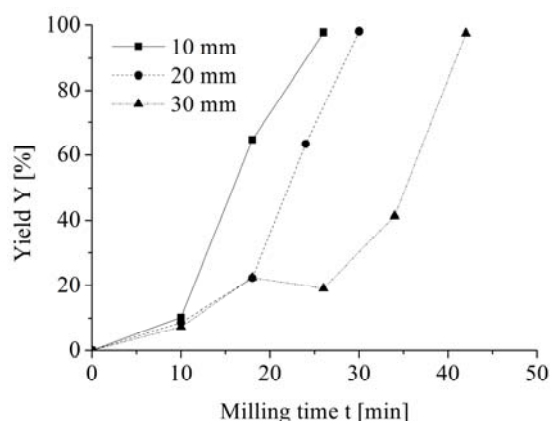
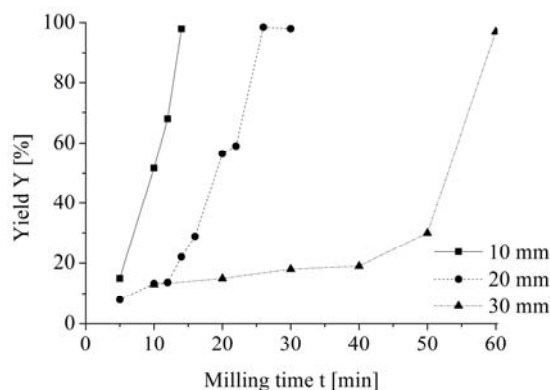
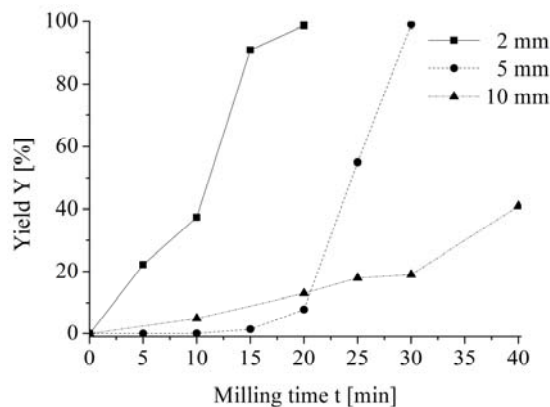


Figure 2 Influence of milling time, $t_{reaction}$, and milling ball diameter, d_{MB} , on the yield of the model reaction, Y (Scheme 1), for different ball mills and experimental conditions: **P7-45-20** (top; $rpm = 800 min^{-1}$, $\Phi_{MB,packing} = 0.45$ for $d_{MB} = 2$ and 5 mm, $\Phi_{MB,packing} = 0.50$ for $d_{MB} = 10 mm$), **P6-250-100** (middle; $rpm = 650 min^{-1}$, $\Phi_{MB,packing} = 0.28-0.30$), and **P6-500-200** (bottom; $rpm = 450 min^{-1}$, $\Phi_{MB,packing} = 0.50$). For indication of the experimental conditions see Table 1 in the experimental section and the given explanations.

Figure 2 provides an overview on the time-dependent yield changing d_{MB} , the experimental setup and linked to it, $n_{initial,i}$. Experiments have been carried out under the premise of nearly constant $m_{MB,total}$, thus if d_{MB} was changed n_{MB} had to be adopted. The correlation between those three parameters is provided within the Electronic Supporting Information. A general trend, which is significant for all cases is the fact that smaller milling balls result in lower $t_{97\%}$ independently from the chosen ball mill and $n_{initial,i}$ which increases from top to bottom. This effect is highlighted for the results at lowest scale (**P7-45-20**). With

