

How Mechanical and Chemical Features Affect the Green Synthesis of 1*H*-Pyrazoles in a Ball Mill

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S Supporting Information

ABSTRACT: This work investigated the chemical and mechanical factors that affect cyclocondensation reactions in a ball mill. Chemical characteristics such as the use or non-use of a catalyst, amount of catalyst and reactants, and product formation, as well as the yield and mechanical factors such as rotation frequency and the number, diameter, and material of the milling balls were evaluated. It was found that a rotation frequency of 450 rpm is efficient for energy transfer to the reactants because the conversion is higher at this rotation. The reaction was highly dependent on the time (3 min) and amount of *p*-TSA (*p*-toluenesulfonic acid) utilized as catalyst (10 mol %). Five steel balls of 10 mm were considered to be the ideal number for the efficient mixing of the particles. For this work, the ideal conditions determined were used for the green synthesis of a series of 1*H*-pyrazoles.

KEYWORDS: Green synthesis, Ball mill, Eutectic mixtures, Mechanical parameters, Differential scanning calorimetry, Pyrazoles



INTRODUCTION

Synthetic methods under solvent-free conditions are aimed at green or sustainable chemistry^{1,2} because waste and energy costs are reduced. In these reactions, steps such as solvent purification, solvent evaporation, or solvent heating/cooling during the workup are dispensable. Additionally, energy sources such as microwave and ultrasonic irradiation and mechanochemical techniques (grinding and ball milling) have been shown to be viable alternatives for saving energy.^{1,3} In particular, the use of ball milling under solvent-free organic reactions has emerged as an excellent activation method.^{4–8} The efficient mixing and continuous particle refinement allowed by the equipment leads to high reaction rates (decreased diffusion barriers)⁹ and higher selectivity and yields compared to reactions performed in solution.¹⁰ Additionally, the possibility of adjusting instrumental parameters makes ball milling results more reproducible.^{10–13} Instrumental parameters such as rotation frequency, time, and oscillation frequency, as well as the number, mass, diameter, and material of the milling balls and their effects on the results of organic reaction have been studied. Szuppa et al.¹³ have shown that both the number of milling balls and the rotation frequency have a significant influence on the outcome of γ -terpinene to *p*-cymene oxidation because the variation of these parameters allows fine-tuning of the reaction conditions. Schmidt et al.¹⁰ evaluated the influence of milling time, oscillation frequency, number of milling balls, and the addition of small quantities of solvents for the halogenation of aromatic compounds. They

observed that all these factors directly affect reaction conversion. The examples aforementioned show that the magnitude to which these variables influence the development and implementation of chemical reactions in ball mill equipment is extremely important because these parameters directly affect the greenness and efficiency of the process.

Among heterocycles, pyrazole derivatives are important compounds that have attracted much more attention in recent time due to their usefulness in the field of drug discovery and agricultural research. Our research group has been working with pyrazole chemistry over the last 25 years.^{14–16} Pyrazoles have been used as chelating metal ions¹⁷ and also as starting materials for the construction of condensed heterocyclic systems.¹⁸ Thus, the academic community and industry are constantly searching for a fast green method to obtain these heterocycles. To the best of our knowledge, the best parameters for obtaining heterocycles by cyclocondensation reactions involving ball mill reactors have not previously been reported. Thus, the aim of this work was to evaluate all possible variables in a cyclocondensation reaction to obtain a pyrazole series and investigate how mechanical and chemical factors affect the performance of the reactions.

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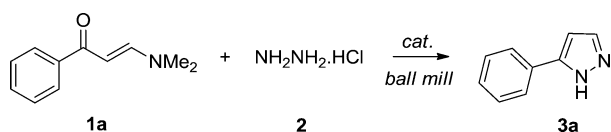
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RESULTS AND DISCUSSION

To investigate the mechanochemical effects induced by ball milling, the reaction of enaminone **1a** and hydrazine hydrochloride **2** to form *1H*-pyrazole **3a** was used as the model system (Scheme 1).

Scheme 1. Acid-Catalyzed Cyclocondensation of Enaminone 1a with Hydrazine Hydrochloride 2



Chemical parameters such as the use or non-use of a catalyst, amount of catalyst and reactants, product formation and yield, as well as mechanical factors such as rotation frequency and the number, diameter, and material of the milling balls were evaluated.

