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Solvent-free mechanochemical route for green synthesis of pharmaceutically attractive phenol-hydrazones

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A series of hydrazones, as potential therapeutic agents, were successfully synthesized in a vibratory ball-mill from various substituted organic hydrazines and phenol aldehydes. The degrees of conversion were increased by high electronic density on the amino group of the hydrazine reactant, as well as low steric hindrance around both the reactive sites. In this particular case, the flexibility of the chain bearing the amino reactive site of hydrazine was highlighted as a factor influencing the reaction rate. The results showed that the hydrazones could be obtained in more than 99% of transformation, without concurring by-products. This is highly adapted to the synthesis of active pharmaceutical ingredients, requiring a high level of purity. Added to the fact that neither environmentally unadvisable reagent, none additive nor catalysts were added to achieve the transformation, this synthesis provides a good example and a prefiguration of an efficient green pharmaceutical process.

Introduction

Nowadays there is an urgent need for research and industry to invent new, clear and less expensive ways to produce chemicals. All areas of chemistry play important roles in this context. Among them, catalysis and solvent-free systems are the most explored, using different types of energy to perform reactions, including microwave, ultrasound, photochemical and mechanical procedures.[1-3]

Mechanochemistry has been used for a long time for inorganic materials to generate different phases in the area of mechanical alloying.[4,5] More recently, the possibility of using mechanical energy to synthesize organic molecules in milling devices opened up a new area of chemistry. Current application and advances of mechanochemistry can be found to almost all kinds of organic transformations such as cocrystals formation and classic organic syntheses.[6,7]

In the pharmaceutical area, where the concept of *Green Pharmacy* is more than ever newsworthy,[8-13] the mechanical action is used to produce transformation in molecular crystals to enhance properties such as tableting and bioavailability.[14-17] But, the applications of mechanochemistry for pharmaceuticals go beyond associations at a supramolecular level, including the improvement of active ingredients synthesis, as well as the design of new potential ones. As example, Tan et al. prepared sulfonyl-(thio)ureas, including anti-diabetic drugs, via mechanosynthesis.[18] But, in particular, mechanochemistry was used to develop nitrogen-containing heterocycles, a series well represented in many therapeutic classes. For example, phthalazoles,[19] phenazines,[20] pyrazoles, pyridazinones,[21] and pyrroles[22] were obtained by mechanosynthesis, but non-heterocyclic nitrogen-containing molecules were also synthesized under mechanical solid-state and solvent-free conditions, including peptides[23-25] imines, azomethines,[26,27] azines,[21] enamines[28] and hydrazones.[28-30] In addition to being a green process, many other attractive aspects of working without solvent were reported, as the yield was usually higher than 90% and generally ≥ 99%, and the selectivity reducing the formation of byproducts and eliminating purification steps for pharmaceutical ingredients and medicines.

The potential application of hydrazones as antioxidant agents, against sepsis and tuberculosis, as vasodilator to treat hypertension, and as antitumor agents, shows that the hydrazones class is considered an important one for new drug development.[31-34] Until now, they have been mainly synthesized by classical methods, involving the reaction of an hydrazine with a carbonyl compound under reflux conditions in diluted media. An industrial drawback is the amount of solvents used (ethanol or toluene usually) inducing a lot of waste and thermal energy needed for an overall time consuming process. In addition, water formation during the reaction may induce

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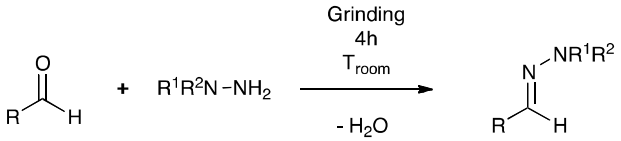
incomplete conversions. There are other reports of hydrazones and derivatives under solvent-free conditions using microwave irradiation to perform them in short times with high yield, but sometimes the use of small amounts of solvent is required and the amount of reagents used is often around 0.5-5 mmol.[35-38] In this context Hajipour et al. reported for the first time the synthesis of hydrazones and semicarbazone derivatives in quantitative yields by milling in mortar with sodium hydroxide and silica gel as solid support acting as facilitator.[38] Later on, Kaupp et al. obtained benzoylhydrazone by millin stoichiometric amounts of benzhydrazine and solid aldehyd ketone.[28] Similarly, by using the kneading method it possible to produce phenylhydrazones in a melt system.[29] N recently, Nun *et al.* carried out the synthesis of hydrazone quantitative yields by milling a large variety of prote hydrazines with equimolar amounts of carbonyl compou The subsequent N-alkylation of some of them was also repo by the same authors.[30]

