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Advanced Mechanochemistry Device for Sustainable Synthetic Processes

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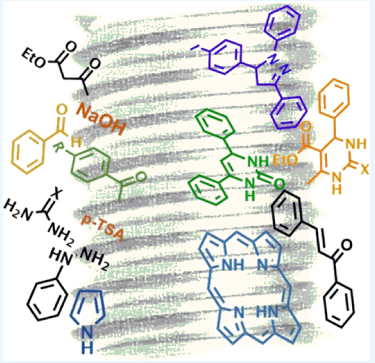
ABSTRACT: Mechanochemistry is an alternative for sustainable solvent-free processes that has taken the big step to become, in the near future, a useful synthetic method for academia and the fine chemical industry. The apparatus available, based on ball milling systems possessing several optimizable variables, requires too many control and optimization experiments to ensure reproducibility, which has limited its widespread utilization so far. Herein, we describe the development of an automatic mechanochemical single-screw device consisting of an electrical motor, a drill, and a drill chamber. The applicability and versatility of the new device are demonstrated by the implementation of di- and multicomponent chemical reactions with high reproducibility, using mechanical action exclusively. As examples, chalcones, dihydropyrimidinones, dihydropyrimidinethiones, pyrazoline, and porphyrins, were synthesized with high yields. The unprecedented sustainability is demonstrated by comparison of EcoScale and *E*-factor values of these processes with those previously described in the literature.



INTRODUCTION

The birth of mechanochemistry applied to organic chemistry is attributed to the preparation of halogenated derivatives of quinhydrone.[1] Despite recent mechanochemistry reset as a powerful technique for the development of sustainable chemical reactions for small organic molecule synthesis, polymer preparation, and solid−solid crystal engineering,[2] the development of dedicated reactors is still a challenge.

It is well established that chemical transformations in organic synthesis are a complex feature that requires energy.[3] The search for less expensive and less time consuming alternative energy sources has been disclosed by the use of microwaves, ultrasonic irradiation, and mechanical action.[2b,4] A mechanochemical reaction may be defined as a "chemical transformation" that is promoted by the absorption of mechanical energy, via compression, shear, or friction. In all cases, the energy input to laboratory-scale reactions is performed by grinding, using a mortar and pestle, or by energy shocks in planetary ball milling, vibrational ball milling, and extrusion.[2b,5]

Manual grinding, just requiring a mortar and a pestle, was the first approach used to perform this type of mechanochemical transformations[6] and, therefore, it could be used in all types of laboratories, including industry, academy, and secondary schools. However, the high dependence on the operator and consequent lack of process reproducibility led to the search and development of alternative machines. Among them, we highlight the ball milling instrument (high-speed ball milling or high-speed vibration milling) and mixer mills. These ball milling systems are automated apparatus that allow energy input control by adjusting the milling frequency.[7] Nevertheless, the reproducibility of mechanochemical transformations using these systems requires the optimization of multiple factors, namely, milling frequency, material and size of the milling balls and jars, and also the number of balls. The laboratory-scale systems were designed for batch processes but they have some constraints regarding large-scale transposition and reactor cleaning issues, particularly when the final reaction crude is not a free-flowing powder.[2b]

Herein, we describe the development of an advanced automatic device for mechanochemistry, which encompasses the simplicity of the classical mortar with the reproducibility of the automated systems. Its potential as an alternative mechanochemistry device for reaction screening and fast production of libraries of molecules was demonstrated by the implementation of several laboratory-scale synthetic processes of synthons for medicinal chemistry, namely, chalcones, dihydropyrimidinones, dihydropyrimidinethiones, pyrazolines, and porphyrins. Multigram experiments indicate the possibility of future transposition to industrial-scale applications. EcoScale and *E*-factor values are presented in support of the excellent

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sustainability of these mechanochemically driven synthetic processes.

RESULT AND DISCUSSION

Mechanochemical Device. The mechanical device is formed by a stainless steel single-screw drill (SSD) (10 cm long and 1 cm of diameter) rotating in a closed fixed stainless steel cylindrical chamber manufactured in our lab from a stainless steel cylinder in which a hole, 2.5 cm deep and with 1.05 cm of diameter (capacity 4.33 cm^3), was drilled. The drill is driven by a direct drive electrical motor (250 rpm) (Figure 1). To generate reactant flow to the top drilling head, i.e., between the surfaces of the drilling top head and the bottom cylindrical chamber, the drill device rotates in the scape direction. This movement originates intense shear stress and turbulent levels, allowing cavitation and intense mixing between reactants, under the achieved high-pressure conditions.

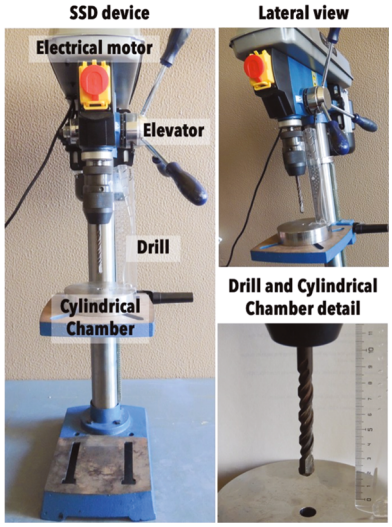
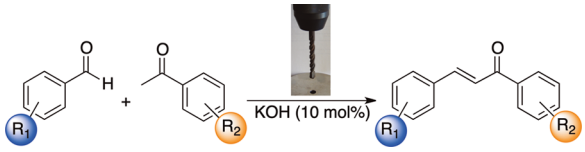


Figure 1. Single-screw drill (SSD) device for mechanochemistry.

