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Mechanosynthesis, a method of choice in solid state synthesis

1. Introduction

"Mechanosynthesis" is the use of mechanical energy to promote chemical reactions. Since the mid-90's, this term has been used in the context of reactions in which molecules are brought together in planned sequences, positions, and orientations as observed by scanning tunneling microscope. K. Eric Drexler is often described as "the founding father of nanotechnology", as he established fundamental principles of molecular engineering and outlined development pathways for advanced nanotechnologies [1]. This approach opened potentially exciting applications in assembly of molecular-scale devices and led to a method for synthesizing diamonds by mechanically removing/adding hydrogen atoms and depositing carbon atoms. In this context, self-assembly is described as "supramolecular synthesis". Hence, weakly guided assembly that relies on weak bonds can similarly be described as "supramolecular mechanosynthesis".

In a more general way, "mechanosynthesis" refers to the process in which reactions are activated mechanically and lead to a variety of molecular or supramolecular compounds, usually starting from solids. The source of mechanical energy used to force molecules to react is classically obtained by grinding a physical mixture of two (or more) different partners in a mortar of a ball mill (Figure 1). Under some experimental conditions, it is advantageous to add a few drops of solvent to the solids leading to so-called liquid-assisted grinding (LAG). In some cases, chemical reactions can also be initiated between a solid reactant and a liquid: in that case, the process is called kneading.

a)

b)

Figure 1: Classical equipment used for solid state mechanosynthesis. a) Mortar and pestle b) Retsch MM400 vibration mill.

Mechanosynthesis offers advantages over conventional chemical synthesis usually occurring in solution or in gas phase. Among the advantages, one finds the possibility of reducing side reactions leading to higher yields and/or better conversions. In many cases, better conversions could be attributed to the elimination of byproducts and volatile reactants when the reaction is carried out at elevated temperatures. The absence of any solvent – or presence of limited amounts of solvent in the case of LAG – is another advantage of this approach and justifies this method as a green alternative to conventional chemical synthesis. This approach is thus attracting interest as a result of environmental and sustainability issues. The term 'solvent-free', usually associated to a mechanochemical synthesis could however be misleading. Indeed, in some cases, 'solvent molecules' can be present in the solid reactants as molecular solvates (*e.g.* hydrated salts). In addition, a solvent-free reaction does not necessary exclude the use of solvent in the subsequent work-up and purification steps.

Examples of such types of reactions can be found in the history of chemistry as illustrated by the reduction of AgCl to Ag by reaction with Zn or Cu in a pestle and mortar carried out by Michael Faraday around 1820. In modern chemistry, molecular mechanochemistry developed significantly in the 1980s and 90s, in particular when applied to the synthesis of co-crystals. Formation of those co-crystals (see also discussion) involves the formation of non-covalent bonds, mainly H-bonds or ionic coordination to metals. At the same period, covalent organic synthesis in solvent-free reactions between solids initiated by grinding was described [2, 3].

Since then, this approach has been generalized to the synthesis of a variety of chemical families including organic, metal-organic, and supramolecular synthesis.