Herein we report the mechanosynthesis of a phe hydrazones series obtained by the solid-state solvent- reaction of an aldehyde with the respective hydrazine. We l already synthesized phenolhydrazones using classical metl and shown to possess strong antioxidant properties cytoprotective effects against the oxidized Low Der Lipoproteins (LDL) that play a key role in the atheroger process and cardiovascular diseases.[39] The mechanosynth of hydrazones were carried out on 2g of reactants betv strictly one equivalent of each partner, in a vibratory ball- with a single ball at an average time of 4 hours at r temperature.

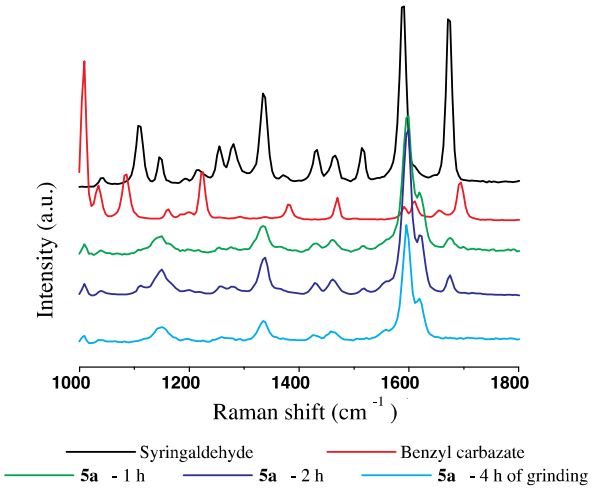
Results and discussion

The classical solvated methods to synthesize hydrazones are generally carried out at low concentration, and require times of 3 to 24 or even 48 hours in reflux of toluene or ethanol in order to obtain good yields. In this framework we applied the mechanical energy using a vibratory mill to produce 24 hydrazones (Table 1). In an aim to compare the respective reactivities of reactants under mechanochemical conditions, a series of hydrazones were synthesized, some of them already described using classical methods by our group.[31,39] Scheme 1 shows the general solid-state mechanosynthesis of hydrazones by reacting a hydrazine and an aldehyde.



Scheme 1 General synthesis of hydrazones in solid-sate by co-grinding of a hydrazine and an aldehyde.

Once the objective of the work was to investigate the production of hydrazones in solid-state, the mandatory conditions of choice of reagents was the melting point above the temperature of synthesis. As the reactions were carried out at room temperature all the reagents presented in Table 1 fulfill the requirement. The syntheses with hydralazine hydrochloride were performed in the presence of 1 equivalent of triethylamine (TEA) in order to liberate the base from its respective salt. Table 1 also summarizes for each synthesis, the time of grinding and the conversion obtained by analysis of ^{1}H NMR spectra. TLC showed the consumption of the reagents and the consequent appearance of the hydrazone, which was confirmed by ^{1}H and ^{13}C NMR analysis demonstrating final conversions of up to 99% (and thus yields) depending on the aldehyde-hydrazine couple and no byproducts were detected. In addition, the progress of the reactions can be followed by RAMAN analysis. This technique could be a rapid way to control mechanochemical reactions without using solvents as reported elsewhere.[40] As an example the reaction of syringaldehyde with



The hydrazones listed in Table 1 were obtained with a high transformation ratio in grinding times of 4h. ^{1}H NMR spectra revealed conversions with respect to the aldehydes and hydrazines over 90% in almost all the explored syntheses and no byproducts were found. In Table 1 we have also introduced conversions (if quantitative) and yields (where purification was needed) for a series of hydrazones obtained by us under classical conditions (1mmol of each reagent/30ml of solvent under reflux for 6-24h).[31,39] For hydralazine hydrochloride reagent the classical reaction was performed in the absence of base (triethylamine) and the hydrazone hydrochloride was isolated.