To evaluate the mechanical effect on solid particle size, 3-hydroxybenzaldehyde was selected as the model compound. In a typical experiment, hydroxybenzaldehyde (50 mg) was placed into the reactor chamber and subjected to drilling for 1 min. The analysis of scanning electron microscopy (SEM) micrographs of the solids before and after drilling shows that the application of shear forces for 1 min promotes the reduction in the particle size to less than 1 μm, originating an almost homogeneous solid with well-defined braking points (Figure 2). This contributes to the increase in the available reactant surface, which is a key issue for the enhancement of solid reactivity.[8]

Device Application in Mechanosynthesis of Organic Compounds. Chalcones have several biological applications[9] and are also useful building blocks for the preparation of other biologically active compounds.[10] Therefore, the evaluation of the device performance in mechanosynthesis was started with chalcone synthesis, as a model reaction, based on the classic Claisen–Schmidt approach.[11] In a typical reaction, benzaldehyde (1 mmol), acetophenone (1 mmol), and solid powdered KOH (10 mol %) were placed in the cylindrical steel chamber of the device, and the mixture was subjected to mechanical action by drilling at 250 rpm, for 5 min, in the total absence of a solvent (Scheme 1).

Scheme 1. Alternative Sustainable Synthetic Approaches for Chalcone Synthesis Using the Single-Screw Drill Reactor Described Herein



Diphenylchalcone was obtained with 95% yield. The analysis of the reaction crude by gas chromatography–mass spectrometry (GC–MS) confirms the formation of the chalcone as a product (Figure 3). After this period, no evidence of self-condensation secondary products is detected. As a comparative reaction, the synthesis of diphenylchalcone was performed using the same reaction conditions under ball milling mechanical activation (MM400 reactor at 25 Hz) with 10 mL jars and two steel balls with 7 mm of diameter, for 10 min. In this case, no evidence of chalcone formation was observed by GC–MS analysis of the crude (Figure 3). These experiments are clear evidence of the advantages of the new mechanical device, applying shear forces when compared with the shock pressure used in ball milling systems. The increase in the reaction rate with shear stress has been previously explained and predicted by closely related atomic- and molecular-based theoretical models, considering plastic flow,

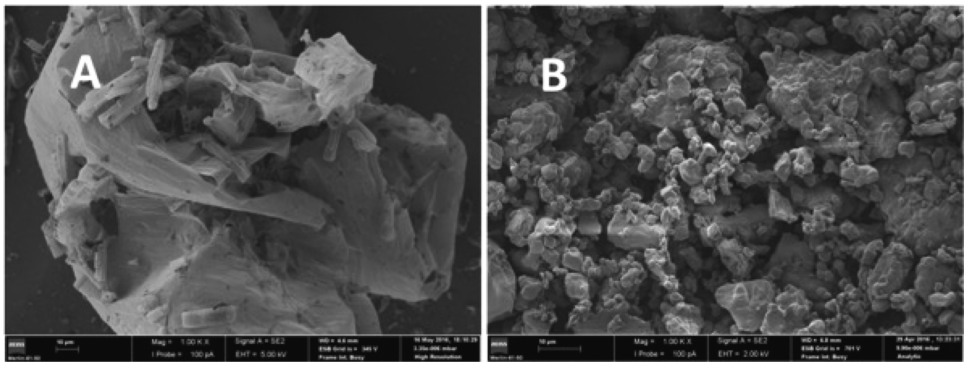


Figure 2. SEM micrograph of a commercial sample of 3-hydroxybenzaldehyde before ((A) scale 10 μm) and after 1 min of grinding in the mechanical device ((B) scale 10 μm).

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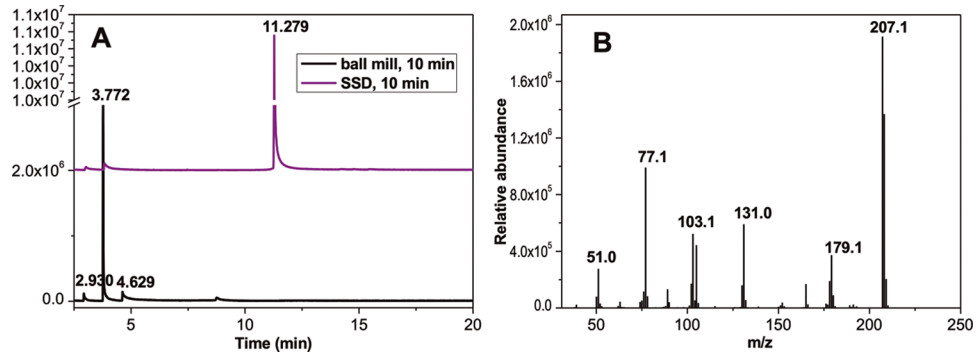
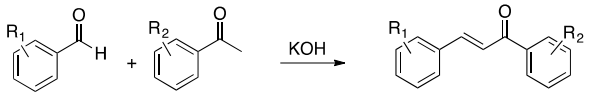


Figure 3. GC−MS chromatograms of the reaction crude after 10 min under mechanical action using the new mechanical device (purple line) and in the ball milling system MM400 (black line) (A) and mass spectra of the chalcone (M^+ = 207) corresponding to the chromatographic peak at 11.28 min (B).

high-pressure elastohydrodynamic friction, solid−solid friction, and atomic-scale wear.[12]

Using the SSD reactor and following the above-described procedure, chalcone **1** was obtained with 95% isolated yield (Table 2, entry 1) in just 5 min (10 mol % catalysts (KOH)). Three independent reactions afforded 95, 94, and 95% yields (94.6 ± 0.7, 95% confidence interval (CI) [93.9, 95.3]), which is strong evidence of the reproducibility of the reaction outcome achieved with this new SSD reactor. The general scope of this methodology was then evaluated using selected aromatic aldehydes and ketones, yields up to 99% having been obtained (Table 1).