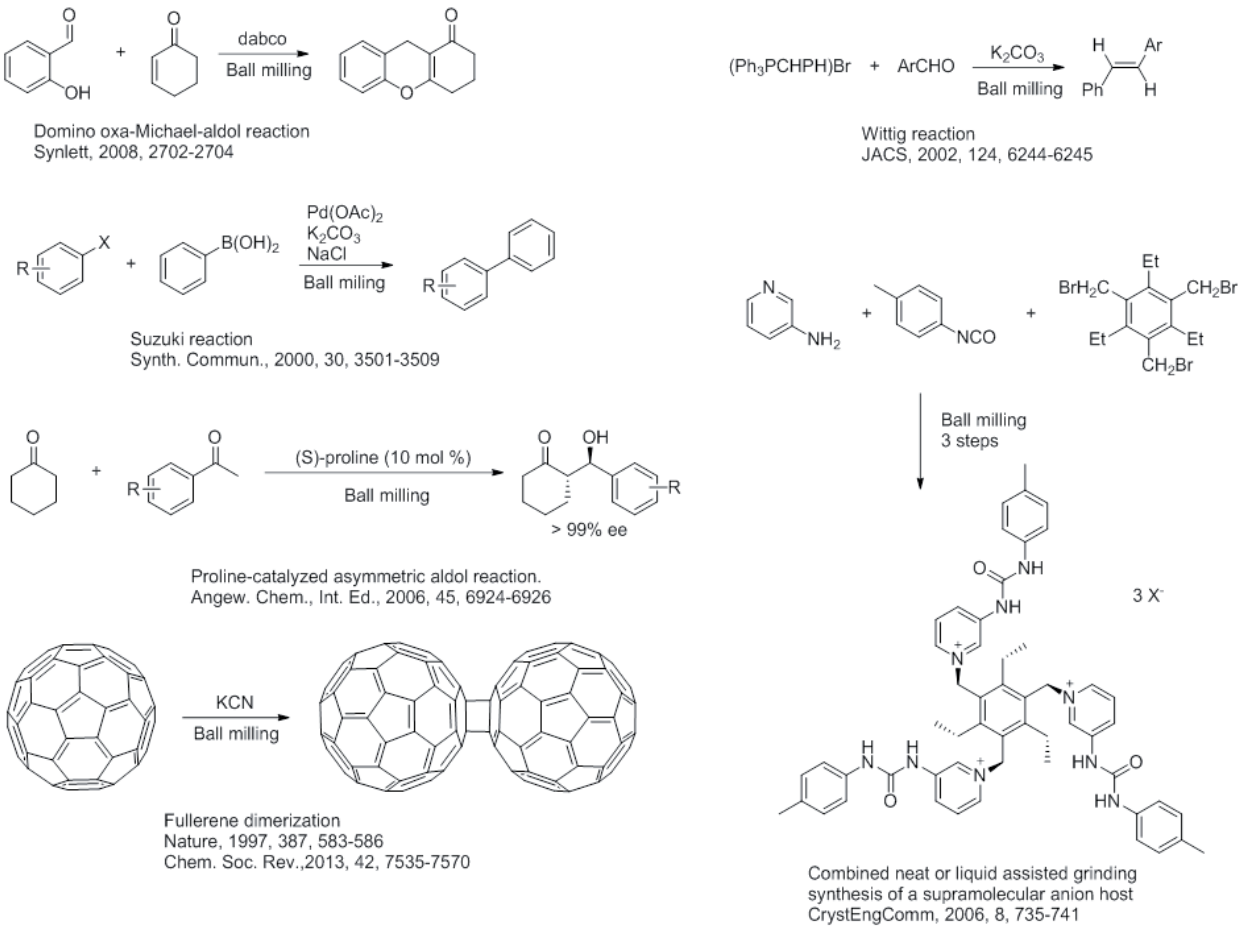


Figure 2: Selected examples of reactions performed by mechanochemistry.

Reviews cover those aspects [4-7] and some examples of reactions are provided in Figure 2.

The mechanisms underlying the process are still poorly understood. Among the processes that potentially explain the efficiency associated with mechanosynthesis are mass transfer mediated by a vapor phase and mechanochemical reactions mediated by an eutectic or by an amorphous phase (*e.g.* [8]).

Classical methods for the characterization of the solids obtained after mechanosynthesis include X-ray diffraction analysis of the powder samples and calorimetric measurements (melting points of reactants and/or products). Changes induced by the reaction can also be followed by IR spectroscopy and NMR (either directly on the solid samples or after dissolution in an appropriate solvent). Solid-state reactions can also in some cases lead to changes in color. These changes offer an interesting opportunity to visually account for chemical changes induced by mechanical stress. Recently, new methods have been designed and developed to monitor *in situ* the changes that accompany solid-state reactions [9].

In the present short contribution, we focus on two selected applications of mechanosynthesis related to project areas developed by our group. The first application deals with the solid-state preparation of co-crystals using grinding. The second application describes the formation of new covalent products starting from solid reactants. This second area is exemplified by the formation and characterization of (na)phthalimides and imines after grinding of corresponding (na)phthalic anhydrates or aryl ketones and amines.

The selected examples illustrate the rather advanced experimental setup and underline the efficacy of the solid-state formation of desired products in good to excellent yields. Structural characterization by X-ray diffraction of products and potential reaction intermediates also suggests that the solid state reaction could proceed *via* intra-solid rearrangements that potentially involve co-crystal intermediates.

2. Case studies on selected examples from de lab.

2.1. Mechanosynthesis of co-crystals

The development of new solid forms of active pharmaceutical ingredients (APIs) is an important aspect of pharmaceutical solid material sciences. Over the past decade mechanochemical methods, have appeared as efficient methods for the synthesis of single- and multi-component crystalline solids (co-crystals and salts). Applications of mechanochemistry in the synthesis and discovery of new pharmaceutical forms have been presented [10, 11]. Neat grinding and liquid-assisted grinding are as highly efficient means to synthesise and screen pharmaceutical co-crystals.

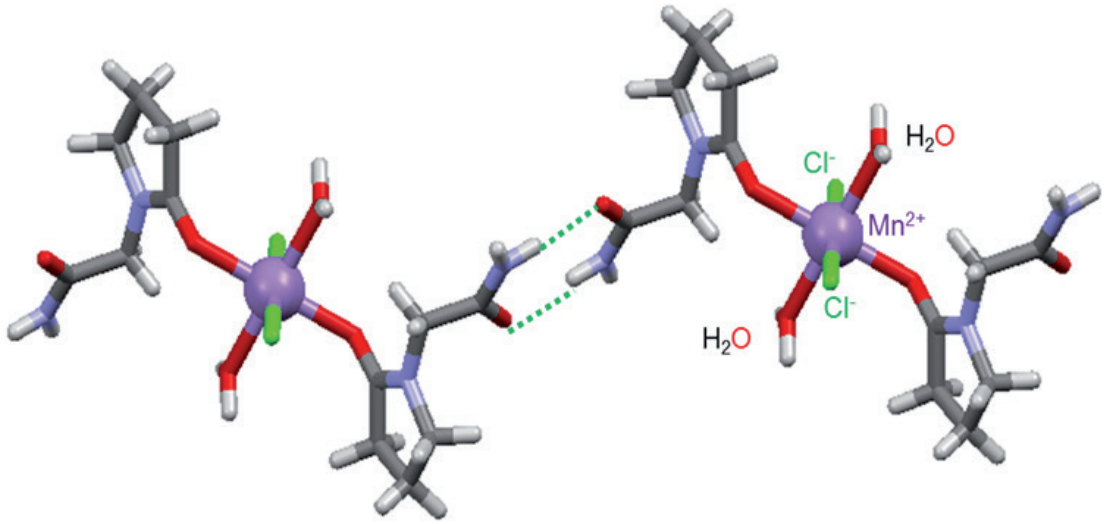
Co-crystallization of sulfadimidine with a variety of carboxylic acid co-crystal formers (*e.g.* benzoic, anthranilic, salicylic, and acetylsalicylic acids (aspirin) by grinding were among the first pharmaceutically relevant molecules to be reported in the 90s [12].