Amount of Reactants. The first parameter investigated was the optimal amount of reagents to be used in the milling beaker. The molar ratio between **1a** and **2** was 1:1.2, respectively, and this ratio was maintained in all experiments. The reaction had been previously performed using grinding and an oil bath, and the addition of an acid catalyst (*p*-TSA) was necessary.²⁰ The use of an acid catalyst was also necessary in the experiments with a ball mill, because in its absence, there is no product formation, even after longer reaction times (30 min). In order to establish the optimal amount of **1a**, experiments were performed with 1, 3, and 5 mmol of **1a**. The experiments were performed at three predetermined rotation frequencies (150, 200, and 250 rpm) but with the same time (6 min). The number of balls (five) and the quantity of catalyst (10 mol %) were kept constant. Entries 1–3 (Table 1)

Table 1. Amount of 1a and Rotation Frequencies of the Reaction Conversion^a

entry	1a (mmol)	rotation frequency (rpm)	conversion (%) ^b
1	1	150	95
2	1	200	91
3	1	250	83
4	3	150	26
5	3	200	68
6	3	250	100
7	5	150	33
8	5	200	72
9	5	250	100

^aReaction conditions: 10 mol % of *p*-TSA, 6 min, steel beaker (25 mL), and steel milling balls (5 mm × 10 mm diameter). ^bDetermined by GC-MS.

demonstrate that conversion decreases when the rotational frequency is increased from 150 to 250 rpm. This could be due to the low efficiency of effective shocks inside the milling beaker and the small volume occupied by the reagent. In subsequent experiments (Table 1, entries 4–6), the amount of **1a** was increased to 3 mmol. In this case, an increase in conversion was observed when higher rotational frequencies were used. Using a frequency of 250 rpm led to 100% conversion. After this, the amount of reactant was increased to 5 mmol of **1a**, and consequently, a higher conversion was observed when the frequency was raised (Table 1, entries 7–9).

On the basis of the experiments detailed above, the optimal amount to use in the milling beaker was 3 mmol of **1a** (entry 6) because the use of greater amounts of reagents leads to similar results (Figure 1).

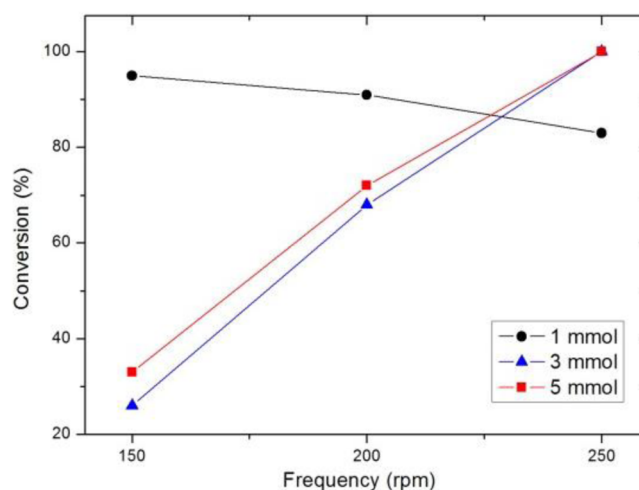


Figure 1. Variation in the conversion of products as a function of rotation frequency.

Different Catalysts. Different catalysts were tested to evaluate the conversion of **1a**. For these experiments, some catalysts were selected with differing properties such as physical state (solid or liquid), pK_a value, and melting point.¹⁹ Initially, the acidic inorganic salts (NaHSO_4 and KHSO_4) were tested, and it was observed that NaHSO_4 showed a higher conversion (23%) over KHSO_4 (14%), probably due to the lower melting point of the former (melting points of 58 and 214 °C, respectively). In the following experiments, four ionic liquids, namely, $[\text{BMIM}][\text{Br}]$, $[\text{HMIM}][p\text{-TSA}]$, $[\text{HMIM}][\text{HSO}_4]$, and $[\text{BMIM}][\text{BF}_4]$, were tested. However, the use of ionic liquids demonstrated poor results for obtaining **3a** ($\leq 5\%$). Subsequently, two Lewis acids ($\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) in the solid state and one ($\text{BF}_3 \cdot \text{OEt}_2$) in the liquid state at room temperature were tested; however, the expected conversion of *1H*-pyrazol was not observed. The organic acids *p*-TSA, benzoic acid, 3,5 dinitrobenzoic acid and nitrilotriacetic acid were also investigated. However, only *p*-TSA demonstrated satisfactory results (64%) in this condition.