Table 1. Effect of Substituents on Aldehydes and Acetophenones on the Mechanochemical Synthesis of Chalcones



entry	compound	R_1	R_2	yield (%)[a]
1	**1**	H	H	95
2	**2**	3-OCH_3	H	79
3	**3**	4-OCH_3	H	95 [94[b]]
4	**4**	3,4,5-OCH_3	H	86
5	**5**	2-NO_2	H	98
6	**6**	4-I	H	71
7	**7**	H	4-OCH_3	98
8	**8**	3,4,5-OCH_3	4-OCH_3	99
9	**9**	4-OCH_3	4-OCH_3	83
10	**10**	4-OCH_3	4-NO_2	98
11	**11**	3,4,5-OCH_3	4-NH_2	98

[a]Yields obtained by drilling 1 mmol of aldehyde, 1 mmol of acetophenone, and 10 mol % of KOH (10 mol %), in the SSD device for 5 min followed by recrystallization from ethanol. Yield values are the mean of two independent experiments; in all cases, the standard deviation was below 3. [b]One-gram scale-up (5×).

It is noteworthy that, regardless of the solid or liquid state of the reactant mixture, high yields were obtained (Table 1). Contrary to the other described methodologies,[13] the use of the SSD machine led to high overall yields, whether the nature of the R group is electron-donating (e.g., OCH_3) (Table 1, entries 2, 3, 7, and 8) or electron-withdrawing (e.g., NO_2) (Table 1, entries 5 and 10). In addition, this synthetic process gives a notable improvement in the synthesis of aminated chalcones, well reckoned medicinal chemistry building blocks, since it avoids the use of the previous multistep low-yield synthetic strategies (20−60%).[14] A remarkable result was obtained when 4-aminoacetophenone was condensed with 3,4,5-trimethoxybenzaldehyde, allowing the isolation of the corresponding chalcone **11** in excellent yield (98%, Table 1, entry 11).

As a selected example, the synthesis of chalcone **3** was performed under a multigram scale, using methoxybenzaldehyde and acetophenone (5 mmol), and the overall isolated yields were similar to those previously obtained in small scale conditions (94%, Table 1, entry 3). These results demonstrate that the new SSD device allows reaction scale-up to the gram scale.

The Biginelli reaction,[15] involving Lewis or Brønsted acid-catalyzed condensation of an aldehyde, a *β*-ketoester, and urea or thiourea, ranks as one of the most recognized and widely employed multicomponent reactions for the preparation of pharmacologically relevant 3,4-dihydropyrimidines bearing substituents at the C-4, C-5, and C-6.[16] Therefore, we evaluated the device usefulness for performing multicomponent reactions, aiming at the synthesis of N-heterocyclic compounds with diverse applications in medicinal chemistry, namely, dihydropyrimidinones, dihydropyrimidinethiones, and pyrazolines (Scheme 2).

In a typical reaction, the arylaldehyde (2.5 mmol), methyl acetoacetate (2.5 mmol), urea or thiourea (2.5 mmol), and *p*-toluenesulfonic acid (8 mol %) as catalysts were placed in the drilling jar. Then, the mixture was subjected to mechanochemical activation by drilling for 20 min. After work-up, the desired Biginelli compounds **12**−**15** were obtained in high yields without the need for any additional solvent (Table 2, entries 1−4). This SSD device allowed the synthesis of dihydropyrimidinones **12**−**14** via a multicomponent reaction, in yields similar to those previously reported,[17] avoiding the use of solvents and decreasing energy consumption since the reaction is performed in very short reaction times.

Another relevant example of the versatility of this new device is the synthesis of methyl 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**15**), an analogue of monastrol, a well know anticancer drug. This dihydropyrimidinethione was obtained in good yield (Table 2, entry 4) despite low reactivity of thiourea when compared with urea under the solvent-free conditions described.

The SSD machine was also used for the synthesis of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ones or thiones. These

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Scheme 2. Multicomponent Reactions for the Synthesis of Dihydropyrimidinones, Dihydropyrimidinethiones, and Pyrazolines under Mechanical Activation

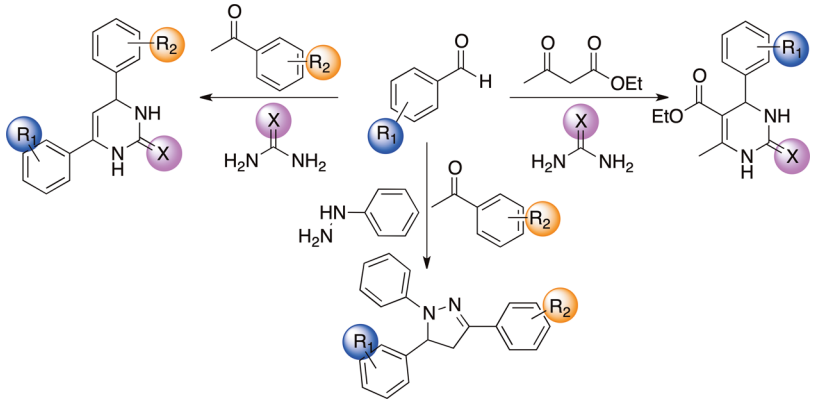
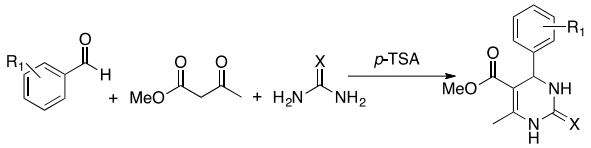


