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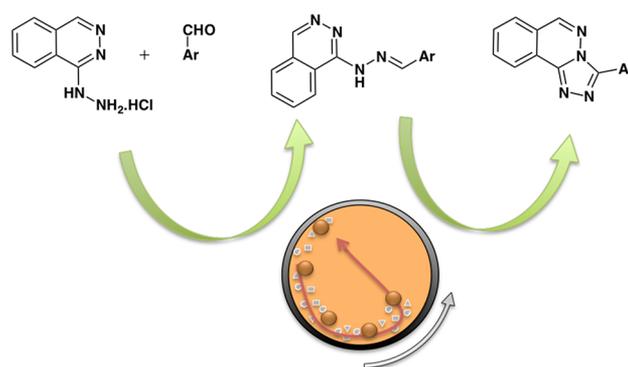
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# Study of the Two Steps and One-Pot Two-Step Mechanochemical Synthesis of Annulated 1,2,4-Triazoles

Lori Gonnet,\* Christiane André-Barrès, Brigitte Guidetti, Alain Chamayou, Christophe Menendez, Michel Baron, Rachel Calvet, and Michel Baltas\*

**ABSTRACT:** The mechanochemical synthesis of 1,2,4-triazoles by using a planetary ball-mill is studied starting from hydralazine hydrochloride. Excellent conditions were found for achieving total conversion to intermediate hydrazones in a few minutes in the presence of pyrogenic S13 silica as grinding auxiliary. The conversion to annulated 1,2,4-triazoles was optimal with iodobenzene diacetate (IBD) when using nonphenolic hydrazones, while SeO<sub>2</sub> was found to be efficient for phenolic compounds. The one-pot two-step synthesis was also successfully conducted for the first time leading to annulated 1,2,4-triazoles. Finally, green metrics showed the efficiency of the method in comparison to the conventional syntheses of hydrazone 10 and triazole 13.



**KEYWORDS:** Hydrazones, Annulated triazoles, Mechanochemistry, Ball-milling, Pyrogenic silica, Green metrics

## INTRODUCTION

Creativity in organic synthesis has rendered possible the synthesis of incredible large, different, and complex families of molecules. Nevertheless, upon the end of the last century, chemists were conscious that organic synthesis generally suffers from the large amounts of toxic waste that are produced during syntheses.<sup>1</sup> In that respect, green chemistry and sustainability are becoming increasingly important.<sup>2,3</sup> The green chemistry field has defined metrics to evaluate the environmental impact of chemical processes where solvents are identified as the major contributors of undesirable waste.<sup>4,5</sup> The reduction of solvent waste became a major motivation for the development of solvent-free synthetic reaction protocols.<sup>6–9</sup> In addition, insolubility problems in organic solvents can be overcome under these conditions. While solvent-free reactions can be carried out with classical laboratory equipment or by using microwave heating, the application of organic synthesis mechanochemistry is a continuously improving field of research. Ball milling was found to be an excellent method for many named organic reactions.<sup>7–14</sup> The mechanochemical reaction environment can be modified further by the addition of a small amount of liquid. The so-called liquid-assisted grinding (LAG) has become an important technique in the expanding mechanochemistry field.<sup>15,16</sup> One of several challenges in the organic synthesis mechanochemistry field is the attainment of the ability to run one-pot two-step or more syntheses in various multistep synthetic processes. One-pot procedures usually require solvent compatibility and have to

address the possibility of side product formation.<sup>17</sup> The one-pot procedures in the mechanochemistry field have the advantage of overcoming these problems and especially the use of solvents compatible with several consecutive steps. In that respect, mechanochemistry amplifies sustainability metrics by running back-to-back solventless reactions. Multistep mechanochemical procedures have been successfully applied to the syntheses of O-glycosides,<sup>18</sup> bioactive hydantoins,<sup>19</sup> extended ipitycenes,<sup>20</sup> amides<sup>21</sup> and organometallics,<sup>22</sup> and metalation/transmetalation procedures<sup>23</sup> where problems can occur with the use of solution based synthesis due to limited solubility.

The 1,2,4-triazole-based, biologically active compounds have found enormous applications in medicinal and agricultural sciences. A great number of drugs are extensively used in clinics. Among them, we can point to the antifungal fluconazole 1, antitumoral letrozole 2, and the antiviral ribavirin 3, (Figure 1)<sup>24</sup> while several triazole based compounds like epoxiconazole 4 play an important role in agriculture ensuring proper harvest and crops (Figure 1).<sup>25</sup> We also cite the very recent discovery of the orally bioavailable compound 5 CNS penetrant negative allosteric modulator<sup>26</sup>

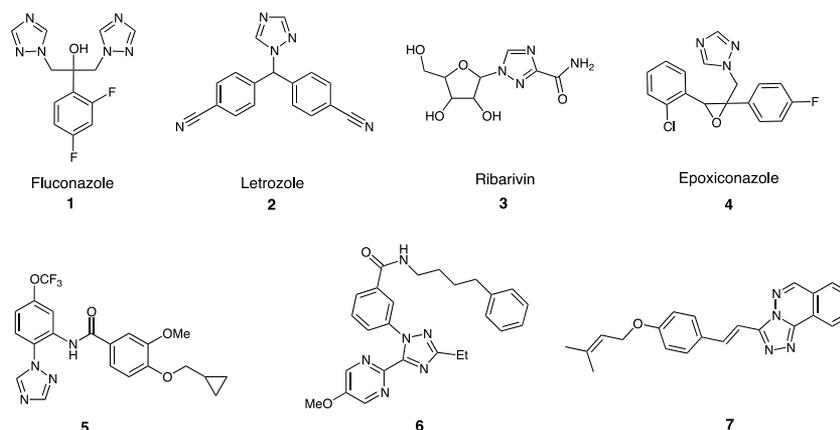


Figure 1. Triazoles with biological activities.

Table 1. Powder Parameters of Solid Auxiliaries without Grinding and after 15 min of Grinding in Parentheses

Compound	Density $\rho$ (g/cm <sup>3</sup> )	Granulometry ( $\mu\text{m}$ )		Specific surface area (m <sup>2</sup> /g)	
		$d_{50}$	$d_{3-2}$	$a_{\text{BET}}$ (N <sub>2</sub> )	$a_{\text{calculated}}$ (eq 1)
Fontainebleau sand	2.658 (2.652)	246 (36)	240 (4)	Too low (0.9)	0.009 (0.53)
Silica gel	2.102 (2.177)	126 (6)	118 (3)	456 (419)	0.02 (0.86)
Pyrogenic S13 silica	2.543 (2.322)	23 (18)	17 (4)	137 (80)	0.09 (0.63)
Pyrogenic N20 silica	2.598 (2.342)	38 (14)	23 (4)	196 (162)	0.09 (0.55)
Pyrogenic T40 silica	2.695 (2.473)	33 (14)	27 (5)	414 (184)	0.09 (0.67)