10 mm balls after 40 min a yield of 40% was found, $t_{97\%}$ for 5 and 2 mm ball were 30 and 20 min, respectively. Thus, it seemed to be obvious, that SF (Eq. 3) dominates the energy transfer to the substrates and the single stress energy (Eq. 2) is less important for the present case. Keeping $m_{MB,total}$ constant while decreasing d_{MB} (and increasing n_{MB}) results in an increase of the active surface area of the milling balls which is proportional to $(d_{MB})^2$. Since the active surface area is important for the energy transfer to the substrates beside particle refinement these findings are comprehensible. Besides this striking evidences on the influence of d_{MB} it should be noted that literature reports the opposite effect: if $m_{MB,total}$ is kept constant d_{MB} has no influence.^{1, 40} However, it has to be mentioned that authors did not investigate the time dependency. Literally speaking, if the observed yields are in the top part of the sigmoidal curves in every case, such conclusions become evident. Furthermore, the different complexity of the reactions themselves as well $n_{initial,i}$ should be taken into account. Figure 2 evidently reveals, that $t_{reaction}$ has a tremendous effect also, and thus has to be considered in the interpretation of those experiments.

Analysis of the data from Figure 2 for the experiments at low scale (P7) allows for some additional insights. First of all the question might come up, why at the large scale experiments (P6) no milling balls with $d_{MB} < 10$ mm were applied. Even during experiments at the smaller scale (P7) it was observed, that working with $d_{MB} = 2$ mm results in an enclosure of the milling balls in the substrate-product mixture and no further movement was possible (Figure 3). Especially at high rpm such observations were made. To avoid such effects, which are more critical at a larger scale, it was decided not to use those milling balls. Although, in future experiments this should be reconsidered, since it is well known that SBMs are often operated with $d_{MB} < 1$ mm. On the other hand, the application of 20 or 30 mm balls in the low-scale PBM (P7; like in P6) is critical, since in that case this PBM in combination with 45 ml beakers had to be operated with $n_{MB} < 3$. This would result in severe abrasion (high impact energies) and should be avoided using PBMs, in contrast to MBMs. Those may be operated with one or two milling balls only.



Figure 3 Hindered milling ball movement by enclosure of the milling balls in the substrate-product mixture. Reaction conditions: P7-45-20, $rpm = 1000 \text{ min}^{-1}$, $d_{MB} = 2 \text{ mm}$, $\Phi_{MB,packing} = 0.46$.

Comparison of the data in Figure 2 with $d_{MB} = 10$ mm at different scales leads to variations of the values for $t_{97\%}$. Whereas with P7-45-20 even after 40 min milling no quantitative conversion was observed, $t_{97\%}$ were 12 and 26 min using P6-250-100 and P6-500-200 as experimental conditions, respectively. With 20 mm balls, values of 26 and 30 min were found. Thus, at lower scale the effect of decreasing d_{MB} is more pronounced at first sight. A

more detailed analysis revealed that two other important parameters were changed beside the scale-up from 100 to 200 mmol for $n_{initial,i}$, respectively. One was rpm , an increase of rpm for P6-500-200 to 650 min^{-1} resulted for $d_{MB} = 10$ mm in a $t_{97\%}$ -value of 9 min (Figure 1). The second difference becomes obvious when calculating the milling ball filling degree (with respect to ball packing), $\Phi_{MB,packing}$ (Eq. 1), which was different and ranges from 0.28-0.30 (P6-250-100) to 0.50 (P6-500-200). Thus, this parameter also influences the results, which will be discussed in the following chapter.

Influence of the milling ball filling degree

Figure 4 visualizes the influence of $\Phi_{MB,packing}$ on the yield of the model reaction for different d_{MB} . Experiments have been conducted in the large PBM in 250 ml milling beakers at a constant reaction time of 12 min and $rpm = 650 \text{ min}^{-1}$ (P5-250-100), which are the optimal conditions already outlined for $\Phi_{MB,packing} = 0.28-0.30$ in Figure 2. The results strikingly indicate the importance of this parameter, since independent from d_{MB} the curves pass through a maximum, which is in the range of $0.43 \leq \Phi_{MB,packing} \leq 0.50$.