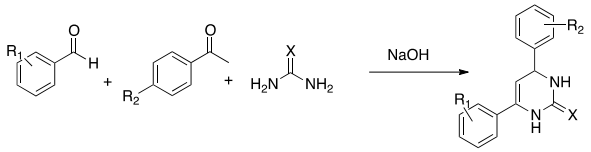
Table 2. Synthesis of Biginelli Compounds and Monastrol Derivatives



entry	compound	R_1	X	yield (%)[a]
1	**12**	4-OCH_3	O	98
2	**13**	3,4,5-OCH_3	O	96
3	**14**	H	O	98
4	**15**	3-OH	S	55[b]

[a]Yields obtained by drilling 2.5 mmol of aldehyde, 2.5 mmol of methyl acetoacetate, 2.5 mmol of urea, and 2 mol % of *p*-toluenesulfonic acid (*p*-TSA) in the SSD device for 20 min followed by recrystallization from ethanol. Yield values are the mean of two independent experiments; in all cases, the standard deviation was below 3. [b]Yield obtained by drilling a mixture of 2.5 mmol of 3-hydroxybenzaldehyde, 2.5 mmol of methyl acetoacetate, 2.5 mmol of thiourea, and 2 mol % of *p*-TSA in the SSD device for 20 min, followed by recrystallization in ethanol.

Table 3. Synthesis of 4,6-Diaryl-dihydropyrimidinones and Thiones 16−19



entry	compound	R_1	R_2	X	yield (%)[a]
1	**16**	H	Br	O	80[b]
2	**17**	H	Br	S	50
3	**18**	4-Br	Cl	S	96
4	**19**	3-OH	Br	S	47

[a]Yields obtained by drilling 5 mmol of the aldehyde, 5 mmol of ketone, 7.5 mmol of thiourea, and 5 mmol of NaOH in the SSD device for 5 min, followed by recrystallization from ethanol. Yield values are the mean of two independent experiments; in all cases, the standard deviation was below 3. [b]Yield obtained by drilling 5 mmol of aldehyde, 5 mmol of ketone, 7.5 mmol of urea, and 5 mmol of NaOH in the SSD device for 5 min, followed by recrystallization from ethanol.

types of compounds could be obtained using a one-step solvent-free methodology via condensation of arylaldehydes with acetophenones and urea catalyzed by a Lewis acid.[18] Alternatively, a two-step methodology involving the synthesis of chalcone followed by condensation with thiourea may be used.[19]

The use of the SSD reactor allowed the preparation of 4,6-diaryldihydropyrimidin-2(1*H*)-ones and thiones **16−19**, with yields up to 96%, through a solvent-free multicomponent reaction. In a typical reaction aldehyde, acetophenone, urea or thiourea (1:1:1.5 ratio), and NaOH (1 equiv) were drilled at room temperature for 10 min, and the desired 4,6-diaryl-dihydropyrimidinones and thiones were obtained in good yields, particularly considering that it is a three-component reaction and the low reactivity of thiourea when compared with urea (Table 3, entries 1−4). This is another relevant example to support the versatility of the new device for mechanochemistry.

Pyrazoline **20** was also obtained under mechanical activation via a multicomponent reaction of aldehyde, acetophenone, and phenylhydrazine. In a typical reaction, 4-iodobenzaldehyde (1.5 mmol), acetophenone (1.5 mmol), phenylhydrazine (2.25 mmol), and solid powdered KOH (1.5 mmol) were placed in the cylindrical steel chamber of the device, and the mixture was subjected to mechanical action by drilling for 1 h, in the total absence of the solvent (Scheme 3). Compound **20** was obtained, after recrystallization in ethanol, with 42% yield. It is worth mentioning that, under drilling conditions, it was possible to obtain the pyrazoline in one-step, solvent-free conditions, avoiding the isolation step.[20] The presence of iodine makes compound **20** a powerful synthon for the development of multifunctional molecules with great interest for medicinal chemists.

Finally, the SSD device was used for the mechanochemical synthesis of porphyrins. These compounds are tetrapyrrolic macrocycles with diverse uses as catalysts,[21] in the development of new materials[22] and also as active compounds in various biological applications.[23] The synthesis of these compounds was recently achieved under microwave irradiation[24] and under mechanical activation[25] using ball milling devices, reaching remarkable sustainability scores when compared with the more classic methodologies. The great relevance of porphyrins in several industrial applications motivated the evaluation of their synthesis using this new device.

5,10,15,20-Tetrakis(4-methoxyphenyl)porphyrin, selected as a model compound, was successfully synthesized in a two-step

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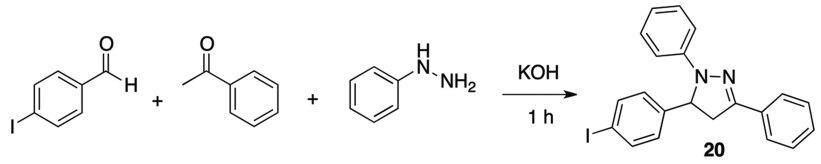
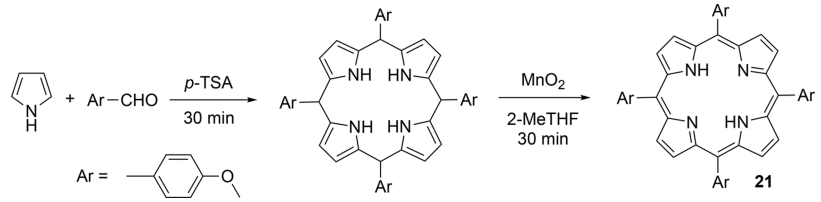
Scheme 3. Multicomponent Reaction for the Synthesis of Pyrazoline 20



Scheme 4. Two-Step Synthesis of 5,10,15,20-Tetrakis(4-methoxyphenyl)porphyrin



methodology under mechanical activation using our SSD device. Briefly, the porphyrinogen was obtained by drilling an equimolar mixture of pyrrole and 4-methoxyphenylbenzaldehyde (2.5 mmol) in the presence of *p*-toluenesulfonic acid (*p*-TSA) (0.5 mmol) for 30 min. Then, the reaction crude (pink solid) was oxidized to porphyrin by drilling it in the presence of MnO_2 (10 mmol) and 0.2 mL of 2-methyltetrahydrofurane (2-MeTHF) for 30 min. After work-up, porphyrin **21** was obtained with 20% yield (Scheme 4).