In collaboration with the pharmaceutical industry, our group has been active in the study of co-crystals of racetams (*e.g.* [13]). In this context, *Piracetam*, (2-oxo-1-pyrrolidineacetamide), is a good example. It illustrates the possibility of formation of a variety of co-crystals using H-bonds or coordination to a metal cation (Figure 3). In these studies, organic acids (*e.g.* gentisic acid, *p*-hydroxybenzoïc acid, tartaric acid, citric acid, mandelic acid) and inorganic salts have been selected as co-formers. Interestingly, co-crystallization of racetams with Li^+ salts leads to ionic co-crystals and opens the perspective of formation of co-drugs, *i.e.* the co-administration of two (or more) pharmaceutical ingredients co-crystallized in a single solid form (*e.g.* [14, 15]). Many of these solids were obtained by mechanosynthesis.

In a similar context, we showed that amino-acids are interesting co-formers for the synthesis of pharmaceutical co-crystals [16]. These co-formers lead to zwitterionic co-crystals as exemplified in the case of the 1:1 *L*-prolinium – *S*-naproxene co-crystal (Figure 3c).

a)

b)



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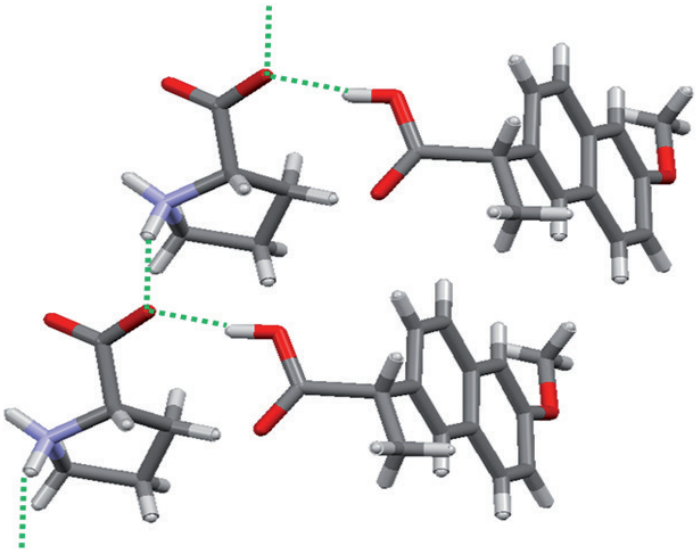


Figure 3 : Examples of pharmaceutical co-crystals. a) 1:1 piracétam - *p*-hydroxybenzoïc acid pharmaceutical co-crystal (CCDC code DAVPEW) stabilized by carboxylic acid – amide (heterosynthon) H-bonds (depicted as green dotted lines); b) 1:2 piracétam – Mn^{2+} ionic co-crystal; coordination clusters are connected by amide-amide (homosynthon) H-bonds (CCDC code LEDZUP); c) 1:1 *L*-prolinium – *S*-naproxene (CCDC code FEVZUD).

One of the main reasons to prepare pharmaceutical co-crystals using mechanochemistry is the fact that the resulting solids can present enhanced physico-chemical properties [17]. This is illustrated, in the case of caffeine or theophylline that form co-crystals with dicarboxylic acids [18, 19]. Co-crystals obtained with oxalic acid by mechanosynthesis, demonstrate enhanced hydration stability compared to the solid APIs.

Similarly, co-crystallization of nicotinamide with *S*-ibuprofen and *RS*-ibuprofen by liquid-assisted grinding leads to solids with higher melting points, as a result of extended hydrogen bonding [20].

Besides synthesis of pharmaceutical co-crystals, mechanosynthesis has been successfully used for the synthesis of pharmaceutical salts. For example, salts of trimethoprim and pyrimethamine with pharmaceutically acceptable carboxylic acids (*e.g.* formic, acetic, maleic, fumaric, succinic, glutaric or salicylic) have been obtained by by grinding [21].

Mechanochemistry is also used for the synthesis of metal complexes and metal-organic frameworks [7]. Using this principle, Braga and co-workers used mechanical grinding to prepare derivatives of the neuroleptic drug gabapentin with zinc and copper(II) chlorides [22]. In collaboration with the same group, we showed that the ionic-cocrystal obtained by grinding piracetam with lithium salts afford new solids with improved physico-chemical properties [14]. The PIR.LiCl.2H_2O co-crystal obtained by grinding converts to an anhydrous form at ca.75°C, which is then stable up to ca. 240°C, when it melts.