The reason for this behavior relates to the trajectories of the milling balls in their milling beakers. According to Eqs. 2 and 3 the overall stress energy depends on SE and SF . If $\Phi_{MB,packing}$ is < 0.4 the number of stress events, SN , and therefore also SF and the medium SE are reduced which leads to the observed effect regarding the yield. Although, the movement of the milling balls inside the beakers is not distorted. For an efficient energy transfer the grinding bodies need space for acceleration and movement through the milling beaker. In case of $\Phi_{MB,packing} > 0.5$ the free space for the trajectories is restricted or completely blocked and the milling balls cannot be accelerated, take their way through the vessel, and cause impacts (Figure 4).^{11, 36, 52, 53} Thus, SF is decreased (see Eq. 3). Beside hampered acceleration, inefficient energy transfer, and decreased SF ; centrifugal transport of the milling balls along the milling beakers wall (see Figure 3)⁵⁴ can cause increased abrasion of the milling beaker.^{11, 52}

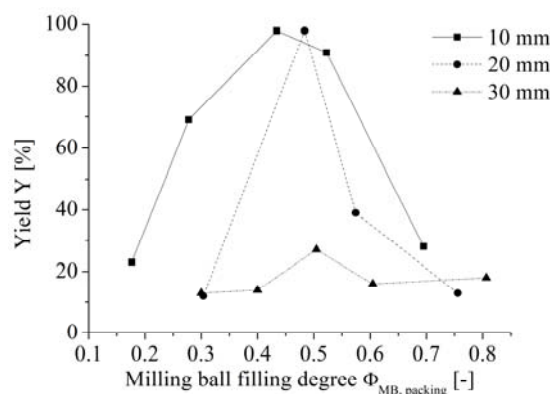


Figure 4 Influence of milling ball filling degree, $\Phi_{MB,packing}$ (Eq. 1), and milling ball diameter, d_{MB} , on the yield of the model reaction, Y (Scheme 1), for experiments using P6-250-100 ($rpm = 650 \text{ min}^{-1}$, $t_{reaction} = 12 \text{ min}$). For indication of the experimental conditions see Table 1 in the experimental section and the given explanations.

Manufacturers of PBMs generally advise their customers to leave at least 33% of $V_{B,total}$ for the trajectories of the milling balls and

the geometrical volume, $V_{\text{MB,material}}$, of the milling balls should not exceed 33%.⁵² However, $\Phi_{\text{MB,packing}}$ (Eq. 1) considers the packing volume of the milling balls. This is reasonable from an engineering point of view since the filling process of a milling beaker with milling balls results in a ball packing, whereas the void volume, V_{void} , depends on the space filling degree, $1-\varepsilon$ (Eq 4).

$$V_{\text{MB,packing}} = V_{\text{MB,material}} + V_{\text{void}} = \frac{V_{\text{MB,material}}}{1-\varepsilon} \quad (4)$$

The space filling degree can be calculated from the porosity, ε , of the packing, which can be measured or calculated similar to powders. The geometric volume of the milling balls, $V_{\text{MB,material}}$, as well as the correlated geometric filling degree, $\Phi_{\text{MB,material}}$, can be calculated according to the following equation.

$$\begin{aligned} \Phi_{\text{MB,material}} &= \frac{V_{\text{MB,material}}}{V_{\text{B,total}}} = \frac{\pi \cdot d_{\text{MB}}^3 \cdot n_{\text{MB}}}{6 \cdot V_{\text{B,total}}} \\ &\equiv \frac{m_{\text{MB,total}}}{V_{\text{B,total}} \cdot \rho_{\text{MSZ}}} \cong \Phi_{\text{MB,packing}} (1-\varepsilon) \end{aligned} \quad (5)$$

Based on parameters like d_{MB} and n_{MB} or $m_{\text{MB,total}}$ and the material density of the milling balls, ρ_{MSZ} , the value of $\Phi_{\text{MB,material}}$ can be estimated. According to Eq. 4 and the assumption that $\rho_{\text{MSZ}} \gg \rho_{\text{air}}$ (which allows to neglect the mass of the void volume) it is possible to correlate $\Phi_{\text{MB,material}}$ and $\Phi_{\text{MB,packing}}$ by consideration of ε . Recalculation of the values for $\Phi_{\text{MB,packing}}$ from Figure 4 results in $\Phi_{\text{MB,material}}$ of 0.26, 0.27, and 0.28 for $d_{\text{MB}} = 10, 20, \text{ and } 30 \text{ mm}$, respectively (see Electronic Supporting Information). This is roughly in accordance to the manufacturers' advice. Actually, the optimal values for $\Phi_{\text{MB,packing}}$ (Figure 4) and thus those for $\Phi_{\text{MB,material}}$ are slightly lower, which means n_{MB} could be reduced, improving the overall process costs.