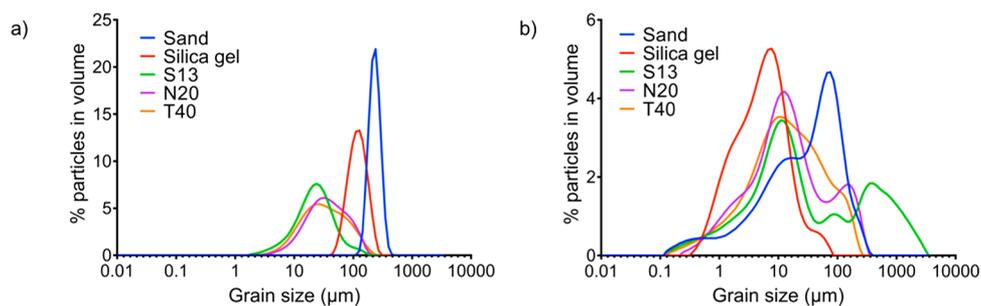


Figure 2. Particle size distributions of solid auxiliaries (a) before and (b) after 15 min of grinding.

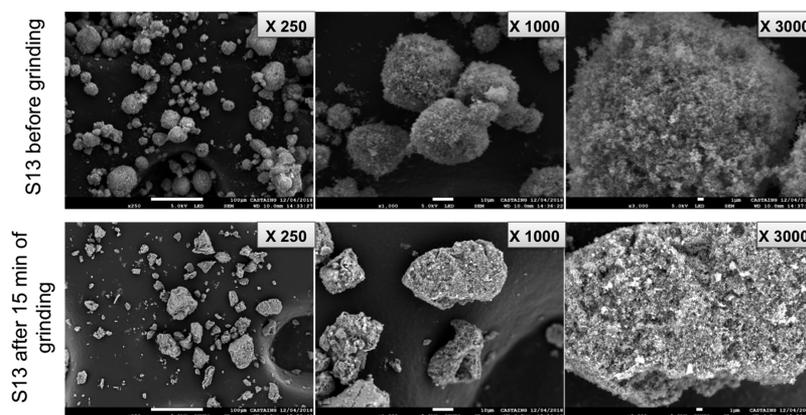


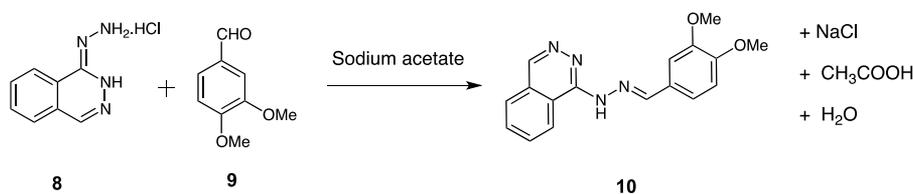
Figure 3. SEM analyses before (top) and after 15 min of grinding (bottom).

and also a series of 1,5-diaryl-1,2,4-triazole compounds **6** as novel agents against pancreatic cancer metastasis<sup>27</sup> (Figure 1).

For some years now, we have explored the possibility of styryl annulated 1,2,4 triazoles derivatives as potential antituberculosis agents<sup>28,29</sup> and found triazolophthalazine **7**, with an excellent antitubercular potency (MIC = 1.4  $\mu\text{M}$ ) in

comparison with others, and more importantly, with good cytotoxicity toward HCT116 human cells (IC<sub>50</sub> = 449  $\mu\text{M}$ ; 160  $\mu\text{g}/\text{mL}$  and selectivity index SI = 320).

Their extensive medicinal, agrochemical, and other potential applications have resulted in a major effort to develop synthetic methods that include three categories of synthetic objectives:



**Figure 4.** Synthesis of hydrazone **10** from hydralazine **8** and 3,4-dimethoxybenzaldehyde **9**.

(a) cyclizations to form the triazole ring, (b) transformations of heterocyclic compounds to construct the triazole ring, (c) substitutions on the 1,2,4 triazole ring (for recent reviews, see references 30 and 31).

Several years ago, we launched a research program in the area of mechanochemistry.<sup>32–34</sup> One of the topics we focused on and reported about was the mechanochemical synthesis of various hydrazones<sup>35</sup> and hydrazones bearing the isoniazide frame as potential antituberculosis agents.<sup>36</sup> In addition, through the long-standing program concerning the conception and synthesis of new antituberculosis compounds, we found and developed annulated 1,2,4-triazoles as important compounds with new modes of action.<sup>28,29</sup>

In connection with these two programs, we report here the two steps and one-pot two-step mechanochemical synthesis of 1,2,4-triazoles from hydrazones, in the presence and absence of grinding auxiliaries.

Moreover, it is noteworthy to point out that there is only one reported synthesis of 1,2,4-triazole-fused heterocycles under electrochemical (green) conditions<sup>37</sup> but no synthesis under mechanochemical ones.

## RESULTS AND DISCUSSION

**Surface Analyses of Grinding Auxiliaries.** Grinding auxiliaries have been, since some years now, often used in

**Table 2. Screening of Mechanochemical Conditions for the Synthesis of Hydrazone 10**

Entry	Method	Time (min)	Additive		Yield (%)
			Compound	Grain size $d_{50}$ ( $\mu\text{m}$ )/developed surface ( $\text{m}^2$ )	
1	EtOH, reflux <sup>a</sup>	60			100
2	P7, 500 rpm	15			43
3	P7, 500 rpm	2 × 15			73
4	P7, 500 rpm	3 × 15			100
5	P7, 800 rpm	15			46
6	P7, 800 rpm	2 × 15			100
7	P7, 800 rpm	15	Sand	246/0.005	40
8	P7, 800 rpm	15	Sand after 15 min grinding	37/0.5	38
9	P7, 800 rpm	15	Silica gel	126/228	87
10	P7, 800 rpm	5	S13 silica	23/68.5	90
11	P7, 800 rpm	15	S13 silica	23/68.5	100

<sup>a</sup>C =  $0.25 \times 10^{-3}$  mol/L.

organic mechanochemical synthesis.<sup>13,38–40</sup> In this work, we focused on the use of three kinds of auxiliaries that are Fontainebleau sand, silica gel (63–200  $\mu\text{m}$ ), and pyrogenic silicas HDK S13, N20, and T40 from the Wacker Company. Their physical properties were first examined. The aim was to determine parameters like their specific surface areas, granulometry, and density before and after 15 min of grinding, which is the grinding time for most of our experiments (Table 1).

A very weak change of the densities of the auxiliaries is observed after 15 min of grinding. For sand and silica gel, the modification is less than 4%, while for pyrogenic silicas, the decrease after grinding attains 10% (Table 1).

With regard to granulometry measurements, dry dispersions at 0.5 bar have been used. Median diameters ( $d_{50}$ ) and Sauter mean diameters ( $d_{3-2}$ ) were determined before and after grinding, and values are reported in Table 1.