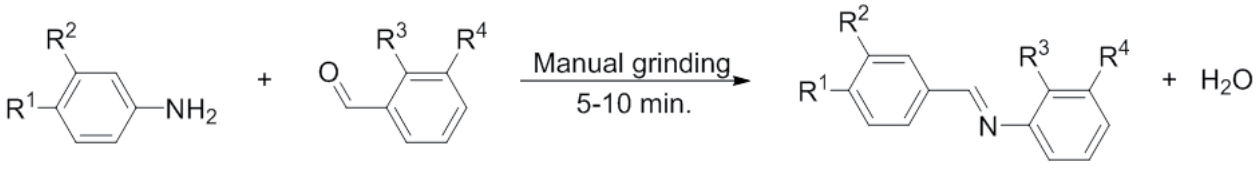
Co-crystallization of carbamazepine with saccharin was used as a model to study the mechanism of neat grinding co-crystallization [23]. These authors show that co-crystallization of saccharin and carbamazepine proceeds through an intermediate amorphous phase.

The ability to construct pharmaceutical co-crystals on a large scale is an important issue for the industrial applications of mechanosynthesis. Recent advances have been made as proposed by C. Medina et al. [24] including a scalable solvent-free process for pharmaceutical co-crystallization by using twin screw extrusion.
In most cases pharmaceutical co-crystals with improved properties are discovered by a trial-and-error process. In this process, mechanosynthesis, in particular LAG, plays a key role. The fact that the outcome of such co-crystallization synthesis remains largely unpredictable opens interesting perspectives in terms of Intellectual Properties and patents. This makes mechanosynthesis of co-crystals an attractive approach for the pharmaceutical industry.

2.2. Mechanosynthesis of imines

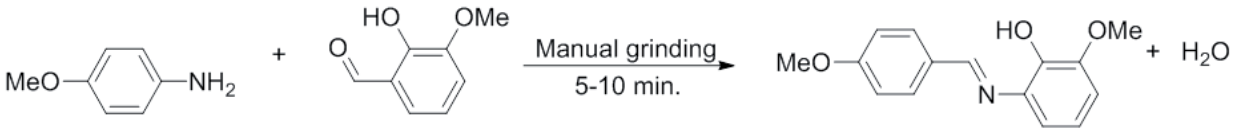
The second application consists in the formation of new covalent products starting from solid reactants. To confirm the viability of the technique, we entered this field by studying the synthesis of various imines from a series of amines and aldehydes as starting material. (Scheme 1)

Mixtures of a selected amine (p-toluidine, p-anisidine or 2-nitroaniline) and an aldehyde (benzaldehyde or o- vanillin) (Scheme 1) were ground using mortar and pestle for 5 to 10 min. For benzaldehyde, which is a liquid at room temperature, the resulting wet paste was ground (kneaded) following the general procedure. The ground products obtained were characterized by calorimetry (melting point),



R^1 = H, Me, OMe
R^2 = H, NO_2
R^3 = H, OH
R^4 = H, OMe

Scheme 1: Formation of imines from corresponding substituted benzaldehyde and aniline derivatives.



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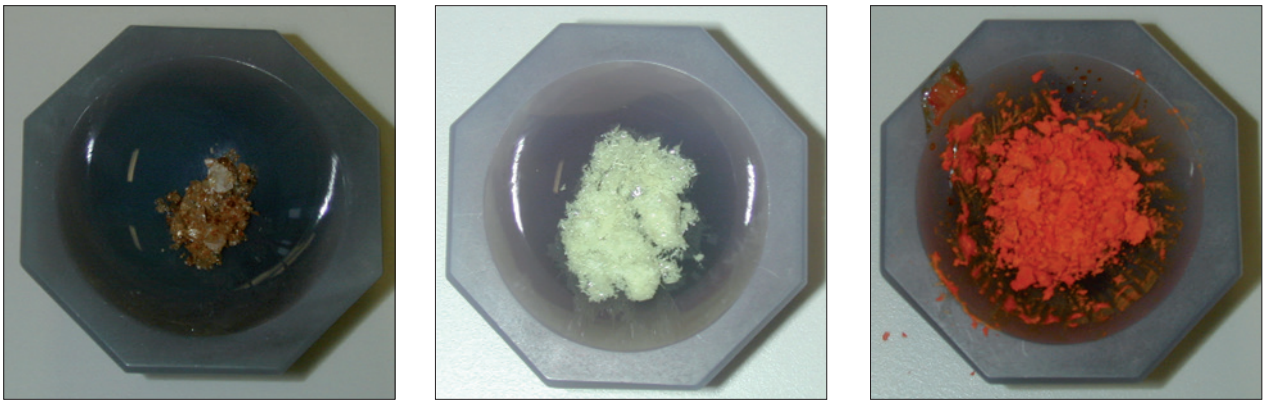