Figure 4 indicates that for $d_{\text{MB}} = 30 \text{ mm}$ within 12 min the yield did not increase over a value of roughly 25% (see also Figure 2, middle). In order to evaluate those data additional experiments have been conducted allowing to compare the time required to reach quantitative yield, $t_{97\%}$, and $\Phi_{\text{MB,packing}}$. Results are presented in Figure 5 for the general conditions **P6-250-100** (top) and at enlarged scale **P6-500-200** (bottom). Although, the values slightly differ, it is obvious for the small-scale experiments that independently from d_{MB} the curves pass through a minimum, whose location regarding the values for $\Phi_{\text{MB,packing}}$ is almost identical to those shown in Figure 4. At an optimized filling degree $t_{97\%}$ ranges from 12-18 min. Enlarging $V_{\text{B,total}}$ and $n_{\text{initial,i}}$ narrows down the optimum value for $\Phi_{\text{MB,packing}}$ to exactly 0.50 for 20 and 30 mm milling balls. For the Knoevenagel condensation with $d_{\text{MB}} = 10 \text{ mm}$ (**P6-500-200**) no minimum was detected.

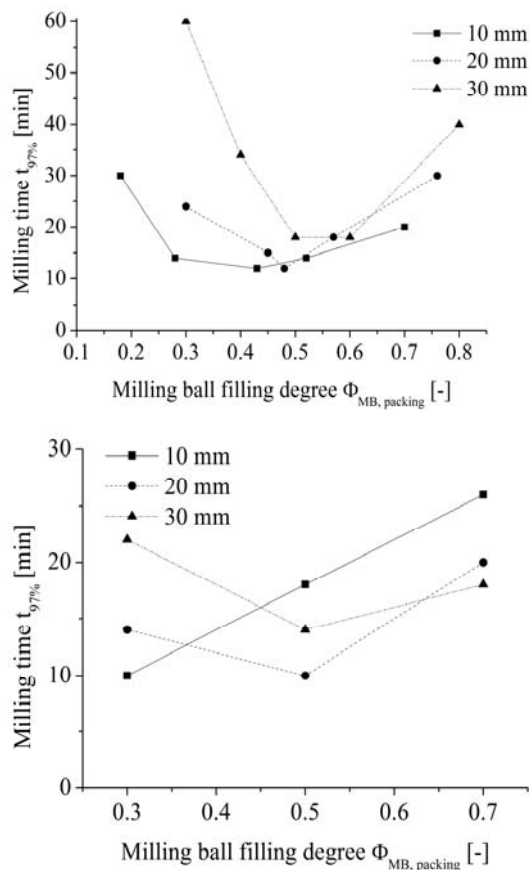


Figure 5 Influence of milling ball filling degree, $\Phi_{\text{MB,packing}}$ (Eq. 1), and milling ball diameter, d_{MB} , on the time to reach quantitative yield, $t_{97\%}$, for different basic experimental conditions **P6-250-100** (top; $\text{rpm} = 650 \text{ min}^{-1}$), and **P6-500-200** (bottom; $\text{rpm} = 550 \text{ min}^{-1}$). For indication of the experimental conditions see Table 1 in the experimental section and the given explanations.