The effects of grinding included the drastic decrease of  $d_{50}$  for sand and silica gel indicating that the energy upon grinding can dramatically modify their granulometry. This is not the case for the pyrogenic silicas, which already have a low grain size before grinding. The particle size distributions were also determined and presented in Figure 2.

As we can see, for all the grinding auxiliaries used, the solid particle size distribution became less homogeneous after grinding. This is especially the case for pyrogenic silicas where the diameter of the particle agglomerates can vary between 12 and 310  $\mu\text{m}$  for pyrogenic N20 and T40 silicas and between 12 and 3000  $\mu\text{m}$  for pyrogenic S13 silica. It seems likely that grinding transforms pyrogenic silicas to smaller particles but also consolidates larger agglomerates.

Specific surface areas were measured by nitrogen adsorption at 77 K and application of the BET equation and were also calculated after determination of the density and the particle diameter  $d_{3,2}$ . In this latter case, the specific surfaces take only into account spherical particles without pores. The specific surface area calculation is indicated in eq 1

$$a_{\text{calculated}} = \frac{6}{\rho \times d_{3,2}} \quad (1)$$

The specific surface area of sand before grinding cannot be determined while after grinding, the BET equation gave an approximate value of 0.9  $\text{m}^2/\text{g}$ . This value is close to the calculated one (0.53  $\text{m}^2/\text{g}$ ); indeed, we can consider sand as a spherical particle without pores. For silica gel and pyrogenic silicas, large variations between BET and calculation were observed. Indeed, silica gel is known as a mesoporous material and pyrogenic silicas are constituted of primary particles aggregates, which provide an important specific surface area.

After grinding, a smaller surface was calculated for sand. Indeed, the granulometry decreases sharply after 15 min of grinding (246  $\mu\text{m}$  before grinding and 37  $\mu\text{m}$  after grinding), thus increasing the specific surface area calculated. Finally, with

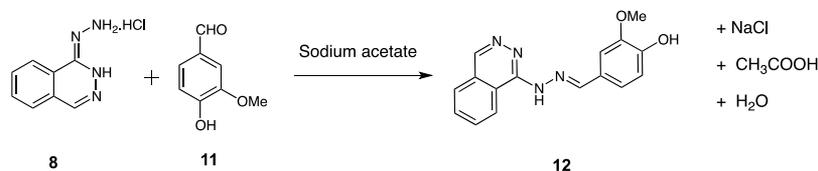


Figure 5. Synthesis of hydrazone 12 from hydralazine 8 and vanillin 11.

Table 3. Screening of Mechanochemical Conditions for the Synthesis of Hydrazone 12

Entry	Method	Time (min)	Additive		Yield (%)
			Compound	Grain sized <sub>50</sub> (μm)/developed surface (m <sup>2</sup> )	
1	EtOH, reflux <sup>a</sup>	60			90
2	P7, 500 rpm	15			40
3	P7, 500 rpm	2 × 15			66
4	P7, 500 rpm	3 × 15			76
5	P7, 800 rpm	15			45
6	P7, 800 rpm	2 × 15			92
7	P7, 800 rpm	3 × 15			100
8	P7, 800 rpm	15	Sand	246/0.005	78
9	P7, 800 rpm	15	Silica gel	126/228	95
10	P7, 800 rpm	5	S13 silica	23/68.5	63
11	P7, 800 rpm	15	S13 silica	23/68.5	100

<sup>a</sup>C = 0.25 × 10<sup>-3</sup> mol/L.

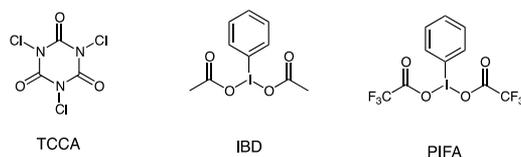


Figure 6. Cycling agents: TCCA, IBD, and PIFA.

the  $S_{\text{BET}}$  surfaces, there is a very weak decrease after 15 min of grinding for the silica gel (8%) while a very important one for the pyrogenic silicas (41%) (Table 1). Indeed, pyrogenic silicas are in the form of aerated agglomerates and these agglomerates can be compacted during grinding.

MEB analyses of the S13 silica before and after 15 min of grinding are in agreement with our previous assumption of compaction (Figure 3). In fact, they show clearly the morphology that is porous and spacious having the appearance of a grape before grinding. After 15 min of grinding, the

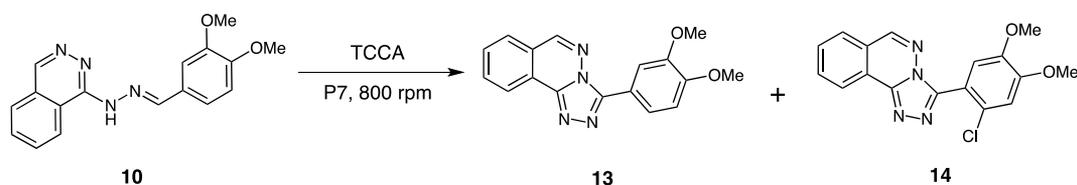


Figure 7. Cyclization of hydrazone 10 using TCCA.

Table 4. Screening of Mechanochemical Conditions for the Synthesis of Triazole 13 Using TCCA

Entry	equiv TCCA	Time (min)	Yield (%)	
			13	14
1	1	15	3	35
2	0.1	15	30	<5
3	4 × 0.1	4 × 10	18	15

morphology becomes quite different; the grapes are much more compacted and less spacious; nevertheless, the size of the individual particles remains the same as also indicated by the granulometric measurements.

**Synthesis of Hydrazones.** We reported in 2014 (Oliveira et al.), our first results concerning the synthesis of hydrazones by mechanochemical means using the vibratory mill Pulverisette 0 (P0) (Fritsch, Germany)<sup>35</sup> and reacting a suitable aldehyde with selected hydrazines in an equimolar ratio. In most of the cases, mechanochemical synthesis afforded hydrazones in very good to quantitative yields after 2–4 h of reaction. The syntheses of hydrazones by solid–solid techniques including mechanochemical ones have already been reported by various groups.<sup>41,42</sup>

In the study reported here, we focused on the synthesis of hydrazones starting from hydralazine hydrochloride and reacting it with various aldehydes. Hydralazine hydrochloride was used because the corresponding hydrazones might cyclize in a second step to afford the annulated 1,2,4-triazoles.

A planetary ball-mill, Pulverisette 7 (P7) (Fritsch, Germany) bearing 20 mL jars and five balls in zirconium oxide (10 mm diameter, 14.7 g for 5 balls), was used. Model studies were first run with 3,4-dimethoxybenzaldehyde and vanillin. The reaction was conducted in the presence of sodium acetate, on a 5 mmol scale with or without three types of grinding auxiliaries including Fontainebleau sand, silica gel, and various pyrogenic silicas.