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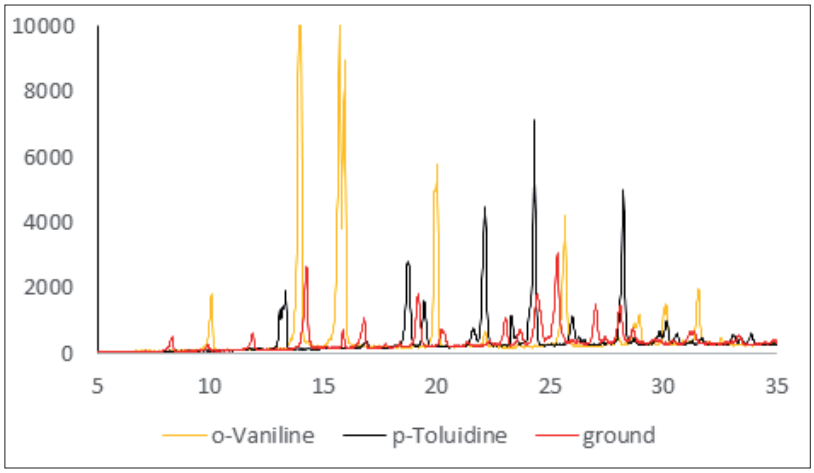

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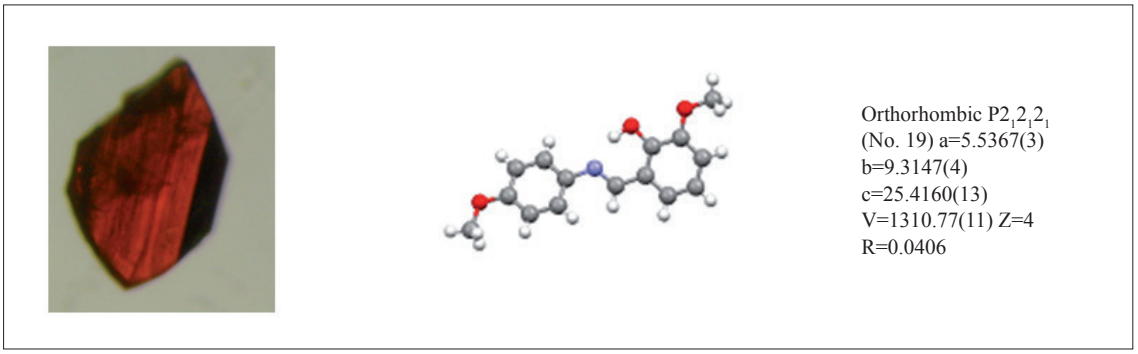


Figure 4 : Mechanosynthesis of (E)-2-methoxy-6-(((4-methoxyphenyl)imino)methyl)phenol obtained by grinding **p-toluidine** and **o- vanillin**. a) visual aspects of the reaction : p-toluidine (1) o- vanillin (2) Grinding of o- vanillin and p-toluidine after 5 minutes (3); b) comparison of powder X-ray data; c) Single crystal structure of the final product after recrystallization from EtOAc/HOAc.

NMR, powder X-ray diffraction (PXRD) and, when possible, by single X-ray crystallography (SCXRD).

Results are illustrated in the case of p-toluidine and o- vanillin (Figure 4). X-ray diffraction data measured on both powders and single crystals confirm unambiguously the formation of the product. NMR data indicate 100% conversion of the reactants. The advancement of the reaction can be monitored by observing a color change. We noticed a transition from brown and white for reagents to orange for the product (Figure 3a).

Similarly, in the case of 2-nitroaniline and o- vanillin, X-ray diffraction data confirm the formation of the product ((E)-2-methoxy-6-(((3-nitrophenyl) imino)methyl)phenol). NMR data indicate 100% conversion of the reactants. Here, we obtained two polymorphic forms of the product. One shows coplanarity between the two aromatic rings. The other crystal structure shows a twist angle of 27 ° between the two aromatic rings.

In the case of 2-nitroaniline and benzaldehyde, the grinding at room temperature does not lead to the formation of the desired product, but leads instead to a simple mixture of reagents. However, heating of the ground sample at 50°C results in the formation of the desired (E)-N-(3-nitrophenyl)-1-phenylmethanimine.

These examples confirm data published in literature (*e.g.* [25]) and illustrate the viability of mechanosynthesis as a simple, clean, and efficient method for the preparation of hydoxy-substituted Schiff bases. The resulting molecules have potential applications as photo and thermo-chromic materials.

2.3. Mechanosynthesis of imides

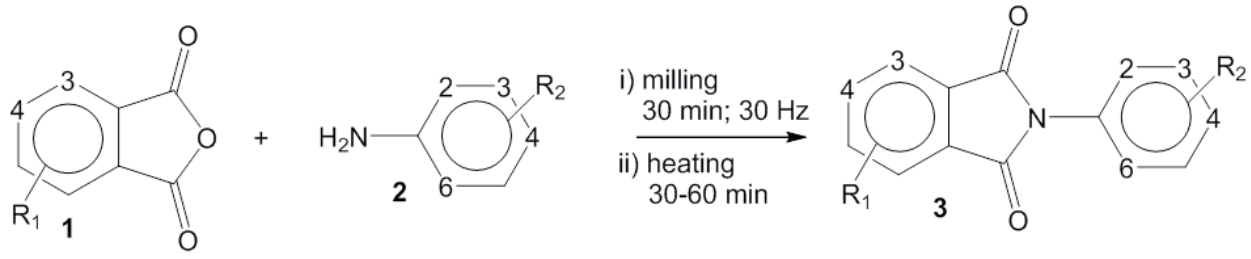
2.3.1. Phthalimides

Classically, synthesis of phthalimides is performed by dehydrative condensation of phthalic anhydride at high temperatures with primary amines, when the amine is available. When the amine is not readily accessible, the direct N-alkylation of phthalimides with alcohols under Mitsunobu conditions and of potassium phthalimide with alkyl halides (Gabriel Synthesis) are popular alternative approaches.