This result may be related to the low melting point of *p*-TSA (106 °C) together with a low pK_a value (−2.8) because this reaction depends on activation of the electrophilic center of the substrate **1a**. Finally, some organic and inorganic bases were tested (NaOH , DMAP, Et_3N); however, these also resulted in a poor conversion of **3a** ($< 5\%$). Considering that the forces generated by the planetary ball mill can cause wear on the surface of the milling balls and that this wear contaminates the milling beaker,²¹ it is important to evaluate if contamination by Fe^0 catalyzes the reaction. This type of contamination sometimes assists certain reactions^{22–24} because it can act as a co-catalyst. However, when reactions were performed in the presence of Fe^0 , the conversion was negligible, which shows that, if it is present it does not affect the conversion of the reaction. All reactions were performed without solvent, utilizing 3 mmol of **1a**, 3.6 mmol of **2**, 10 mol % of catalyst, 400 rpm (6.66 Hz), 3 min in a stainless steel beaker ($V = 25$ mL), with 5 stainless steel balls ($d = 10$ mm) at room temperature. The

conversions were determined with GC-MS measurements. Through this study, it is observed that *p*-TSA is the best catalyst for this reaction because it is the only one that results in 100% conversion.

Catalyst Amount. The amount of catalyst has been shown to be crucial in reactions performed in ball mill equipment.^{25,26} As mentioned above, using *p*-TSA as catalyst, the cyclocondensation reaction between **1a** and **2** results in products with good yields. The influence of amount of *p*-TSA over variation in the conversion of product **3a** was evaluated. As expected, the results demonstrate that the reaction is strongly influenced by the amount of catalyst (Table 2). For entries 1–

Table 2. Evaluation of the *p*-TSA Amount on the Conversion of the Product

entry	<i>p</i> -TSA (mol %)	time (min)	conversion (%) ^b
1	5	1	27
2	10	1	54
3	15	1	68
4	20	1	78
5	5	2	34
6	10	2	56
7	15	2	83
8	20	2	93
9	5	3	48
10	10	3	100
11	15	3	100
12	20	3	100

^aReaction conditions: 3 mmol of **1a**, 3.6 mmol of **2**, steel beaker (25 mL), steel milling balls (5 mm × 10 mm), and 450 rpm. ^bDetermined by GC-MS.

4, which had a reaction time of 1 min, an increase in conversion was observed with an increase in the amount of catalyst (Table 2). The same behavior was observed in experiments performed for 2 or 3 min (Table 2, entries 5–12). Figure 2 shows the effect that the amount of catalyst and the reaction time have on the conversion of **1a**. Also, it was demonstrated that a near quantitative conversion (Table 2, entry 8) is reached in a shorter time (2 min). However, the best condition for the amount of catalyst was found to be 10 mol % of *p*-TSA when

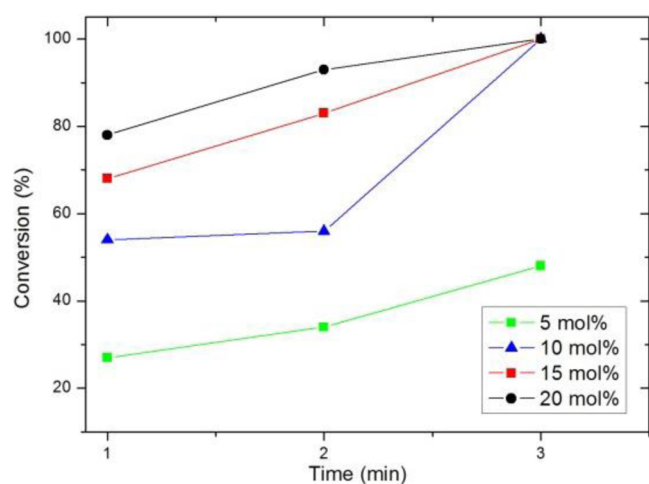


Figure 2. Variation of the product conversion as a function of *p*-TSA amount.

the conditions of 3 min and 450 rpm are used (Table 2, entry 10).