**Synthesis from 3,4-Dimethoxybenzaldehyde.** First, the reaction between hydralazine 8 and 3,4-dimethoxybenzaldehyde 9 (Figure 4) in the presence of sodium acetate (1 equiv each) was conducted under several conditions (Table 2).

The conventional reaction was conducted in EtOH solution under reflux and followed by TLC. Total conversion was observed after 1 h of reaction (Table 2, entry 1). By using mechanochemical means, we first modified two parameters, i.e., the rotation speed and the time of reaction with a sequence

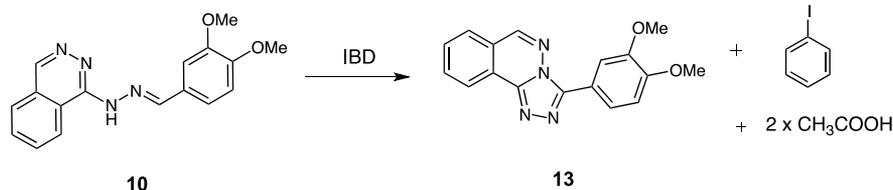


Figure 8. Cyclization of hydrazone 10 using IBD.

Table 5. Screening of Mechanochemical Conditions for the Synthesis of Triazole 13 Using IBD

Entry	Method	Time (min)	Additives		Yield (%)
			Compound	Grain size $d_{50}(\mu\text{m})$ / developed surface ( $\text{m}^2$ )	
1	$\text{CH}_2\text{Cl}_2^a$	240			84
2	P7, 800 rpm	15			68
3	P7, 800 rpm	3 × 15			97
4	P7, 800 rpm	15	Sand	246/0.005	63
5	P7, 800 rpm	15	Silica gel	126/228	73
6	P7, 800 rpm	15	S13 silica	23/68.5	93

<sup>a</sup>C =  $0.13 \times 10^{-3}$  mol/L.

Table 6. Impact of Silica Developed Surface

Entry	Type	Pyrogenic silicas			Yield (%)
		Wt (mg)	Specific surface ( $\text{m}^2/\text{g}$ )	Developed surface ( $\text{m}^2$ )	
1					68
2	S13	500	137	68	93
3	N20	350	196	68	85
4	T40	170	414	68	82
5	T40	500	414	207	92

of 15 min and then a 5 min pause followed by another cycle. After sampling, all reactions were followed immediately by  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ). For 15 min of reaction, we observe almost identical conversions of 43% and 46% with rotation speeds of 500 and 800 rpm respectively (Table 2, entries 2, 5). While operating at longer periods ( $2 \times 15$  min), a quantitative conversion was attained when running the reaction at 800 rpm, and a much lesser one (73% of conversion) was obtained when operating at 500 rpm. (Table 2, entries 6, 3, respectively). Finally, the conversion is quantitative at 500 rpm after 3 cycles of 15 min (Table 2, entry 4). The same reaction was then conducted in the presence of grinding auxiliaries (500 mg). Aldehyde 9 was first adsorbed on the grinding auxiliary. The rotation speed was maintained at 800 rpm (Table 2, entries 7–11). Sand (ground or not ground alone) gave the same results than those without auxiliary grinding (Table 2, entries 5, 7, 8). Indeed, sand does not adsorb water, acetic acid was generated during the reaction, and its grain size sharply decreased by grinding ( $246 \mu\text{m}$  before grinding and  $37 \mu\text{m}$  after grinding, Table 1). So, part of the energy provided by the balls is used to reduce the size of the sand grains and not for the reaction. The use of silicas provides better yields than sand. While silica gel afforded 87% conversion after 15 min of milling, pyrogenic S13 afforded excellent conversion after 5 min of milling and a quantitative one after 15 min of milling (Table 2, entries 9, 10,

11). These better results, in comparison to sand auxiliary, can be explained by the capacity of silicas to adsorb water and acetic acid. Moreover, like sand, the granulometry of silica gel was sharply decreased ( $126 \mu\text{m}$  before grinding and  $11 \mu\text{m}$  after grinding, Table 1) contrary to that of pyrogenic S13 silica ( $23 \mu\text{m}$  before grinding and  $18 \mu\text{m}$  after grinding, Table 1). So, the energy provided by balls was also used to grind silica gel and to a much lesser extent for S13. We can observe that the yield increases with a smaller grain size of grinding auxiliaries that is not affected by milling. In regard to these results, we can hypothesize that grinding auxiliaries can report the energy of the balls on the reactant powder without loss of energy and thus produce a faster reaction. Moreover, the developed surface of grinding auxiliaries does not seem to have an effect on the reaction. Indeed, a better yield was obtained with pyrogenic silica ( $68.5 \text{ m}^2$ ) than with silica gel ( $228 \text{ m}^2$ ) (Table 2, entries 9, 11). The reaction was conducted as before (Table 2, entry 11). The solid material was washed with  $\text{CH}_2\text{Cl}_2$ , filtered, and dried to eliminate organic molecules. Particles size distribution measurements were carried out (see SI, page S10, Figure S1) and compared with those of pyrogenic silica S13 before milling and after 15 min of milling. However, it is noteworthy that the purifying post treatment of pyrogenic S13 silica may modify the surface properties and consequently alter the observed agglomerates. This is the reason why a deeper interpretation could be hazardous.

**Synthesis from Vanillin.** The same study was conducted with vanillin 11 (Figure 5, Table 3).

Results of the reactions in the absence of grinding auxiliary and with varying, respectively, the rotation speed and the time of milling are presented in Table 3. The reaction is slower than that with 3,4-dimethoxybenzaldehyde 9.

Conversions at low rotation speed (500 rpm) are between 40% and 76% after 15 min to  $3 \times 15$  min of milling (Table 3, entries 2, 3, 4). For a higher speed of rotation, three cycles of 15 min of milling are necessary to obtain quantitative conversion (Table 3, entry 7). The same reaction was then conducted in the presence of grinding auxiliaries as was done previously. The rotation speed was maintained at 800 rpm. In all cases, we observe an increase in the conversion to hydrazone. As before, this is especially the case with the pyrogenic S13 silica where a total conversion is obtained after 15 min of grinding, for the same reasons mentioned before (Table 3, entry 11). As previously observed, an increase of developed surface does not accelerate the reaction (Table 3, entries 9, 11).

**Synthesis of Annulated 1,2,4-Triazoles.** Intramolecular cyclization of hydrazones to form 1,2,4-heterocyclic systems has been reported in the literature, most often by the use of three oxidizing agents: trichloroisocyanuric acid (TCCA),<sup>43,44</sup> iodobenzene diacetate (IBD),<sup>45,46</sup> or its fluorinated analogue phenyl iodine bis(trifluoroacetate) (PIFA)<sup>47,48</sup> (Figure 6).