Mechanochemistry is an interesting alternative for the synthesis of these compounds and we have tested this reaction on a series of model phthalimides (**3**, Scheme 2).

Solid mixtures of different substituted phthalic anhydric acids, **1,** and substituted anilines, **2,** were ground using a Retsch MM400 ball mill operating at 30Hz for 30 min. For 2,6-dimethyl-aniline (**2i**, Scheme 2), which is a liquid at room temperature, the resulting wet paste was ground following the general procedure. The ground products obtained were further heated in a metal block thermostat (MBT 250, Kleinfeld). In each case, the outcome was characterized by calorimetry (melting point), NMR, powder X-ray diffraction (PXRD) and, when possible, by single X-ray crystallography (SCXRD).

In all cases, the heated ground product corresponded to a new solid. Its color was different from the one of the starting reactants and its physicochemical properties (in particular melting points) were distinct from those of the starting phthalic anhydrates and anilines.



R_1 = H (**a**), 4-COOH (**b**), 3-NO_2 (**c**), 4-NO_2 (**d**)

R_2 = 2,6-diMe (**i**), 4-Me (**m**), 2,6-diCl (**j**), 4-OMe (**n**), 2,6-diBr (**k**), 3-NO_2 (**o**), 2,4-diCl (**l**), 2-COOH (**p**),

Scheme 2 : Formation of phthalimides (**3**) from corresponding substituted phthalic anhydrates (**1**) and aniline derivatives (**2**).

For example, grinding of phthalic anhydrate (**1a**) with aniline derivatives led to either an amorphous solid (with aniline **2i**) or a physical mixture (with anilines **2k** and **2n**) of the starting reactants. Heating of the resulting solids allowed formation of the corresponding phthalimides (**3ai**, **3ak** and **3an**) as white crystalline powders.

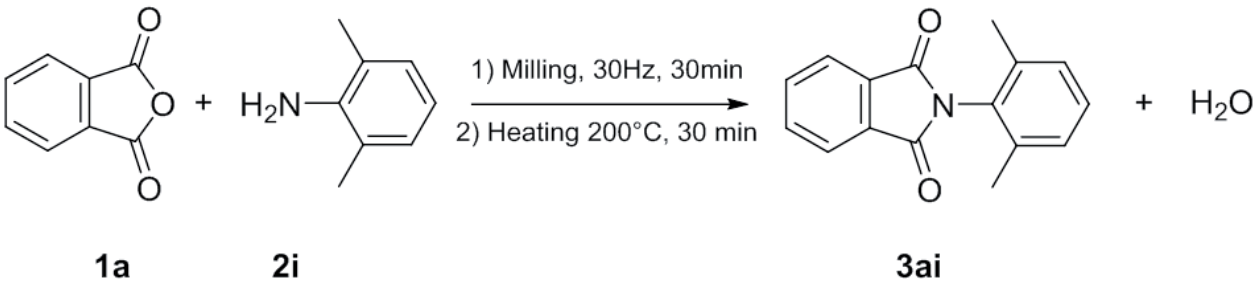
In the case of N-phthaloyl-2,6-dimethylaniline (**3ai**, m.p. 204°C), X-ray diffraction data measured on both powders and single crystals (Figure 5) confirm unambiguously the formation of the product. NMR data indicates 100% conversion of the reactants. Interestingly, the powder diffractogram of the ground product (2θ = 7, 10, and 13.5°) is not only different from the starting phthalic anhydrate (**1a**, 2θ = 13, 17, and 23°) [2,6-dimethyl-aniline (**2i**) is a liquid] but also from the final N-phthaloyl-2,6-dimethylaniline (**3ai**, 2θ = 11, 15, 19 and 22°) product obtained after heating. This suggests that the unheated solid corresponds to an intermediate state that needs to be heated to form the final phthalimide product.

Among other applications, phthalimides are suitable protective groups in peptide synthesis. Some of these compounds are also of potential interest in drug design.

2.3.2. Naphthalimides

Naphthalimides can also be obtained by mechanochemistry starting from naphthalic anhydrate and an amine as illustrated here.