Influence of the substrate filling degree

During the experiments conducted up to now the batch size, $n_{\text{initial,i}}$, was not varied within in the ball milling systems utilized (**P7-45-20**: $n_{\text{initial,i}} = 20 \text{ mmol}$, **P6-250-100**: $n_{\text{initial,i}} = 100 \text{ mmol}$, **P6-500-200**: $n_{\text{initial,i}} = 200 \text{ mmol}$). Changing this value in order to increase the scale of reaction would consequently result in different conditions regarding the ratio of substrate amount (GS) and milling balls. One possibility to measure this ratio is the so called "ball-to-powder-ratio" which is often applied to ascribe experimental conditions in the field of inorganic synthesis in ball mills or dry comminution.^{11, 55} This value is often expressed as mass ratio, which makes this parameter an inapplicable one to describe the general relationships from an engineering perspective. The large discrepancy with respect to material or bulk densities makes a comparison of different systems impossible. Although the weighed-in mass is important in general, in order to describe the correlation to other values like $\Phi_{\text{MB,packing}}$ or $V_{\text{B,total}}$ a volume-based parameter has to be applied. Since the substrates and the product are free-flowing powders, their bulk volume, $V_{\text{GS,packing}}$, can be calculated according to Eq. 6 considering the individual masses, $m_{\text{GS,i}}$, and bulk densities, $\rho_{\text{GS,i}}$.

$$\Phi_{\text{GS,packing}} = \frac{V_{\text{GS,packing}}}{V_{\text{B,total}}} \cong \frac{\sum_i^n \frac{m_{\text{GS},i}}{\rho_{\text{GS},i}}}{V_{\text{B,total}}} \quad (6)$$

Correlation to $V_{\text{B,total}}$ leads to the filling degree of the substrates, $\Phi_{\text{GS,packing}}$, which is limited by the total beaker volume and the geometric filling degree of the milling balls: $0 \leq \Phi_{\text{GS,packing}} \leq 1 - \Phi_{\text{MB,material}}$. Due to the low porosity and the high space filling degree of the substrate packing with respect to that of the milling balls, the void volume is neglected in the first approximation and the total volumetric filling degree of the milling beaker, Φ_{total} , can be calculated as shown in Eq. 7.

$$\Phi_{\text{total}} = \Phi_{\text{MB,material}} + \Phi_{\text{GS,packing}} \quad (7)$$

This parameter ranges from $0 \leq \Phi_{\text{total}} \leq 1$, which resemble the empty and the completely filled milling beaker. With respect to wet and dry comminution processes another parameter is introduced in Eq. 8 describing the filling degree, Φ_{GS} , in relation to the void volume of the milling balls' packing.

$$\Phi_{\text{GS}} = \frac{V_{\text{GS,packing}}}{V_{\text{MB,packing}} - V_{\text{MB,material}}} = \begin{cases} < 1 \\ = 1 \\ > 1 \end{cases} \quad (8)$$

In order to illustrate the meaning of Φ_{GS} three cases are exemplified. If $\Phi_{\text{GS}} < 1$, the substrates are located in the free room of the milling balls' packing. The upper limit is exemplified by $\Phi_{\text{GS}} = 1$ which means that the void volume in the ball packing is completely filled with the substrate(s). The third case, $\Phi_{\text{GS}} > 1$, indicates a substrate volume, which is higher than V_{void} . Practically this implies the substrates cover-up the ball packing. The upper limit is restricted by the milling beaker volume.

Table 2 summarizes the results for two different $V_{\text{B,total}}$ and varying $n_{\text{initial},i}$. The calculation of Φ_{GS} leads to values of > 1 indicating that the substrate volume is significantly higher than V_{void} of the ball packing. The total filling degree, Φ_{total} , ranges from 0.55-0.85 and 0.58-0.73 for the 250 and the 500 ml beakers, respectively. The most interesting effect can be found in the last column of Table 2. Despite the high values for Φ_{total} the times to reach quantitative yield were 30 and 10 min, depending on $V_{\text{B,total}}$. The variations found were negligible, which leads to the conclusion that the substrate filling degree has no significant influence in the investigated parameter range. Even a residual free volume for milling ball movement of 15% ($1 - \Phi_{\text{total}} = 1 - 0.85$) of the original beaker volume is apparently enough to achieve high conversion. However, it should be taken into account that organic substrates are light-weight materials with a low Youngs modulus. (Reactive) treatment of harder (inorganic) materials might lead to other results. However, since conditions with roughly $\Phi_{\text{total}} \geq 75\%$ are realizable for organic synthesis in ball mills a scale-up and technological change to dry-operated SBM seemed to be possible.