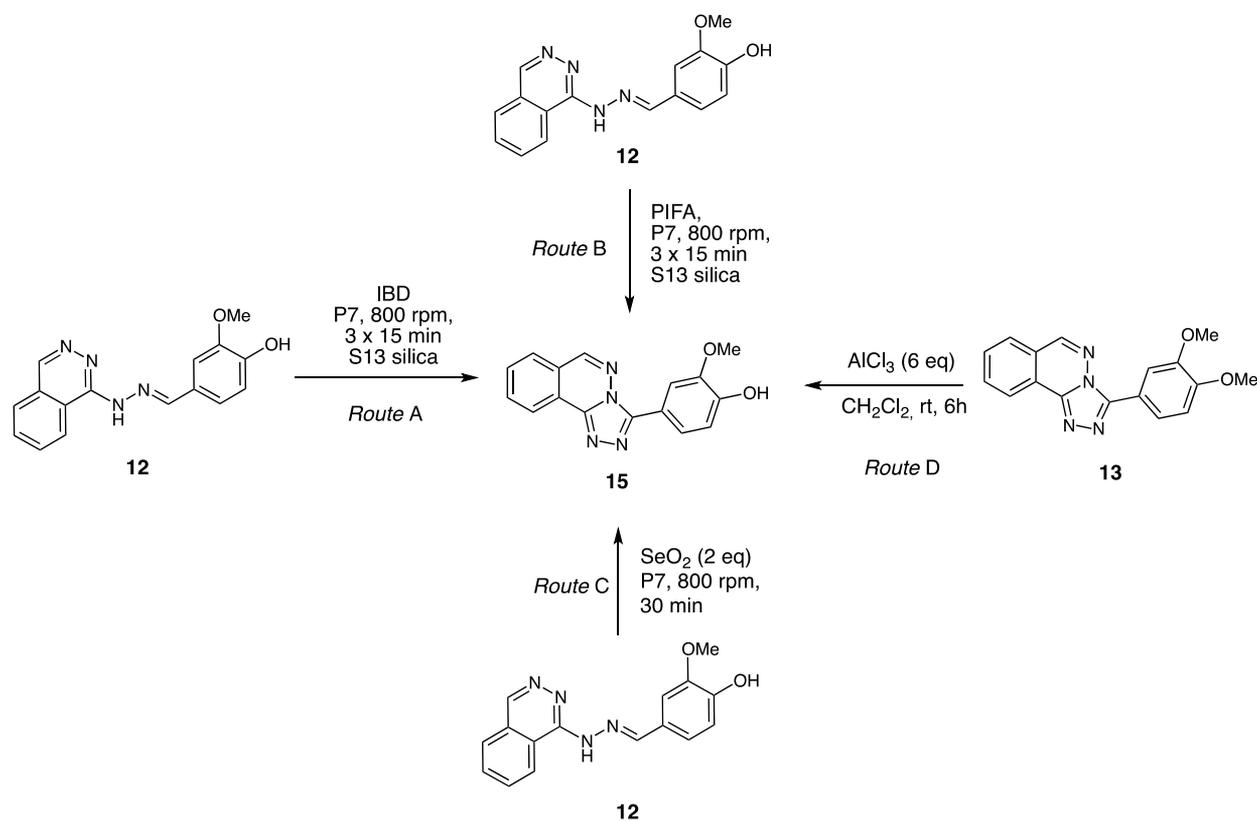


Figure 9. Different routes for the triazole 15 synthesis.

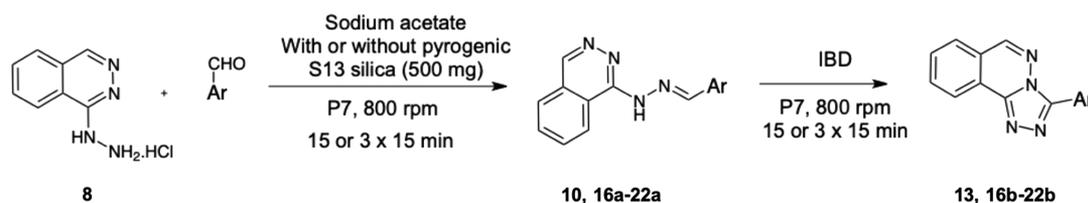


Figure 10. One-pot two-step procedure for the synthesis of 1,2,4-triazoles 13, 16b–22b.

We first checked the reaction between hydrazone 10 and TCCA under mechanochemical conditions at 800 rpm (Figure 7). Results are reported in Table 4.

When using 1 equiv of TCCA, with a rotation speed of 800 rpm, we observe, after 15 min of milling, the disappearance of the starting hydrazones. Among the complex mixture, we could purify and identify two compounds: the desired triazole 13 obtained in 3% yield and the monochlorinated triazole 14 in 35% yield (Table 4, entry 1). Extensive NMR analysis showed that the chlorine atom was introduced at the 6 position of the dimethoxy aryl fragment.

When using 0.1 equiv of TCCA under the same conditions, we obtain, after careful purification, the desired 1,2,4-triazole 13 in 30% yield along with a small amount of the same monochlorinated compound 14 (Table 4, entry 2). Finally, when we introduce 0.1 equiv of TCCA every 10 min of milling and stop the reaction after 40 min of milling, we again obtain, after careful purification, compounds 13 and 14 in 18% and 15% yields respectively (Table 4, entry 3).

TCCA acts just like a chlorinating agent and therefore is not a good choice to obtain desired triazoles. This major drawback was also reported by Sniady et al.<sup>44</sup>

Next, we tried IBD as the oxidizing agent for the cyclization of hydrazone 10 (Figure 8). Different reaction conditions under mechanochemical means were tested along with the conventional reaction in solution, by using 1 equiv of IBD (Table 5).

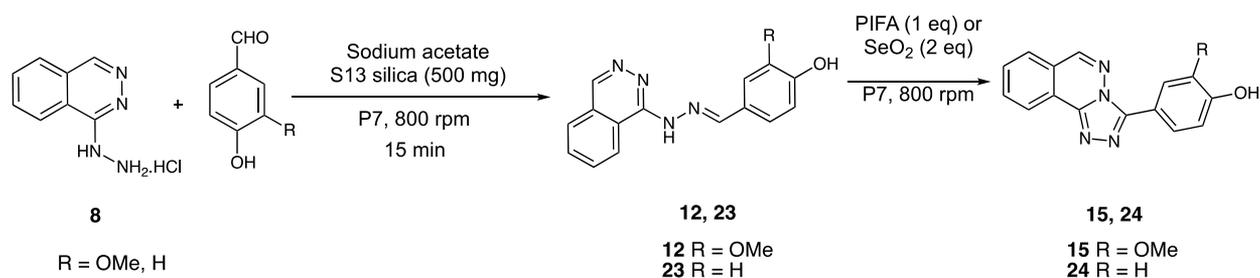
The reaction in dichloromethane (DCM) at room temperature afforded, after 4 h, the triazole 13 in 84% yield after purification (Table 5, entry 1).