For example, the reaction of 3-nitro-1,8-naphthalic anhydride, 3NNA, with either 2,6-dimethylaniline, DMA (a liquid) or 2,6-dibromolaniline, DBA, (white crystalline solid) can be initiated by grinding together the reactants. These mechanochemical reactions can be followed by a change in color, as illustrated in Figure 6.



a) b)

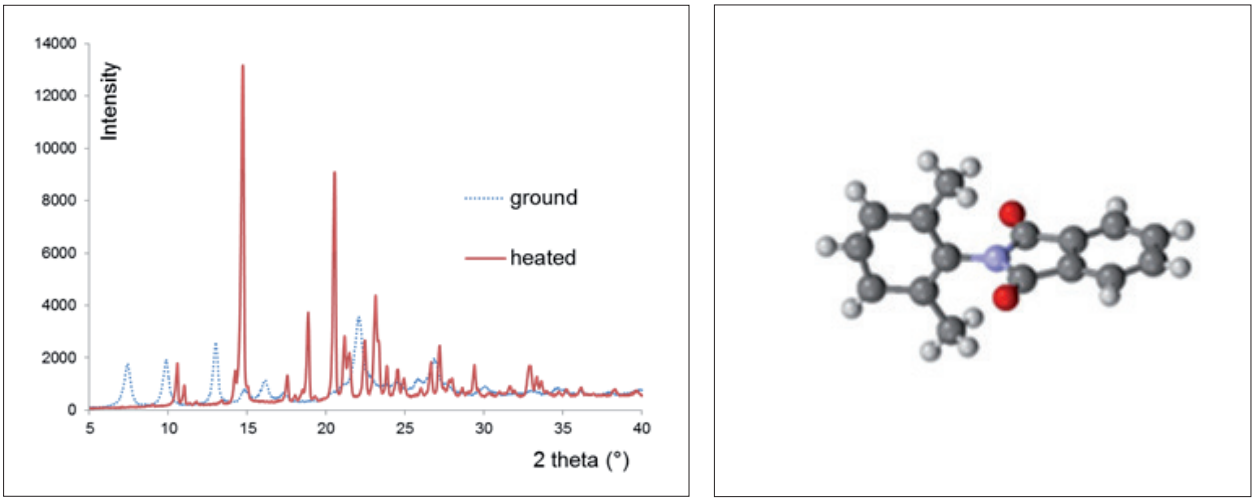


Figure 5: X-ray diffraction analysis of the solid corresponding to N-phthaloyl-2,6-dimethylaniline (**3ai**), obtained after grinding of **1a** and **2i** and heating to 200°C. a) Powder diffractograms recorded before and after heating of the ground sample and b) single crystal structure confirming formation of the phthalimide product.

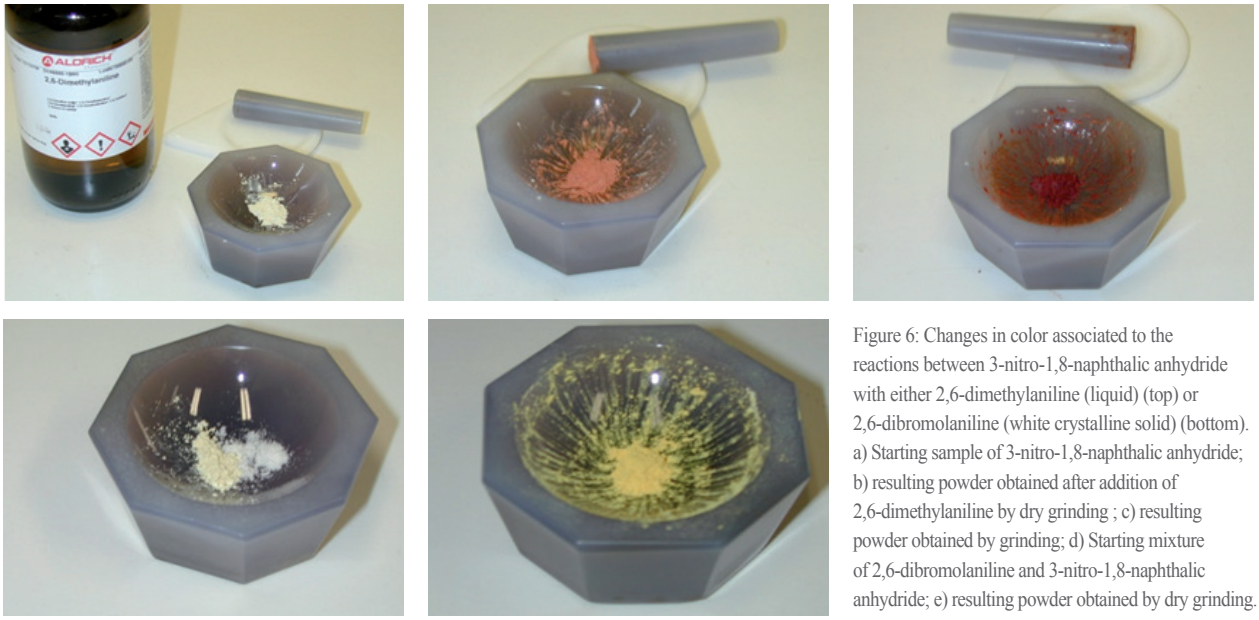


Figure 6: Changes in color associated to the reactions between 3-nitro-1,8-naphthalic anhydride with either 2,6-dimethylaniline (liquid) (top) or 2,6-dibromolaniline (white crystalline solid) (bottom). a) Starting sample of 3-nitro-1,8-naphthalic anhydride; b) resulting powder obtained after addition of 2,6-dimethylaniline by dry grinding ; c) resulting powder obtained by grinding; d) Starting mixture of 2,6-dibromolaniline and 3-nitro-1,8-naphthalic anhydride; e) resulting powder obtained by dry grinding.