Table 2 Experimental results for variation of the batch size, $n_{\text{initial},i}$, and the effect on the filling degrees, Φ_i [-],^a and the time to reach quantitative yield, $t_{97\%}$, for the model reaction in Scheme 1.

$n_{\text{initial},i}$ [mmol]	$\Phi_{\text{MB,material}}$	$\Phi_{\text{MB,packing}}$	$\Phi_{\text{GS,packing}}$	Φ_{GS}	Φ_{total}	$t_{97\%}$ [min]
P6-250 ($V_{\text{B,total}} = 250$ ml, $d_{\text{MB}} = 20$ mm, $n_{\text{MB}} = 15$, $rpm = 550$ min ⁻¹)						
100	0.25	0.45	0.30	1.42	0.55	30
125	0.25	0.45	0.38	1.78	0.63	28
150	0.25	0.45	0.45	2.13	0.70	30
175	0.25	0.45	0.53	2.49	0.78	29
200	0.25	0.45	0.60	2.84	0.85	28
P6-500 ($V_{\text{B,total}} = 500$ ml, $d_{\text{MB}} = 20$ mm, $n_{\text{MB}} = 33$, $rpm = 650$ min ⁻¹)						
200	0.28	0.50	0.30	1.28	0.58	10
300	0.28	0.50	0.45	1.92	0.73	10

^a Calculation according to the equations given in parentheses: $\Phi_{\text{MB,material}}$ (Eq. 5), $\Phi_{\text{MB,packing}}$ (Eq. 1), $\Phi_{\text{GS,packing}}$ (Eq. 6), Φ_{GS} (Eq. 8), and Φ_{total} (Eq. 7).

Influence of the milling beaker volume

As Table 2 indicates the initial beaker volume, $V_{\text{B,total}}$, is of importance for the efficiency of the reaction in terms of $t_{97\%}$. If the volume is increased, generally the inner diameter, d_{B} , of the milling beaker increases, since its height is limited due to constructional prerequisites (clamping device of the milling beaker on the sun disk). The SE (Eqs. 2 and 3) distributed by impacts of the milling balls depend on the centrifugal force which is proportional to the rotation axis of the system. Thus, enlargement of the beaker volume should result in higher medium SE and the same results in terms of yield should be observed in shorter reaction time or at lower frequency. Results shown in Figure 6 revealed that at $rpm = 650$ min⁻¹ the $t_{97\%}$ -values are in the range of 10-20 min depending on $\Phi_{\text{GS,packing}}$ and $V_{\text{B,total}}$. By a decrease rpm the gap between the $t_{97\%}$ -values for the 250 and 500 ml beaker become larger, whereas reactions at a larger scale

required generally longer reaction times. However it should be considered that the absolute reaction rate is higher since $n_{\text{initial},i}$ is doubled. Thus, the considerations were confirmed by experiment.

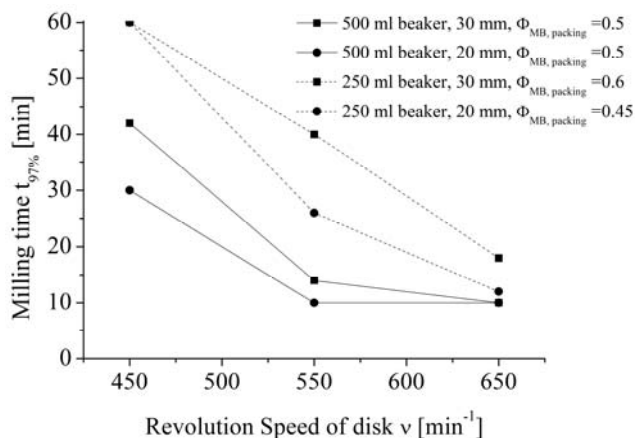


Figure 6 Influence of beaker size, $V_{\text{B,total}}$, and revolution speed of the sun disk, rpm , on the time to reach quantitative yield, $t_{97\%}$, for experiments in the large-scale ball mill (P6-250-100, P6-500-200). For indication of the experimental conditions see Table 1 in the experimental section and the given explanations.