Reaction Time and Milling Speed. On the basis of the established conditions, a series of experiments using reaction times between 3 and 6 min were performed (Table 3, entries 1–8). Considering the results of Table 3, it was clear that the reaction can be performed in shorter times; however, a higher rotation frequency must be used. When the reaction time was either 5 or 4 min and rotation frequencies of 350 or 400 rpm were used (Table 3, entries 2–5), the conversion was 100%. When the reaction was tested at 3 min, the 100% conversion was also achieved at 500 and 450 rpm; however, at 400 rpm, a substantial reduction in conversion (36%) was observed (Table 3, entries 6–8).

Table 3. Reaction Optimization between **1a and **2**^a**

entry	time (min)	rotation frequency (rpm)	conversion (%) ^b
1	6	250	100
2	5	400	100
3	5	350	100
4	4	400	100
5	4	350	100
6	3	500	100
7	3	450	100
8	3	400	64

^aReaction conditions: 3 mmol of **1a**, 3.6 mmol of **2**, 10 mol % of *p*-TSA, steel beaker (25 mL), and steel milling balls (5 mm × 10 mm). ^bDetermined by GC-MS.

At 400 rpm and using short reaction times (1 and 2 min), low conversions (28% and 42%) were obtained. The most significant effect was found in the transition from 3 to 4 min, where there was a variation in conversion of 36% (Table 3, entries 4 and 8). The results obtained with these experiments demonstrated that the reaction is highly dependent on time, and a greater time results in higher conversion (Figure 3). Thus, to evaluate other variables, the reactions were performed for 3 min at 450 rpm.

Number of Balls in the Ball Mill. The number of balls is responsible for the energy transfer to the reaction system. In general, a greater number will result in the transfer of more energy to the reagents, thus leading to higher yields.^{13,23,25,27,28}

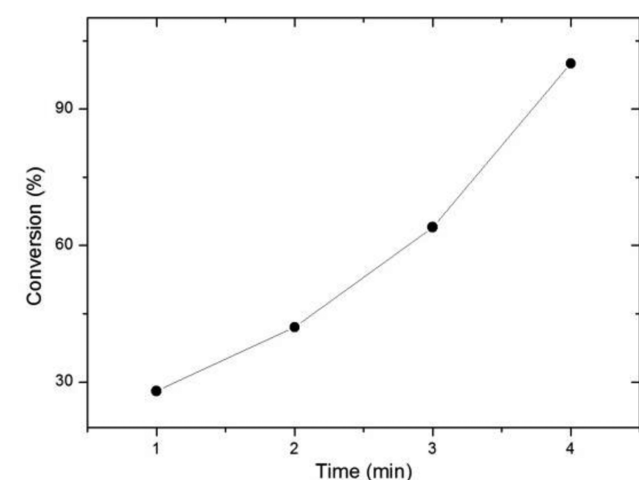


Figure 3. Variation of the product conversion as a function of time.

In this context, the number of balls for obtaining the product **3a** was evaluated, with the material (steel) of all the balls and the diameter (10 mm) being kept constant. The number of balls per milling beaker depends on the volume of the beaker. Reagents and balls must occupy a maximum of two-thirds of the beaker because empty space is necessary for the movement of the balls.²⁹ The reaction was not performed without milling balls because the balls are responsible for the energy transfer to the reactants. The reaction with 1 ball (Table 4, entry 1) did

Table 4. Evaluation of How the Number of Milling Balls Affects the Conversion of the Product^a

entry	number of balls ^b	conversion (%) ^c
1	1	0
2	2	4
3	3	19
4	4	49
5	5	64
6	6	50
7	7	22

^aReaction conditions: 3 mmol **1a**, 3.6 mmol **2**, 10 mol % *p*-TSA, 3 min, steel beaker (25 mL), and 400 rpm. ^bSteel milling balls (10 mm). ^cDetermined by GC-MS.

not result in conversion to the product, thus indicating that the energy transferred by this ball is not sufficient to initiate the reaction. Product **3a** starts to be formed only with the use of more than one milling ball. Increasing the number of balls leads to an increase in the conversion rates (Table 4, entries 2–5) due to more efficient energy transfer, and therefore, higher temperatures are reached. However, less impressive results were obtained with 6 and 7 balls (Table 4, entries 6 and 7) due to the energy loss resulting from the excessive volume occupied by them, which makes the collisions less effective between the balls or between the balls and the walls of the beaker. Thus, the ideal number of balls for the milling beaker is 5 balls (diameter of 10 mm).