The mechanochemical route, maybe due to its original mechanism, seems to be more efficient when comparing the results with the classical ones under reflux and heat. With regard to the couplings with isoniazid, hydrazones are obtained through analogous conversions and yields between the classical and mechanochemical method. The same is true for benzyl carbazate where the conversions and yields are almost quantitative in both cases. For the 2-hydrazinobenzothiazole, reactions appear better under classical conditions, while for hydralazine hydrochloride and 3-aminorhodanine the mechanochemical route appears much more optimal. It is worth pointing out that with regard to the hydrazones formation with 3-aminorhodanin, conversion and yields can be greatly improved in favor of the mechanochemical process but also by performing the later reaction for 8h (tested as an example with this hydrazine); almost quantitative conversions and yields (no further purification needed) were obtained. This example is a clear illustration of the potential of mechanochemistry as a green route to synthesize active pharmaceutical ingredients. The reactivity of the hydrazines observed by mechanochemical

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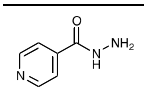
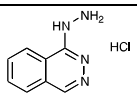
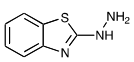
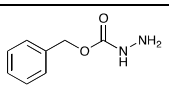
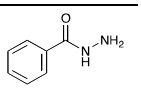
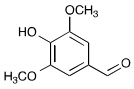
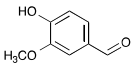
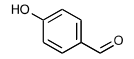
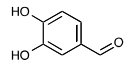
route could be explained as a result of electronic effects and the solid form influences.

Table 1 Solids aldehydes (column) and hydrazines (line) used for the synthesis of hydrazones and degree of conversion[a] for corresponding hydrazones for 4 hours of grinding as well as the yields[b] from classical method in parentheses.

		Hydrazines (R^1R^2N-NH_2)					
		1	**2**	**3**	**4**	**5**	**6**
	Aldehydes (RCHO)	 Isoniazid mp: 171-173 °C	 Hydralazine hydrochloride[c] mp: 273 °C	 2-hydrazonibenzothiazole mp: 198-202 °C	 3-aminorhodanine mp: 100-103 °C	 Benzyl carbazate mp: 65-68 °C	 Benzhydrazine mp: 112-114 °C
a	 Syringaldehyde mp: 110-113 °C	**1a** **90 %** (97 %)	**2a** **99 %** (75 %)	**3a** **92 %** (97 %)	**4a** **88 %** **≥ 99 %**[d] (70 %)	**5a** **≥ 99 %** (90 %)	**6a** **≥ 99 %**
b	 Vanillin mp: 81-83 °C	**1b** **90 %** (90%)	**2b** **99 %** (90 %)	**3b** **94 %** (99 %)	**4b** **84 %** **≥ 99 %**[d] (37 %)	**5b** **≥ 99 %** (99%)	**6b** **≥ 99 %**
c	 4-hydroxybenzaldehyde mp: 112-116 °C	**1c** **95 %**	**2c** **99 %**	**3c** **95 %**	**4c** **93 %** **≥ 99 %**[d]	**5c** **≥ 99 %**	**6c** **≥ 99 %**
d	 3,4-dihydroxybenzaldehyde mp: 150-157 °C	**1d** **88 %** (81 %)	**2d** **99 %** (81%)	**3d** **98 %** (74 %)	**4d** **86 %** **≥ 99 %**[d]	**5d** **≥ 99 %** (99 %)	**6d** **≥ 99 %**

[a]Determined by ^{1}H NMR. In reactions where ^{1}H NMR indicated a conversion lower than quantitative, the degree of conversion was calculated from the corresponding NMR intensities of the product and the unreacted aldehyde or hydrazine. [b]Yields obtained by the classical method with 1mmol/30 mL under reflux in times from 8 to 24 h (See Ref. 38 and 46). [c]These syntheses with hydralazine hydrochloride were performed in presence of 1 equivalent of triethylamine (TEA) and the hydrazone was obtained after washing with water to eliminate the TEA salt. [d]Conversion after 8 hours of grinding.