Figure 7 compares the previous results energy-wise. Interestingly experiments at the largest scale (P6-500-200) revealed an energy minimum at $rpm = 550 \text{ min}^{-1}$ with respect to the overall energy input, E_{brutto} , as well as to the molar energy consumption, E_{m} (Eq. 9).¹⁰ Thus, the higher the reaction scale the lower is the specific energy demand, at least at medium rpm . Increase of the revolution speed to its maximum revealed similar results energy-wise for reactions in 250 and 500 ml beakers. It should be pointed out that neither E_{brutto} nor E_{m} are identical to the (medium) stress energy outlined in Eqs. 2 and 3.

$$E_{\text{m}} = \frac{E_{\text{brutto}}}{n_{\text{initial},i} \cdot Y} \quad (9)$$

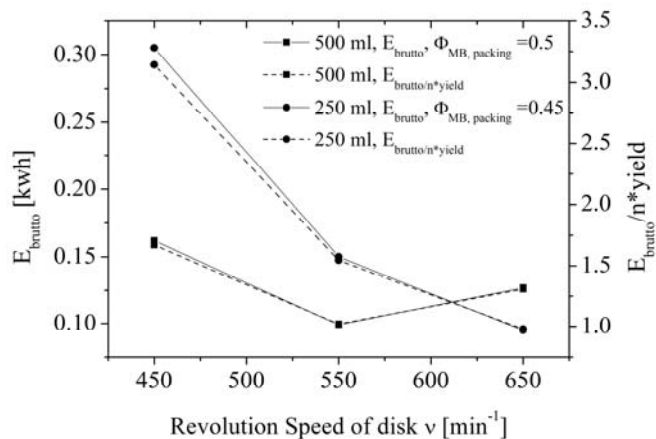


Figure 7 Influence of beaker size, $V_{\text{B,total}}$, and revolution speed of the sun disk, rpm , on the energy consumed for experiments in the large-scale ball mill (P6-250-100, P6-500-200). For indication of the experimental conditions see Table 1 in the experimental section and the given explanations.

Conclusion

The aim of the present study was to investigate the influence of technological and process parameters relevant to the scale-up of an organic model reaction carried out in planetary ball mills. As model reaction the Knoevenagel condensation of Vanillin and

Barbituric acid was chosen, since the substrates are available in high quantity at reasonable costs and sufficient purity, the reaction is selective and no other reagents or additives were required, and the reaction progress can be followed with analytical methods which avoid possible post reactions in solution.

Several parameters have been investigated. Generally, it was demonstrated that the combination of at least two parameters leads to interesting insights in the relationship between them. It was possible to scale up the model reaction from a 20 to 300 mmol-scale which resulted in scale-up factors of 15 and 11 with respect to scale-up of the batch size and the reactor volume, respectively. The experiments demonstrated that the increase of the batch size as well as the reactor volume did not necessarily lead to an increase of the reaction time. Especially, the variation of the milling ball diameter, d_{MB} , the rotation frequency, rpm , and the filling degree of the milling beakers considering the ball packing, $\Phi_{\text{MB, packing}}$, and the substrates, Φ_{GS} , allowed to fine-tune the reaction conditions. With respect to d_{MB} it was found that small milling balls are advantageous, since the number of stress events is considerably increased. Contrarily to comminution processes, the stress energy seemed to be less important. This allows to conclude that the reaction is rather thermally-initiated than *real* mechano-chemical. Although, the influence of rpm exemplifies the importance of the mechanical processes in order to increase the system's kinetic energy, *i.e.* the system's temperature, and the homogeneity of the heterogeneous solid-solid mixture. Experiments regarding the influence of the filling degrees revealed, that $\Phi_{\text{MB, packing}}$ should be in the range of 0.5, which is identical to an overall milling ball volume of roughly 25% of the total beaker volume. With respect to Φ_{GS} it was found that up to 50% of the beaker's total volume can be taken up by the substrates without a disadvantageous effect on the reaction yield.

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Notes and references

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