The resulting solids have been characterized (NMR, melting points, crystallography) and do correspond to naphthalimides. Conversion to the final products is favored by heating of the samples, similarly to what we observed for phthalimides.

We have generalized these reactions to other anhydrates, including 1,4,5,8-naphthalenetetracarboxylic dianhydride. Similar reactions have been described in literature. In particular, Zaworotko very elegantly showed that during the course of the mechanochemical procedures for preparing N-organophthalimides, intermediate co-crystals could be isolated; he therefore introduced the term "co-crystal controlled solid-state synthesis, C^3S^3" to this mechanochemical approach [26].

2.3.3. Maleinimides

To prove that mechanochemistry is functional for the synthesis of compounds of pharmaceutical interest, we studied synthesis of RG108 analogues, compounds that show potential as epigenetic modulators. To illustrate this, we use as example of this project the synthesis of a maleimic derivate of RG108, **4** (Figure 7). Room temperature grinding of maleic anhydride and L-tryptophan led to the formation of a first intermediate product, **4-O**. This compound appears to be the open form of desired product **4**. Heating the ground solid sample at 120 °C led to the formation of a mixture of **4-O** and final product **4**, as deduced by NMR analysis of the final solid.

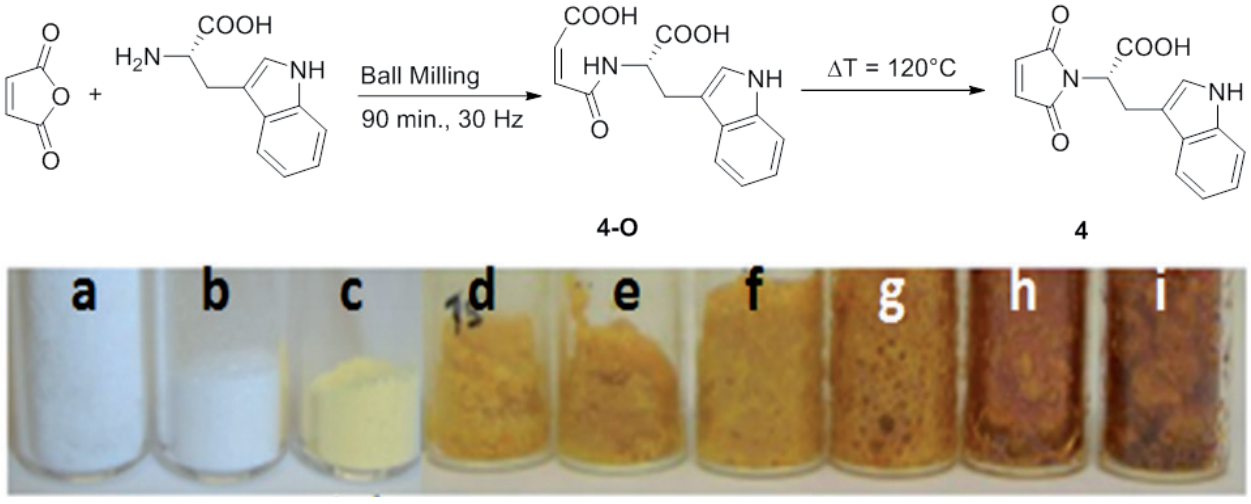


Figure 7: Synthetic route to compound **4** *via* mechanochemistry. Changes in color related to the synthetic steps : a) maleic anhydride b) L-tryptophan c) after 90' of ball milling d) milling for 15' at 100°C e) milling for 15' at 110°C f) milling for 15' at 120°C g) milling for 15' at 130°C h) milling for 15' at 145°C i) milling for 15' at 160°C.

We have studied the influence of the heating on the formation of **4** from its open form (Figure 7a-i). Grinding of reactant results in the complete conversion of reagents (a, b) to **4**-O (pale yellow powder (c)). Heating to 120°C leads to the formation of **4** (orange powder). At higher temperatures, there is decomposition of reagents.

This last example illustrates the importance of mechanosynthesis of compounds of pharmaceutical interest.

3. Conclusion

Mechanosynthesis offers advantages over more conventional chemical synthesis usually occurring in solution or in gas phase. Among the advantages, one finds the possibility of reducing side reactions leading to higher yields and/or better conversions.

In the present contribution, selected applications of mechanosynthesis related to projects areas developed in our group have been presented. The first application dealt with the solid-state preparation of co-crystals. The second application described formation of imines and (na)phthalimides after grinding of corresponding aryl ketones or (na) phthalic anhydrates and amines.

The selected examples illustrate a relative advanced experimental setup and underlines the efficacy of solid-state formation of desired products in good to excellent yields. Structural characterization by X-ray diffraction of products and potential reaction intermediates also suggests that the solid state reaction could proceed *via* intra-solid rearrangements that potentially involves co-crystal intermediates.

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