The mechanochemical reaction leads to triazole 13 in 68% yield after 15 min of milling and in the absence of any auxiliary. Excellent conversion was obtained after 3 x 15 min of grinding (Table 5, entries 2, 3). While sand as grinding auxiliary gave comparable result (63% yield), silica had an increase of yield (73%) as a consequence (Table 5, entries 4, 5). Again, gratifyingly, pyrogenic silica S13 gave the best result (Table 5, entry 6). After 15 min of milling, triazole 13 was obtained in 93% yield after purification.

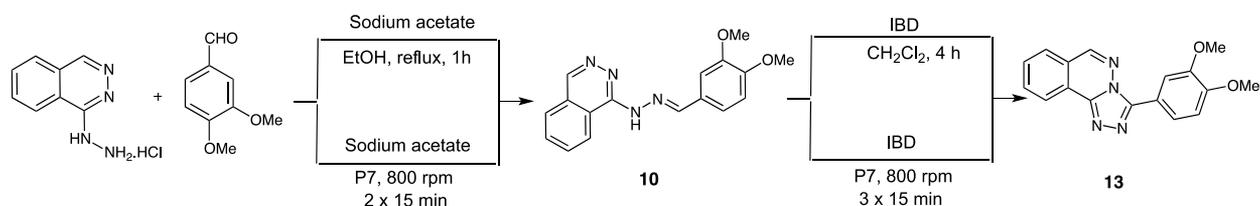
A brief insight in the role of silicas was attempted through the following experiments: hydrazone 10 was allowed to react with one equivalent of IBD in the presence of pyrogenic grinding auxiliaries where we modified either the weighted mass or the developed surface of the auxiliaries. Pyrogenic S13, N20, and T40 have the same nature as silicas and almost

**Table 7. One-Pot Two-Step Procedure for the Synthesis of Triazoles 13, 16b–22b**

Entry	IBD eq	Compound	Aldehyde	Yield (%)
1	1	<b>13</b>		94
2	1	<b>16b</b>		93
3	1	<b>17b</b>		97
4	1	<b>18b</b>		98
5	1	<b>19b</b>		93
6	1	<b>20b</b>		98
7	1	<b>21b</b>		85
8	1.5	<b>21b</b>		97
9	1	<b>22b</b>		65
10	1.5	<b>22b</b>		96



**Figure 11.** One-pot two-step synthesis for the formation of 1,2,4-triazole **15** and **24**.



**Figure 12.** Comparison of the two-step procedure reactions in solution and using mechanochemistry.

identical granulometry but different specific surface areas. Mechanochemical reaction was conducted for 15 min at 800 rpm; results are presented in [Table 6](#).

Equivalent yields of compound **13** (93% and 92%, [Table 6](#), entries 2, 5) are obtained when using the same weight (500 mg) but different developed surface areas of silica S13 and T40

**Table 8. Comparative Green Metrics for the Synthesis of Hydrazone 10 and Triazole 13, in Solution/by Mechanochemistry**

Compound	Time (h)	Yield (%)	E-factor	PMI
10	1/0.5	100/100	14/4	15/5
13	4/0.75	84/97	74/12	75/13

(68 and 207 m<sup>2</sup>, respectively). This indicates that the developed surface does not have any effect on the reaction, with regard to better adsorption by products (acetic acid). When using the same developed surface (68 m<sup>2</sup>) but different silica weight (170 to 500 mg, Table 6, entries 2, 3, 4), the yields obtained are lower when decreasing the silica weight. In regard to these results, we could propose that silicas might only have a mechanical effect upon the reaction progress by a more efficient transfer of the mechanical energy from the balls to the reactants.

With regard to the cyclization of hydrazone issued from vanillin and bearing a free hydroxy group, the reaction appeared much more tedious (Figure 9).

While TCCA gave an inseparable mixture of many compounds, IBD or PIFA reagents operate very poorly giving, after purification, less than 8% of triazole 15 along with many other nonisolable compounds (Figure 9, route A and B). After various unsuccessful attempts, we were satisfied to find two methods in order to obtain the phenolic triazole 15. The first one makes use of the potential demethylation at the para position of the triazole 13 issued from 3,4-dimethoxybenzaldehyde 9 (Figure 9, route D). In fact, when using 6 equiv of AlCl<sub>3</sub> in the presence of triazole 13 in methylene chloride, we obtain, after 6 h of reaction at room temperature, careful work up, and purification, the desired triazole 15 in 60% yield. Most gratifyingly, by using 2 equiv of selenium dioxide in the presence of phenolic hydrazone 12 under mechanochemical conditions for 30 min we obtain the cyclized compound, phenolic 1,2,4-triazole 15 in 75% yield (Figure 9, route C).

**One-Pot Two-Step Synthesis of C-3 Substituted 1,2,4-Triazoles.** After having successfully studied the mechanochemical synthesis of hydrazones 10 and 12 and their corresponding triazoles 13 and 15 in a sequential two-step procedure, we attempted the one-pot two-step reaction (Figure 10). The attempt became possible and was successful as the grinding auxiliary for the optimized reactions in each step is the same and initial reagent (sodium acetate) does not affect the second step.

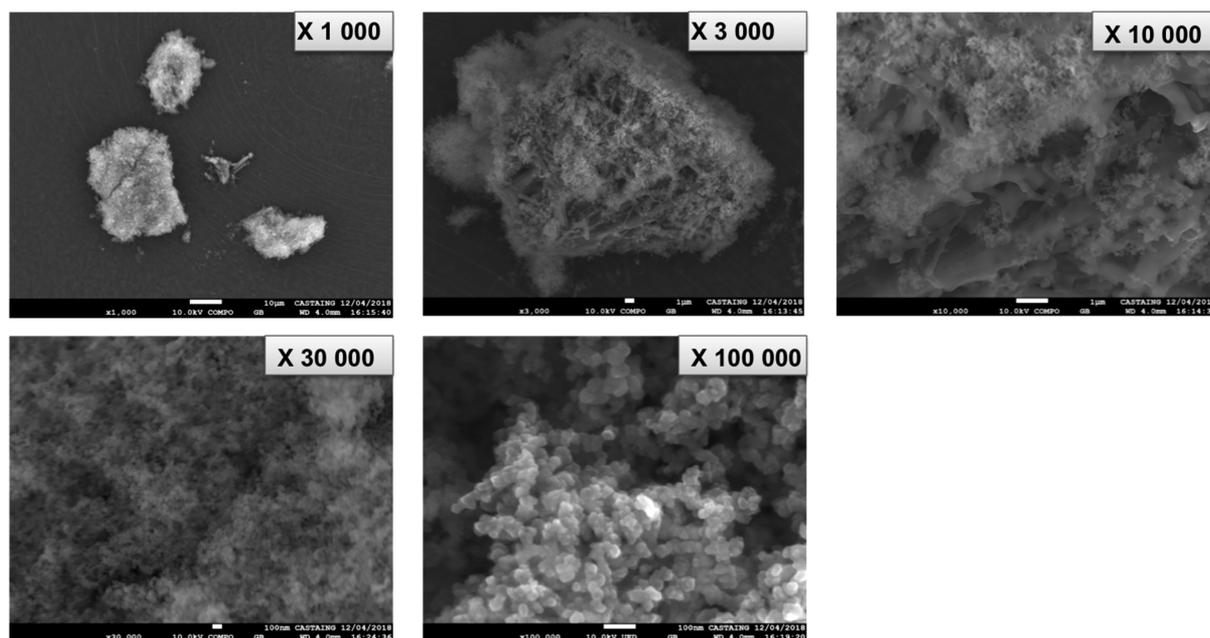
Hydralazine hydrochloride 8 and 3,4-dimethoxybenzaldehyde 9 were reacted together in the presence of sodium acetate and pyrogenic S13 silica for 15 min; hydrazone 10 obtained quantitatively was then reacted with IBD for 15 min in a one-pot two-step procedure. The desired annulated 1,2,4-triazole 13 was thus obtained in 94% overall yield (Table 7, entry 1).