Electronic effects

Substitution patterns on hydrazines (R^1, R^2) may influence the electronic effects and distribution at the terminal NH_2 functionality thus modifying its reactivity. In order to get an insight into the reactivity of the different hydrazines we determined these effects. Table 2 shows the results of natural bond orbital (NBO)[41] analysis to access the partial atomic charges of the hydrazines, which was performed in the B3LYP/6-311+G(d,p)[42] level of theory for the structures of hydrazines obtained by density functional theory (DFT) calculated with Gaussian 09 software.[43] In a preliminary approach, these simulations were used to attribute values to the pure chemical reactivity, making the following comparison possible: the more negative the charge, the more nucleophilic or basic the atom. The most striking difference is observed for 3-aminorhodanine where the charge density on the terminal NH_2 group of the hydrazine appears much less than for all other compounds.

It is reasonable to assume in this case that this effect might explain the lack of reactivity and the low yields especially obtained under classical conditions (70% and 37%). The effect is more pronounced in solution than under mechanochemical conditions, where total conversion is achieved after a more prolonged time. For the other hydrazines used, the charge density differences are small, in accordance with analogous yields obtained under solution conditions.

Table 2 Charge density of the $–NH_2$ group from hydrazines

Hydrazine	Charge density in $–NH_2$ (NBO)[a]
Isoniazid	-0.634
Hydralazine[b]	-0.637
2-hydrazinobenzothiazole	-0.628
3-aminorhodanine	-0.601
Benzyl carbazate	-0.626
Benzhydrazide	-0.637

[a]Natural bond orbital (NBO)[41] analysis performed in the B3LYP/6-311+G(d,p)[42] level of theory for the structures of hydrazines obtained by density functional theory (DFT) calculated with Gaussian 09 software.[43] [b]NBO was performed for hydralazine base.

The charge density on the reactive part of the aldehydes used was also determined. The values obtained under the same level of theory do not indicate any strong preference in favor of one of them (all values are between 0.0413 and 0.0414). We

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can thus assume that the conversion/yields of the hydrazones obtained under classical conditions reflect the NH_2 reactivity.

Despite the fact that the calculations of partial atomic charges represent a great panoramic for the prevision of the nucleophile sites for the explored cases herein, the hydrazines do not follow the expected results in some cases, when mechanochemical conditions are used. This is especially the case for isoniazide, benzhydrazide and benzyl carbazate. Based on this outlook, it is believed that these solid-state mechanosynthesis are not only guided by electronic aspects but for the solid characteristics such as the crystal packing, the solid form, the density, and finally, in summary, the accessibility of reactive sites in organic solids.

The solid-state role

The mechanisms of solid-state transformations during grinding were generally attributed to a formation of eutectic melts,[44] molecular transport through surfaces due to sublimation[45,46] or in the bulk of material[47,48] and to a reaction mediated by amorphous or metastable crystalline phases.[49,50] In this work we focused in the nature of raw materials that could facilitate the reaction or make it harder. In solid crystals, molecules are not free as in gas or in solution, but trapped in the lattice trying to form the most stable arrangement. All the other surrounding molecules interact mainly by van der Waals' forces and/or H-bonding, which govern the crystal packing. In this section some properties of the solid hydrazines were used to discuss the role of the solid-state in the conversion and reactivity. Crystal properties of some hydrazines, such as crystallographic data, the intermolecular interactions resumed here by hydrogen bonds and the absolute density, were employed to postulate a balance between the electronic properties, previously discussed and the steric effects originated from the solid form.