Diameter of the Milling Balls. The diameter of the milling balls used for synthesis is crucial if their mass is not constant.^{27,25} If the total number of balls is kept constant, but the balls are different sizes, different results are obtained (Table 5, entries 1–3 and 4–6). An increase in the diameter of the balls results in a weight variation and, consequently, an increase in kinetic energy, which causes a transfer of more effective energy to the reactants. Thus, higher conversions are expected.²⁷ However, the constant mass adjustment of the balls

Table 5. Evaluation of the Milling Ball's Diameter on the Conversion of the Product^a

entry	number of balls	diameter (mm)	total weight of balls (g)	conversion (%) ^b
1	2	5	1.01	0
2	2	10	8.19	4
3	2	15	23.72	68
4	3	5	1.52	0
5	3	10	12.29	19
6	3	15	35.59	73
7	5	10	20.48	64

^aReaction conditions: 3 mmol of **1a**, 3.6 mmol of **2**, 10 mol % of *p*-TSA, 3 min, steel beaker (25 mL), and 400 rpm. ^bDetermined by GC-MS.

due to the change in the number and diameter results in similar conversions.²⁸ We found that reactions performed with two steel balls (diameter of 15 mm) or five steel balls (diameter of 10 mm) resulted in similar conversions because the total ball mass is very similar (Table 5, entries 3 and 7). As mentioned above, experiments were also conducted to evaluate if larger diameters of the steel balls (15 mm) would result in higher conversions. The results indicated in Table 5 (entries 3 and 6) confirm this. It was also observed that the greater mass for entry 6 than for entry 3 did not have a pronounced effect on the conversion.

Material of the Milling Balls. The material selected for the milling balls is a determining factor for the reaction, and this choice is related to the type of reaction studied. For example, some reactions have higher yields when there is a change from a lower density material to a denser one.^{30–32} In this work, milling balls with different materials (steel and agate) and diameters were tested (Table 6). It was observed that no

Table 6. Evaluation of the Effect That the Milling Ball Material Has on Conversion of the Product^a

entry	material	number of balls	ball diameter (mm)	conversion (%) ^b
1	steel	5	5	0
2	steel	5	10	64
3	agate	5	5	0
4	agate	5	10	24

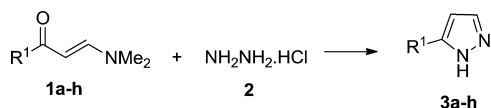
^aReaction conditions: 3 mmol of **1a**, 3.6 mmol of **2**, 10 mol % of *p*-TSA, 3 min, steel beaker (25 mL), and 400 rpm. ^bDetermined by GC-MS.

conversion was obtained in the case of balls with a 5 mm diameter (Table 6, entry 1 and 3). However, balls with a 10 mm diameter showed different results, and the steel balls obtained better conversions than agate balls (Table 6, entry 2 and 4). This result can be explained by the difference in the density of the two materials—the higher density of steel in relation to agate results in higher conversions. Furthermore, as described in the literature data,²⁷ the use of balls and vials of the same material is better than using different materials.

Evaluation of the Wear of Milling Balls. The wear of milling balls for reactions performed in ball mills was also evaluated. The wear was quantified by mass loss (%) and loss of volume (%) for five steel balls with a diameter of 10 mm. Initially, new balls were measured with an analogical micrometer. The total reaction time during which the balls were used was 140 min. After this process, the balls were again measured. The mean diameter ($\sum \text{balls}/5$) was calculated to be 9.977 mm. Then, through the relationship with the initial average diameter (10 mm), an average volume loss of 0.69% per ball was determined. Subsequently, calculations were done to evaluate the average mass loss of the balls. The balls were weighed to obtain the initial mass (4.1 g). After 140 min reaction, the balls were weighed again, and the average mass of the balls used was found to be 4.04 g. Thus, the value for the mass loss was 1.46% on average per ball.