Sustainability. To evaluate the sustainability of these new synthetic processes using mechanochemical reactions with the SSD device and to compare them with those previously described in the literature, *E*-factor[26] and EcoScale[27] values were determined. The data are presented in Table 4.

Table 4. Sustainability Score

entry	reference	yield	*E*-factor	EcoScale
	Chalcone Synthesis			
1	SSD device	95[a]	0.17	74.5
2	Shan et al.[28]	92[a]	0.51	78
3	Zohdi et al.[29]	85[a]	0.60	74.5
4	Palleros[13]	92[b]	0.39	78
	Biginelli Synthesis			
5	SSD device	98[c]	0.22	76
6	M'hamed[17c]	98[c]	0.16	81
7	Bose[17a]	92[c]	0.50	73.5
	4,6-Diaryldihydropyrimidinones			
8	SSD device	82[d]	0.78	63
9	Wang et al.[18a]	82[e]	12.70	47
10	Wang et al.[18b]	94[e]	0.50	62
11	Sabitha et al.[18c]	87[e]	3.65	47.5
	Pyrazoline			
12	SSD device	42	1.70	18
13	Su et al.[20]	87	2.72	40.5
	Porphyrins			
14	SSD device	20	10.37	17
15	Pineiro et al.[25a]	10	21.74	9.5
16	Pereira et al.[24a]	14	7.70	37

[a]Yield obtained for diphenylchalcone. [b]Yield obtained for (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one. [c]Yield obtained from the reaction with benzaldehyde. [d]Yield obtained for compound **16**. [e]Yield obtained for 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one. [f]Considering the synthesis of chalcone described in this work.

The *E*-factor is the ratio of the mass of waste per mass of product: *E*-factor = (total mass of waste/mass of product). Therefore, the lower the value, the more sustainable the process can be considered. The EcoScale is a postsynthetic tool that evaluates other aspects of the synthetic process, namely, the toxicity of the reactants, energy input (time and temperature of the reaction), and procedure safety (see the table in the Supporting Information). All of the procedures to be analyzed start with 100 points, and the points are subtracted as each of the evaluated parameters deviates from the ideal of sustainability. Therefore, the higher the value, the more sustainable the process will be.

Regarding the synthesis of chalcones, the values calculated for both *E*-factor and EcoScale show that the use of the SSD device and solvent-free conditions enhance the sustainability of the process (Table 4, entries 1 and 4). The use of catalytic quantities of KOH as a catalyst and the increase of the reaction yield up to 95% decrease the *E*-factor to 0.17, the lowest value obtained so far for the synthesis of these compounds. Moreover, the low temperature and short reaction time, combined with the smallest amount of KOH used so far, led to the highest EcoScale value (74.5 points).

The comparison of the *E*-factor and EcoScale values of the mechanochemical process using the SSD device with those previously described for the synthesis of dihydropyrimidinones through the multicomponent Biginelli reaction is presented in Table 4, entries 5−7. In this case, the high reaction yield obtained after simple recrystallization in ethanol, associated with the elimination of the solvent and rational use of the acid catalyst, gave the lowest *E*-factor values (0.22) obtained so far and EcoScale of 76 (Table 4, entry 5).

The multicomponent synthesis of 4,6-diaryldihydropyrimidinones and thiones (Table 4, entries 8−11) catalyzed by NaOH under mechanical drilling conditions achieved sustainability scores of 0.78 for the *E*-factor and 63 for the EcoScale (Table 4, entry 8). These scores are comparable with the solvent-free acid-catalyzed multicomponent reaction under microwave irradiation (Table 4, entry 10). The use of a solvent either in the multicomponent acid-catalyzed reaction (Table 4, entry 10) or a two-step methodology using a base as a catalyst (Table 4, entry 11) causes a deviation from the ideal values of sustainability.

The pyrazoline ring was successfully synthetized from aldehyde, acetophenone, and phenylhydrazine using a multicomponent methodology (Table 4, entry 12). The absence of

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the solvent and the use of a catalytic amount of KOH allowed us to obtain a good *E*-factor value (*E*-factor = 1.70, Table 4, entry 12), significantly lower than that obtained for the mechanically activated two-step methodology in the presence of a grinding auxiliary (silica-gel).[20]

Finally, the sustainability scores for the synthesis of porphyrins in the two-step methodology under mechanical activation were calculated (Table 4, entry 14) and compared with those previously described for methodologies using a ball milling device (Table 4, entry 15), showing the improvement achieved by drilling. However, these values are below the *E*-factor and EcoScale values previously obtained by some of us using the water-microwave methodology (Table 4, entry 16).

In summary, these metric calculations reinforce the effective improvement in the reaction sustainability under mechanical activation, using the SSD device, by drilling at room temperature, in solvent-free conditions.

CONCLUSIONS

The home-made single-screw drill device (SSD device) was successfully applied for the automated mechanical activation of several organic reactions, allowing the sustainable synthesis of chalcones, dihydropyrimidinones, thiones, pyrazoline, and porphyrins at room temperature and in short reaction times.

The mechanical activation of solid and liquid mixtures of reactants allowed the preparation of these families of compounds with high yields. The solvent-free, one-pot, and multicomponent procedures developed are in line with the first and eighth principles of green chemistry that postulate great interest in the development of synthetic strategies, avoiding waste and reducing derivatives, respectively. The low *E*-factor and high EcoScale scores obtained for all of the synthetic methodologies also show a remarkable improvement in sustainability when compared with previously described methods. The diversity of compounds synthetized with the SSD device combined with high sustainability scores and easy transposition to multigram scale, open the way for future applicability of the new SSD device to the development of green methodologies for the synthesis of libraries of organic compounds, both at the academic and industrial levels.