The same reaction, when run for 15 min for each step, with different nonphenolic aromatic aldehydes afforded the corresponding triazoles 16–19 in excellent yields, varying between 93% and 98% after two steps (Table 7, entries 2–5). Hydrazones were always obtained in quantitative yield.

Heteroaromatic aldehydes were also allowed to react with hydralazine hydrochloride 8. After some conditions were adjusted due to the insolubility of the final heteroaromatic triazoles 20–22, we found that the best way to obtain them is without any grinding auxiliary and in the presence of 1 or 1.5 equiv of IBD (Table 7, entries 6–10). Under these conditions, after 3 × 15 min of milling for each step and water washing of the crude material, excellent yields of annulated heteroaromatic 1,2,4-triazoles 20–22 were obtained (96–98%).

Finally, the one-pot two-step sequence was also applied for two phenolic aldehydes, i.e., *p*-hydroxy-benzaldehyde and vanillin 11 (Figure 11).

The one-pot two-step reaction was conducted in the presence of either 2 equiv of selenium dioxide or 1 equiv of PIFA. When using SeO<sub>2</sub> and after 30 min of milling, we obtained triazole 15 in 70% yield and triazole 24 in 40%. The reactions in the presence of PIFA were much less efficient,



**Figure 13.** SEM analyses of hydrazone 10 adsorbed on pyrogenic S13 silica.

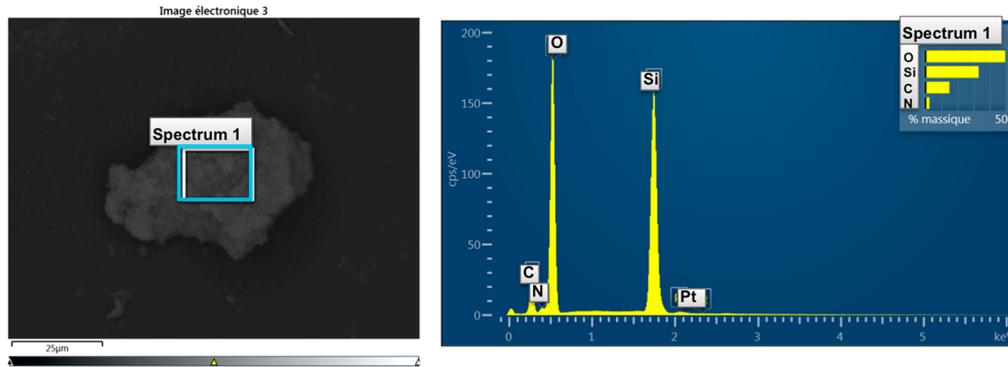


Figure 14. EDS probe of hydrazone 10 adsorbed on pyrogenic S13 silica.

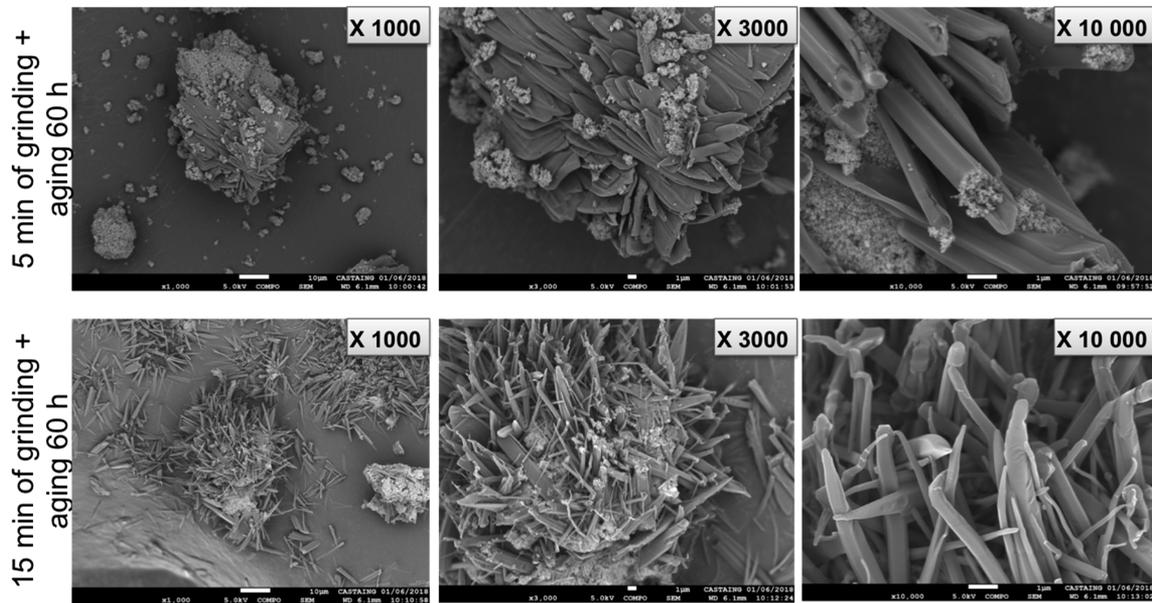


Figure 15. SEM analyses of triazole 13 adsorbed on pyrogenic S13 silica after 5 min (top) and 15 min of grinding (bottom) and after 60 h of aging.