Series of 1*H*-Pyrazole Derivatives. After studying the reaction parameters, a series of 1*H*-pyrazole compounds were obtained by varying enaminone **1** (Table 7). The best condition established (Table 3, entry 7) was used for the synthesis of a series of 1*H*-pyrazoles; however, it was observed that only enaminone **1a** achieved 100% conversion. Therefore, when the enaminones **1b–h** were used, the reaction time was

Table 7. Yields of Isolated Products Obtained in Reactions between Enaminones (1a–h), Hydrazine Hydrochloride (2), and *p*-TSA in a Ball Mill^a and for the Grinding Method^b



entry	comp.	R ¹	time (min)	yield (%) ^a	yield (%) ^b
1	3a	C ₆ H ₄	3	80	90
2	3b	4-CH ₃ C ₆ H ₄	4	77	75
3	3c	4-CH ₃ OC ₆ H ₄	4	79	91
4	3d	4-FC ₆ H ₄	4	67	72
5	3e	4-BrC ₆ H ₄	4	82	85
6	3f	4-IC ₆ H ₄	4	84	-
7	3g	Naft-2-yl	4	83	-
8	3h	Fur-2-yl	4	70	65

^aReaction conditions: 3 mmol of 1a, 3.6 mmol of 2, 10 mol % of *p*-TSA, 3 min, steel beaker (25 mL), steel milling balls (5 mm × 10 mm), and 450 rpm. ^bReaction conditions: 1 mmol of 1a, 1.2 mmol of 2, 20 mol % of *p*-TSA, and 6 min.²⁰

increased to 4 min, and this resulted in a product conversion of 100%. The yield for this series of compounds using the ball mill was compared with the grinding method (Table 7, entries 1–8). The use of a ball mill as an activation method has some advantages over the grinding method, for example, decreasing the reaction time, reducing the amount of catalyst, and, in particular, allowing better reproducibility because there is control of the input power, which means greater reliability of the results obtained.

Melt Phase. Some reactions without solvent, which involve macroscopic organic solids, occur through a molten or liquid phase (melt phase). These organic reactions do not occur in a solid state because they involve the formation of a liquid phase.³³ This liquid phase is probably due to the formation of high thermal energy regions (hot spots) generated by collisions with the grinding balls and the reagents.^{7,8} The theory of hot spots is related to high temperatures (~1000 °C) at shorter times (between 10⁻⁴ and 10⁻³ s⁻¹).³⁴ Some studies performed with different organic reactions identified that the liquid phase corresponds to the existence of a eutectic mixture, which occurs when the mixture's melting temperature is below the melting point of each reagent.^{7,8} In this work, it was found that all reactions that lead to the formation of products go through a liquid phase that is probably related to the melt phase (Figure 4a). The reaction performed without *p*-TSA resulted in 0% conversion. Thus, one can conclude that there is no liquid phase without the *p*-TSA (Figure 4b). Additionally, the liquid phase was not observed in the milling of the mixture of hydrazine hydrochloride and *p*-TSA (Figure 4c). The observation of a liquid phase during the formation of products 3a and 3d–h was detected between 1 and *p*-TSA. When products 3b and 3c were formed, the liquid phase was observed only after the addition of hydrazine 2 (Figure 4d). The formation of a liquid phase for compounds 3a and 3d–h was confirmed by differential scanning calorimetry (DSC) experiments. The DSC results show that all mixtures have a melting point lower than the melting point of the pure separated reagents.

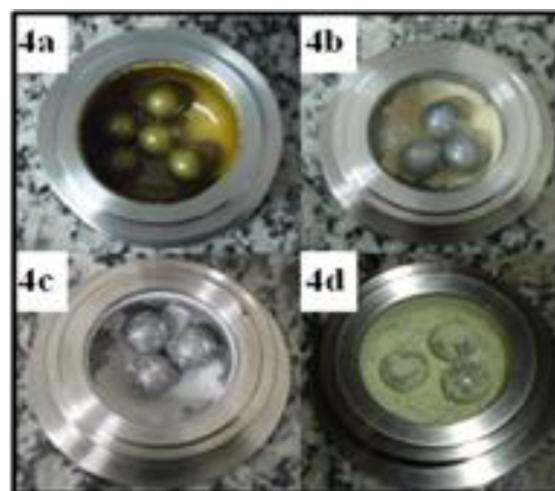


Figure 4. Melt phase evaluation. Liquid phase formation between 1c, 2, and *p*-TSA (4a). Reaction between 1c and 2 without catalyst (4b). Reaction of 2 and *p*-TSA (4c). Reaction between 1c and *p*-TSA (4d).