EXPERIMENTAL SECTION

Aldehydes, acetophenones, urea, thiourea, phenylhydrazine, acetoacetate, pyrrole, KOH, NaOH, ethanol, and 2-methyltetrahydrofurane were purchased from Sigma-Aldrich and were used without further purification. NMR spectra were recorded on a Bruker Avance 400 spectrometer, operating at 400.13 MHz for ^{1}H NMR and 100.62 MHz for ^{13}C NMR. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS). High-resolution mass spectrometry (HR-MS) analysis was carried out on a Bruker micrOTOF apparatus, equipped with a selective electrospray ionization (ESI) detector.

Preparation of Chalcones (1−11). The desired aldehyde (1 mmol), acetophenone (1 mmol), and solid powdered KOH (10 mol %) were placed in a cylindrical steel chamber of the single-screw drill device. Then, mechanical action was applied by drilling at 250 rpm for 5 min. The reaction crude was dissolved in ethanol, and the chalcone was crystallized in pure form as a white or pale-yellow solid.

*3-Phenyl-1-phenylprop-2-en-1-one (**1**).* Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.07−7.99 (m, 2H), 7.82 (d, J = 15.7 Hz, 1H), 7.65 (dd, J = 6.7, 2.8 Hz, 2H), 7.62−7.47 (m, 4H), 7.45−7.39 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 190.70, 144.98, 138.32, 135.00, 132.91, 130.67, 129.08, 128.75, 128.62, 128.57, 122.22. Characterization is in accordance with that previously described.[30]

*3-(3-Methoxyphenyl)-1-phenylprop-2-en-1-one (**2**).* Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.06−7.95 (m, 2H), 7.77 (d, J = 15.7 Hz, 1H), 7.62−7.45 (m, 4H), 7.33 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 6.96 (dd, J = 8.2, 2.5 Hz, 1H), 3.84 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 190.65, 160.03, 144.86, 138.25, 136.33, 132.90, 130.04, 128.72, 128.60, 122.47, 121.18, 116.40, 113.54, 55.42. Characterization is in accordance with that previously described.[30]

*3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (**3**).* Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.03 (d, J = 8.9 Hz, 2H), 7.73 (d, J = 15.6 Hz, 1H), 7.53 (m, 6H), 6.99 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 188.53, 163.70, 142.65, 134.16, 132.30, 131.05, 130.98, 129.85, 124.67, 122.54, 114.05, 55.66. Characterization is in accordance with that previously described.[30]

*3-(3,4,5-Trimethoxyphenyl)-1-phenylprop-2-en-1-one (**4**).* Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.06−7.96 (m, 2H), 7.71 (d, J = 15.6 Hz, 1H), 7.58 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.40 (d, J = 15.6 Hz, 1H), 6.88 (s, 2H), 3.94 (s, 6H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 190.70, 153.61, 145.15, 140.59, 138.41, 132.85, 130.48, 128.74, 128.60, 121.61, 105.80, 61.12, 56.35. Characterization is in accordance with that previously described.[30]

*3-(2-Nitrophenyl)-1-phenylprop-2-en-1-one (**5**).* Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.13 (d, J = 15.7 Hz, 1H), 8.10−8.05 (m, 1H), 8.04−7.98 (m, 2H), 7.63 (m, 7H), 7.32 (d, J = 15.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 190.68, 140.35, 137.56, 133.71, 133.29, 131.50, 130.49, 129.40, 128.94, 128.87, 127.55, 125.15. Characterization is in accordance with that previously described.[30]

*(E)-1-(2-Iodophenyl)-3-phenylprop-2-en-1-one (**6**).* Yield: 71%; ^{1}H NMR (400 MHz, acetone), δ, ppm: 8.00 (d, J = 7.88 Hz, 1H), 7.73 (t, J = 3.66 Hz, 2H), 7.53−7.59 (m, 1H), 7.47−7.51 (m, 1H), 7.46 (d, J = 2.20 Hz, 2H), 7.40−7.46 (m, 2H), 7.28 (dt, J = 1.65, 7.60 Hz, 1H), 7.18 (d, J = 16.12 Hz, 1H); ^{13}C NMR (101 MHz, acetone), δ, ppm: 196.1, 147.3, 146.0, 140.9, 135.6, 132.3, 131.8, 130.0, 129.6, 129.4, 129.2, 126.6, 92.6. Characterization is in accordance with that previously described.[30]

*1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one (**7**).* Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.05 (dd, J = 7.5, 1.5 Hz, 2H), 7.81 (d, J = 15.7 Hz, 1H), 7.64 (dd, J = 6.5, 3.0 Hz, 2H), 7.55 (d, J = 15.7 Hz, 1H), 7.45−7.35 (m, 2H), 6.99 (dd, J = 7.5, 1.5 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 188.85, 163.57, 144.09, 135.22, 131.23, 130.95, 130.45, 129.05, 128.48, 122.03, 113.98, 55.62. Characterization is in accordance with that previously described.[30]

*3-(3,4,5-Trimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**8**).* Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.05−8.02 (m, 2H), 7.71 (d, J = 15.6 Hz, 1H), 7.41 (d, J = 15.6 Hz, 1H), 7.01 (dd, J = 6.6, 4.9 Hz, 2H), 6.88 (s, 2H), 3.92 (s, 6H), 3.89 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 188.84, 163.54, 153.60, 144.27, 140.42, 131.27, 130.93, 130.72, 121.39, 113.97, 105.72, 61.13, 56.36,

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55.63. Characterization is in accordance with that previously described.[30]