Intermolecular hydrogen-bonding is responsible for the stabilization of the crystal structure. Therefore, in order to perform a reaction in solid state it is necessary to dissociate the H-bonding, and, consequently, the stronger the H-bonds, the higher the energy required to dissociate them. DSC measurements were performed, but the melting point and the molar ΔH_{fus} obtained for the reactants do not explain their reactivity in this study (See Table 3S, ESI). On the other hand, as an approximation FTIR spectrometry was used to investigate the hydrogen bond strength of the starting hydrazines both by dilution method and temperature variation in the solid state. The stretching vibrations associated with the NH_2 group of hydrazines were studied depending on the concentration (A = f (concentration) in solution) or □ = f (temperature in solid state), but the results were generally inconclusive, except for the aminorhodanine (the lowest reactive hydrazine by mechanical route). For this hydrazine, in accordance with literature data,[51] the $\nu_s(NH_2)$ and $\nu_{as}(NH_2)$ modes were observed at 3295 and 3325 cm^{-1} in the IR spectrum, respectively. Two additional bands were present at ν3149 and 3233cm^{-1}, which have been assigned to combination band of the CO stretching and NH_2 bending modes and an overtone of the 1536 cm^{-1} band, respectively.[52] In addition, a linear variation of the wavenumber at ν3149 was observed as the temperature increased (from 25 to 85°C), demonstrating for this hydrazine the existence of intermolecular interactions in the solid (See Figure 1S in ESI). On the other hand, the calculated FTIR spectra (in the gas phase at 298° K) do not reveal any intramolecular H-bonds (See Table 1S in ESI). Some data from literature also support this discussion. Recent studies have shown that the crystal packing of aminorhodanine is governed by H bonding.[53] The molecules are linked by N—H…O, N—H…N and N—H…S hydrogen bonds, forming a three-dimensional network that probably reduces the nitrogen reactivity. Similarly, a recent investigation of the crystal structure of isoniazid showed that predominantly C-H···N, C-H···O and N-H···N types of intermolecular hydrogen-bonding interactions are responsible for the molecular packing of the crystal.[54] These interactions form an infinite spiral type structure in the crystal.[55] Molecules also form π—π interactions in the crystal at a distance of 3.760 A°. These intermolecular hydrogen-bonds could help explain the lower reactivity of isoniazid than expected and reducing still more that of aminorhodanine. The crystal arrangements of the other hydrazines are probably guided by hydrogen bonds as well, but no study is described in the literature.

In addition to the hydrogen bonding and stacking, the proximity of the molecules must also influence the accessibility of the reactive nitrogen. The density of the hydrazines was used as a first approach to represent the proximity of the molecules. The values of density were obtained with a helium pycnometer through the real volume, which does not take the empty spaces into consideration, and are given in Table 3 in g cm^{-3}.

Table 3 Absolute density (g cm^{-3}) of the solid hydrazines

Hydrazines	Absolute Density (g cm^{-3})
Isoniazid	1.4318
Hydralazine hydrochloride	1.4799
2-hydrazinobenzothiazole	1.4525
3-aminorhodanine	1.6603
Benzyl carbazate	1.2559
Benzhydrazide	1.3006

The density of benzyl carbazate is the smallest at 1.2559 g cm^{-3}, followed by benzhydrazide, isoniazid, 2-hydrazinobenzothiazole, hydralazine and 3-aminorhodanine with 1.6603 g cm^{-3}. Intuitively, a small density could express farther molecules and more freedom to move. Seen in this way, 3-aminorhodanine has the tighter form and the benzyl carbazate the looser one, with its reactivity in solid state affected by this factor. For the 3-aminorhodanine, the higher density further hampers the access to the reaction site. Isoniazid also has a higher density than the benzyl carbazate and benzhydrazide and is less available in the lattice to react. In the same way that in density charge calculations, hydrazinobenzothiazole occupies a midterm in the series of density and the same is found for the conversions always at about 95%.

One can discuss the influence of the mobility of the reactive site of the hydrazine. The chain bearing the reactive $–NH_2$ can move more readily as the chain is longer, which most likely facilitates its accessibility toward the carbonyl group of the aldehyde. For example, benzyl carbazate presents the longer one and complementary experiments, not presented in the Table 1, for the synthesis of **5a** showed conversions around 88%, 95% for 1 and 2h grinding, respectively, confirming the ability of benzyl carbazate to react quickly under these conditions. The Raman spectra of these runs and the starting materials in solid state are presented in Figure 1. The presence of hydrazone bond C=N at 1600 cm^{-1} and a notable decrease of C=O at 1670 cm^{-1} of the aldehyde when compared with the syringaldehyde shows that after only one hour the major part is the product. On the contrary, the partial intracyclic inclusion of the hydrazino group of 3-aminorhodanine acts by reducing the freedom of the

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reactive site of the hydrazine and the grinding time is extended to 8h to attain transformations of around 99%.