CONCLUSIONS

A fast and solvent-free method for the synthesis of 1H-pyrazoles in a ball mill was developed, and the scope of application was shown with substrate screening. After studying the reaction parameters, the optimum condition was determined to be 3 min, 450 rpm, with five stainless steel balls of 10 mm diameter, and using 10 mol % of *p*-TSA. The short reaction time, lower rotation frequency, and optimum number and optimum material of the balls results in energy savings. The use of an exact amount of a specific catalyst allows the reduction of reactants. The reduced waste generated, the non-addition of milling aids, and the non-purification of the products makes this green chemistry method a real alternative to conventional protocols. In terms of mechanical features, the experiments also showed a high dependence on time and the number of balls because a greater number of balls makes the collisions between the balls and the beaker less effective. The use of balls and a steel milling beaker equates to more expressive results than when agate is used, probably due to the higher density of this material.

EXPERIMENTAL SECTION

Materials. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purifications.

Characterization. ¹H and ¹³C NMR spectra were recorded on a Bruker DPX 400 (¹H at 400.13 MHz and ¹³C at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ±0.01 ppm) and using CDCl₃/TMS solutions. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector and autosampler cross-linked to a HP-5 capillary column (30 m length, 0.32 mm internal diameter), and He was used as the carrier gas. The melting points of compounds were determined using a Microquímica MQAPF 302. The DSC analysis was determined by MDSC Q2000 (Tzero DSC technology, TA Instruments, Inc., U.S.A.). A mechanical cooling system was used for the experimental measurements. Dry high purity (99.999%) nitrogen gas was applied as the purge gas (50 mL min⁻¹). The instrument was initially calibrated in the standard MDSC mode using the extrapolated onset temperatures of the melting indium (156.60 °C) at a heating rate of 10 °C min⁻¹ and the heat from the fusion of indium (28.71 J g⁻¹). The heat capacity calibration was done by running a standard sapphire (α-Al₂O₃) measurement at the

experimental temperature. The heating rate used for the samples was $10\text{ }^{\circ}\text{C min}^{-1}$ from 25 to $300\text{ }^{\circ}\text{C}$, and the sample amount used was between 1 and 5 mg. The sample mass was weighed on a Sartorius M500P microbalance with an accuracy of $\pm 0.001\text{ mg}$. Samples were crimped in hermetic aluminum pans with lids. The milling ball experiments were performed in a Retsch PM100 planetary mill (Retsch GmbH, Germany) using stainless steel and agate balls of 5.0, 10.0, and 15 mm diameter in a stainless steel beaker (25 mL) at room temperature. The measurements of the diameters of the balls were done using a Pantech analogical external micrometer with cast and enameled arc steel with 0–25 mm capacity, 0.01 mm grade, and $\pm 0.002\text{ mm}$ accuracy.

Typical Procedure for Enaminones (1a–h).²⁰ In a flask connected to a reflux condenser, the ketone (20 mmol), *N,N*-dimethylformamide dimethyl acetal (24 mmol), dry toluene (10 mL), and $\text{BF}_3\cdot\text{OEt}_2$ (3 drops) were added. The reaction was performed over 24 h at $95\text{ }^{\circ}\text{C}$. After completion of the reaction time, the solvent was evaporated in a rotary evaporator under reduced pressure, and the solids obtained were recrystallized in hexane.

Typical Procedure for the 1*H*-Pyrazoles (3a–h). Enaminone 1a–h (3 mmol), hydrazine hydrochloride 2 (3.6 mmol), and *p*-TSA (*p*-toluenesulfonic acid, 10 mol %) were placed in a steel milling beaker (25 mL) equipped with five steel milling balls (10 mm diameter). The beaker was sealed and the parameters, such as rotation frequency (450 rpm) and milling time, were set, and then the milling process was started. The reaction mixtures were ball milled for 3 min (for 3a) or 4 min (for 3b–h) in a planetary ball mill. After the milling process, the beakers were opened, and the milling balls were removed. When the reaction was complete, chloroform (20 mL) was added to the mixture, and this was washed three times with 20 mL of water and dried with anhydrous Mg_2SO_4 .

■ ASSOCIATED CONTENT

● Supporting Information

Spectral data for characterization of products and visual aspects of final state of reaction. 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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