*1,3-Bis(4-methoxyphenyl)prop-2-en-1-one (**9**).* Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.06−8.01 (m, 2H), 7.78 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 15.6 Hz, 1H), 7.01−6.96 (m, 4H), 3.89 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 188.94, 163.42, 161.66, 143.96, 131.52, 130.85, 130.25, 127.98, 119.73, 114.53, 113.93, 113.75, 55.63, 55.56. Characterization is in accordance with that previously described.[30]

*3-(4-Methoxyphenyl)-1-(4-nitrophenyl)prop-2-en-1-one (**10**).* Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.33 (t, J = 9.5 Hz, 2H), 8.12 (dd, J = 8.7, 6.6 Hz, 2H), 7.82 (d, J = 15.6 Hz, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 15.6 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 189.15, 162.42, 150.08, 146.86, 143.61, 130.77, 129.45, 127.19, 124.01, 123.95, 119.10, 114.75, 77.48, 77.36, 77.16, 76.84, 55.63. Characterization is in accordance with that previously described.[30]

*1-(4-Aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**11**).* Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.90 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 15.5 Hz, 1H), 7.41 (d, J = 15.5 Hz, 1H), 6.82 (s, 2H), 6.67 (d, J = 8.2 Hz, 1H), 3.88 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 188.04, 153.43, 151.39, 143.25, 140.01, 131.10, 130.88, 128.25, 121.41, 113.84, 113.66, 105.49, 60.99, 60.77, 56.22. Characterization in accordance with that previously described.[31]

Preparation of 4-Aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylates (12−14). A mixture of the selected aldehyde (2.5 mmol), methyl acetoacetate (2.5 mmol), urea (2.5 mmol), and 2 mol % of *p*-TSA was placed in the cylindrical chamber and mechanical action was applied by drilling for 20 min at room temperature. After drilling, a yellow gummy solid was obtained. This was recrystallized from ethanol, yielding the desired 3,4-dihydropyrimidin-2(1*H*)-one as a pale-yellow solid.

*Methyl 4-(4-Methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate (**12**).* Yield: 98%, ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 9.06 (bs, 1H), 7.54 (bs, 1H), 7.15 (d, J = 8.4, 2H), 6.81 (d, J = 8.4, 2H), 5.101 (d, J = 2.8, 1H), 3.75 (s, 3H), 3.54 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 165.38, 158.13, 151.90, 147.92, 136.73, 127.07, 113.22, 99.06, 54.60, 53.05, 50.18, 17.56. Characterization is in accordance with that previously described.[17b]

*Methyl 4-(3,4,5-Trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate (**13**).* Yield: 96%, ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 9.11 (bs, 1H), 7.60 (bs, 1H), 6.50 (s, 2H), 5.12 (d, J = 3.2, 1H), 3.76 (s, 6H), 3.66 (s, 3H), 3.59 (s. 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 165.48, 152.53, 152.03, 148.39, 139.92, 136.639, 103.18, 98.54, 59.58, 55.54, 53.53, 50.34, 17.59. Characterization is in accordance with that previously described.[17b]

*Methyl 6-Methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate (**14**).* Yield: 98%, ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 9.09 (bs, 1H), 7.61 (bs, 1H), 7.30−7.19 (m, 5H), 5.16 (d, J = 2.8, 1H), 3.55 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 165.32, 151.86, 148.25, 144.58, 127.84, 126.67, 125.95, 98.74, 53.65, 50.18, 17.58. Characterization is in accordance with that previously described.[17b]

Preparation of 4-Aryl-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione-5-carboxylate (15). A mixture of the selected aldehyde (2.5 mmol), methyl acetoacetate (2.5 mmol), thiourea (2.5 mmol), and 2 mol % of *p*-TSA was placed in a cylindrical chamber of the single-screw drill device, and mechanical action was applied by drilling at 250 rpm for 20 min at room temperature. After drilling, a yellow gummy solid was obtained. This was recrystallized from ethanol, yielding the desired 3,4-dihydropyrimidine-2(1*H*)-thione as a pale-yellow solid. Yield: 55%, ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 10.18 (bs, 1H), 9.51 (bs, 1H), 9.23 (bs, 1H), 7.07 (t, J = 8, 1H), 6.65−6.62 (m, 3H), 5.10 (d, J = 3.6, 1H), 3.59 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$), δ, ppm: 174.00, 165.31, 157.28, 144.79, 144.44, 128.97, 116.64, 114.34, 113.09, 100.36, 53.69, 50.62, 17.0. Characterization is in accordance with that previously described.[17b]

Preparation of 4-(4-Chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (16). A mixture of the selected aldehyde (5 mmol), ketone (5 mmol), urea (7.5 mmol), and NaOH (5 mmol) was placed in the cylindrical chamber of the single-screw drill device and mechanical action was applied by drilling at 250 rpm, for 5 min, at room temperature. After drilling, a yellow gummy liquid was obtained. This was recrystallized from ethanol, yielding the desired 3,4-dihydropyrimidin-2(1*H*)-one as a white solid. Yield: 80%, ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm: 2.49 (bs, 2H), 6.38−6.94 (m, 5H), 7.07−7.27 (m, 5H). ^{13}C NMR (75 MHz, dimethyl sulfoxide (DMSO)), δ, ppm: 79.02, 97.30, 126.9, 128.9, 128.7, 129.7, 134.3, 137.4, 138.3, 164.0, 165.2. Characterization is in accordance with that previously described.[32]

Preparation of 4,6-Diaryl-3,4-dihydropyrimidine-2(1*H*)-thione (17−19). A mixture of selected aldehyde (5 mmol), ketone (5 mmol), thiourea (7.5 mmol), and NaOH (5 mmol) was placed in the cylindrical chamber of the single-screw drill device and mechanical action was applied by drilling at 250 rpm, for 5 min, at room temperature. After drilling, a yellow gummy liquid was obtained. Recrystallization from ethanol yielded 3,4-dihydropyrimidine-2(1*H*)-thiones as white solids.