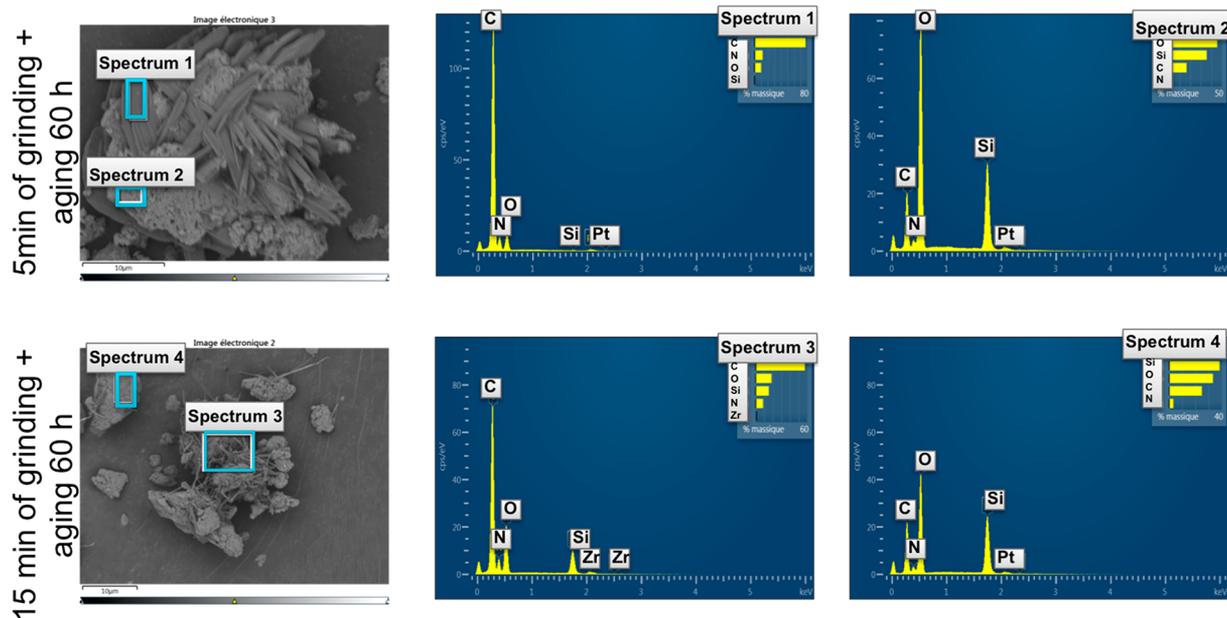


Figure 16. EDS probe of triazole 13 adsorbed on pyrogenic S13 silica.

leading to triazoles **15** and **24** in 8% and 12% of yield, respectively, after  $3 \times 15$  min of grinding (Figure 11).

**Green Metrics.** In solution, syntheses of compounds **10** and **13** were conducted only in a two-step procedure. So, in order to evaluate and benchmark the more sustainable process, we compared it with the two-step mechanochemical method without grinding auxiliary (Figure 12).

Calculations of the green chemistry metrics for both procedures were performed.

The environmental factor, *E*-factor, which is defined in eq 2<sup>1,4</sup>

$$E\text{-factor} = \frac{\text{mass of total waste(kg)}}{\text{mass of product(kg)}} \quad (2)$$

And the process mass intensity (PMI), which is defined in eq 3<sup>4</sup>

$$PMI = \frac{\text{total mass used in the process(kg)}}{\text{mass of product(kg)}} = E\text{-factor} - 1 \quad (3)$$

The results are presented in Table 8.

While metrics such as carbon economy,  $CE^4$  (0.89 for **10** and 0.63 for **13** in solution and using P7), atom economy,  $AE^4$  (0.69/0.69 for **10** and 0.49/0.49 for **13** in solution/using P7), and reaction mass efficiency,  $RME^4$  (0.69/0.69 for **10** and 0.41/0.47 for **13** in solution/using P7) are essentially the same between the mechanochemical and solvent-based procedures. The *E*-factor and the PMI metrics were better with the use of P7 compared to those of the reactions in solution thanks to the solvent reduction (Table 7). Detailed calculations are reported in Supporting Information.

**SEM Analyses in the Presence of Products.** SEM images were also taken for reactions with the pyrogenic S13 silica in two different cases: (i) in the presence of compound **10** once obtained and adsorbed and (ii) with triazole **13** after the mechanochemical reaction of hydrazone **10** with IBD in order to obtain it.

Hydrazone **10** when adsorbed in S13 gave SEM images presented in Figure 13. The morphology of S13 is the same as when no compound is adsorbed, i.e., spacious forming primary particles aggregates, where compound **10** might be present. An elementary analysis of the sample by using an EDS probe (energy dispersive X-ray spectroscopy) of SEM indicates the presence of carbon and nitrogen atoms constitutive of the hydrazone structure along with the Si and O atoms (Figure 14).

In the next experiment, we performed SEM analyses in two samples obtained as follows: the adsorbed hydrazone **10** was allowed to react with IBD under the mechanochemical conditions. One sample was obtained after 5 min of grinding (38% of conversion to triazole **13** measured by <sup>1</sup>H NMR spectroscopy) and allowed to stand at room temperature for 60 h of aging (total conversion measured by <sup>1</sup>H NMR spectroscopy). A second sample was obtained after 15 min of grinding (total conversion to triazole **13** determined by <sup>1</sup>H NMR spectroscopy) and then, as done previously, 60 h of aging under the same conditions. The SEM images thus contain triazole **13** and are presented in Figure 15.

In both cases, we can see crystalline forms confirmed by XRD experiments (see Supporting Information); nevertheless they are different depending on the experiment. The SEM images in the first case are showing the triazole in the form of a

tube where silica is present at both edges of the tube; it seems likely that the aging reaction took place inside the S13 primary particles aggregates; silica is still covering a large part of the triazole. In the second case, triazole is presented in fine needle and silica is much less present in the different extremities.

An elementary analysis of the samples by using an EDS probe (energy dispersive X-ray spectroscopy) of SEM was also performed (Figure 16). Concerning the first experiment, when focusing on the crystal, we can see its composition (carbon, nitrogen, and oxygen atoms) indicating that is the triazole **13** (Figure 16, spectrum 1). We can observe major zones where silica (Si and O atoms) has a strong presence (Figure 16, spectrum 2). The same is also true, respectively, for spectra 3 and 4 (Figure 16).

## CONCLUSION

In the study reported here, we presented the mechanochemical syntheses of 1,2,4-triazoles by using a planetary mill P7 starting from hydrazine hydrochloride **8**. We found, first, excellent conditions for achieving total conversion to intermediate hydrazones with various aromatic heteroaromatic and phenolic aldehydes in a few minutes in the presence of pyrogenic S13 silica as grinding auxiliary. We analyzed its use in the reaction as essentially being energy transfer to the reactants. The conversion to the annulated 1,2,4-triazoles was optimal with IBD when using nonphenolic hydrazones, while SeO<sub>2</sub> was found to be efficient for the latter. We suggest that granulometry and intrinsic constitution of the grinding auxiliary are important in order to optimize the mechanochemical reactions.

SEM images and XRD have shown the morphological forms of grinding auxiliaries before and after grinding and also hydrazone **10** and triazole **13**. For the latter, different crystalline forms were obtained between mechanochemical total conversion of hydrazone **10** and aging of the reaction. The one-pot two-step synthesis was also successfully conducted in all cases. For the first time, annulated 1,2,4-triazoles were obtained in a one-pot two-step procedure by mechanochemical means. Finally, green metrics showed the efficiency of the method in comparison to the conventional syntheses of hydrazone **10** and triazole **13**.

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## Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interest.

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