Finally, Figure 2 summarizes the importance of different characteristics of hydrazines acting potentially in these solid-state mechanosyntheses of hydrazones.

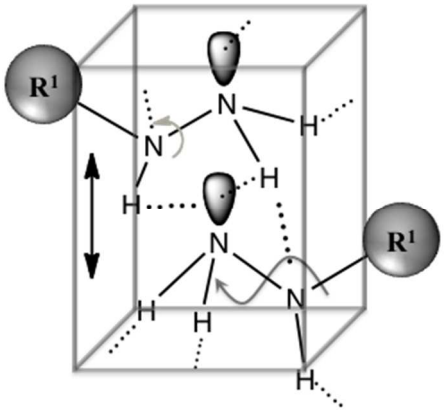

Fig. 2 The electronic and solid-state balance in reactivity of hydrazines. Orbitals are represented only for $-NH_2$, hydrogen bonds are represented by dotted lines, density by vertical arrows and degree of freedom by curved arrows.

Other papers have discussed the electronic effects and the crystal packing for solid-state reactivity. It was observed that the products and kinetics are guided by the crystal packing (subject of topochemistry).[56] Through detailed studies and computer calculations, Gavezzotti had already concluded that a prerequisite for crystal reactivity is the availability of free space around the reaction site.[57] Years later, Sarma *et al.* discussed the role of free volume of some aldehydes for solid-state bromination and found differences in selectivity from solution.[58] More recently, it has been demonstrated that the amount and form of energy and how the mechanical energy is applied concerning the mechanochemical systems, strongly influence the products and kinetics.[59-61] The difference in selectivity of the products from solution and solid syntheses has shown that mechanical energy is capable of surpassing some classical rules in chemistry leading to the comprehension of the same molecule in its different states of aggregation and under different perturbations.[62-67] With regard to the synthesis of hydrazones the results point to a balance between the electronic contributions (orbitals), the strength of hydrogen bonds (dotted lines), the proximity of the molecules, expressed by absolute density (vertical arrow) and the degree of freedom or movement (curved arrows) as suggested in Figure 2. What is not mentioned is that the mechanical energy is essential to favor the reaction by breaking and destabilizing the solid, which increases Gibbs free enthalpy,[50] and by activating on a macro and molecular level.

Conclusions

Several hydrazones were successfully synthesized via the mechanochemistry route by grinding the aldehydes and hydrazines in solid-state at room temperature. Conversion ratios of 85-99% were obtained depending on the hydrazine/aldehyde used, but it was demonstrated that the reactions could reach transformations ≥ 99% by changing the time of grinding as illustrated in the case of 3-aminorhodanine series. This approach seems to be more efficient in the preparation of hydrazones in solid-state and quantities which are more important and easier to scale up in comparison with reactions carried out in solution, under microwave[36-38] or using other milling devices.[28-30, 31]

In conclusion, these considerations helped us to understand the reactivity of the hydrazines, which seem to be the result of a balance of electronic and solid effects. It is still appropriate to say that within the synthesized hydrazones in this study, no difference in the final products was found when compared with the thermal synthesis in reflux of solvent, due, for example, to another mechanism of reaction or excited state.[67] The formation of intermediate metastable phases during grinding were not excluded, but not detected. On the other hand, the properties of the raw materials such as packing guided by hydrogen bonds, the density and freedom of the molecule fit satisfactorily the results.

This solvent-free synthesis of this series of hydrazones can be anticipated as a rational and powerful way forward for the synthesis of active pharmaceutical ingredients.

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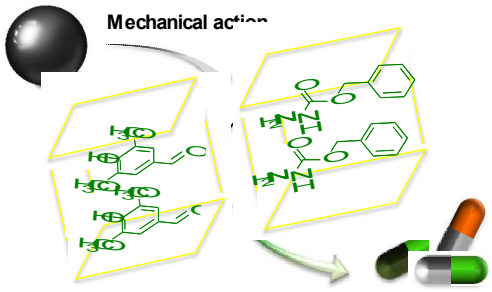

Electronic and steric properties of solid reactants were overpassed to produce, quantitatively, pharmaceutically attractive hydrazones by using green mechanochemical route.