*4-(4-Bromophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione (**17**).* Yield: 50%, ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm: 9.48 (bs, 1H), 8.99 (bs, 1H), 7.50−7.49 (m, 4H), 7.32−7.29 (m, 5H), 5.20 (s, 1H), 5.13 (s, 1H). ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm: 174.74, 142.92, 134.57, 133.17, 131.06, 128.26, 127.77, 125.56, 120.58, 99.68, 54.26. Characterization is in accordance with that previously described.[33]

*6-(4-Bromophenyl)-4-(3-clorophenyl)-3,4-dihydropyrimidine-2(1H)-thione (**18**).* Yield: 95.1%; ^{1}H NMR (400 MHz, DMSO): δ, ppm: 8.20 (d, 2H, J = 8.8 Hz); 7.87(d, 2H, J = 8.8 Hz); 7.67 (d, 2H, J = 8.4 Hz); 7.53 (d, 2H, J = 8.8 Hz); 5.45 (s, 1H); 5.15 (s, 1H). Characterization is in accordance with that previously described.[34]

*6-(4-Bromophenyl)-4-(3-hydroxifenyl)-3,4-dihydropyrimidine-2(1H)-thione (**19**).* Yield: 47.0%, ^{1}H NMR (400 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm: 9.47 (bs, 1H), 9.26 (bs, 1H), 8.91 (bs, 1H), 7.52−7.50 (m, 2H), 7.35−7.33 (m, 3H), 7.13 (t, J = 7.6, 1H), 6.76 (bs, 2H), 6.66 (d, J = 7.6, 1H), 5.22 (s, 1H), 5.03 (s, 1H); ^{13}C NMR (100 MHz, CCl_4/$(CD_3)_2SO$): δ, ppm: 174.66, 157.58, 145.16, 134.01, 133.35, 129.15, 128.37, 127.97, 125.61, 116.74, 114.39, 113.22, 100.72, 54.92; HR-MS (ESI):

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m/z = 283.08993 ($[M + H]^+$, $C_{16}H_{15}N_2OS$: required = 283.08996).

Preparation of 5-(4-Iodophenyl)-1,3-diphenyl-1*H*-pirazole (20). 4-Iodobenzaldehyde (1.5 mmol), acetophenone (1.5 mmol), phenylhydrazine (2.25 mmol), and solid powdered KOH (1.5 mmol) were placed in the cylindrical steel chamber of the single-screw drill device and mechanical action was applied for 1 h, at 250 rpm, in the total absence of the solvent. After mechanical action, the solid obtained was recrystallized from ethanol, yielding the desired pyrazole as a white solid in 42% yield (266 mg, 0.63 mmol). Yield: 42%, ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 7.72 (d, J = 6.9 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.39−7.34 (m, 3H), 7.20 (t, J = 7 Hz, 2H), 7.07 (dd, J = 13.6, 7.9 Hz, 4H), 6.81 (t, J = 6.6 Hz, 1H), 5.22 (dd, J = 12, 7 Hz, 1H), 3.83 (dd, J = 16.6, 12.7 Hz, 1H), 3.10 (dd, J = 16.9, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm = 152.2, 144.8, 142.5, 138.5, 138.4, 129.1, 128.9, 128.7, 128.1, 125.9, 119.5, 113.5, 93.1, 64.1, 43.6. Characterization is in accordance with that previously described.[35]

Synthesis of 5,10,15,20-Tetrakis(4-methoxyphenyl)-porphyrin (21). Pyrrole (2.5 mmol, 0.17 mL) and 4-methoxybenzaldehyde (2.5 mmol) were combined with *p*-toluenesulfonic acid (0.5 mmol, 95.1 mg) in the cylindrical steel chamber. The mixture was drilled at 250 rpm for 30 min, yielding a pink solid. Then, 5 equiv of MnO_2 and 0.2 mL of 2-methyltetrahydrofurane were added and the mixture was drilled again for 30 min. The reaction crude was washed with 2-methyltetrahydrofurane, filtered, and evaporated under vacuum. After work-up, 5,10,15,20-tetrakis(4-methoxyphenyl)-porphyrin was obtained in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm = 8.85 (s, 8H), 8.12 (d, 8H, J = 8.8 Hz), 7.28 (d, 8H, J = 8.8 Hz), 4.05 (s, 12H), −2.8 (s, 2H). Characterization is in accordance with that previously described.[36]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00521.

Metrics calculation, *E*-factor; metrics calculation, EcoScale; data for *E*-factor calculation for chalcone and Biginelli synthesis, 4,6-diaryldihydropyrimidinones synthesis, pyrazoline synthesis, and porphyrin synthesis (Tables S1−S4); data for EcoScale calculation for chalcone and Biginelli synthesis and 4,6-diaryldihydro-pyrimidinones, pyrazoline, and porphyrin synthesis (Tables S5 and S6) (PDF)

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Author Contributions

M. Pereira and M. Pineiro contributed to the experimental design and writing of the manuscript. J. Campos, J. Pimenta, and M. Pineiro, contributed to the design and development of the mechanical device. C. Gomes contributed to the synthesis of chalcones, dihydropyrimidinones, thiones, and porphyrin. L. Damas contributed to the synthesis of pyrazoline, C. Chaves and J. Quaresma contributed to the synthesis of chalcones and dihydropyrimidinones. C. S. Vinagreiro and G. Aquino contributed to the synthesis of chalcones.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

SSD, single-screw drill; *p*-TSA, *p*-toluenesulfonic acid; 2-MeTHF, 2-methyltetrahydrofuran

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