High Throughput Mechanochemistry: Application to Parallel Synthesis of Benzoxazines.

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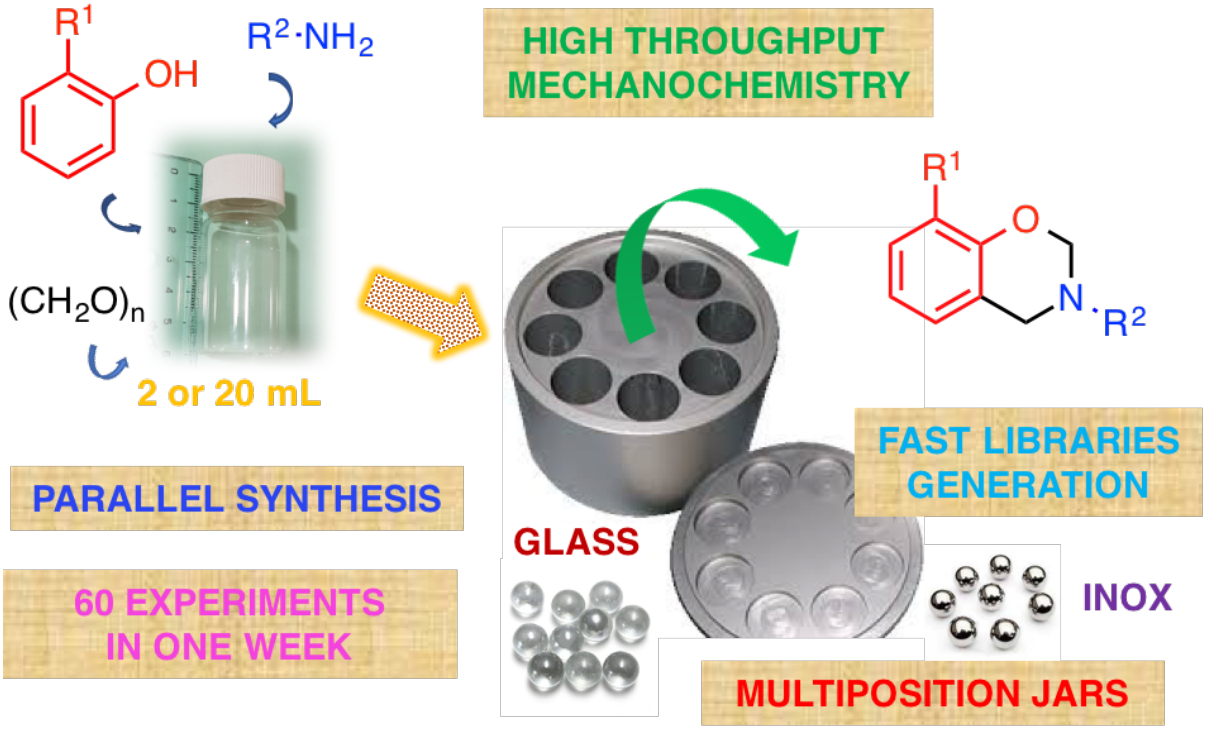
Abstract

We describe herein an unprecedented "*parallel synthesis*" *via* a mechanochemistry to massive access molecules faster, more efficiently and with higher throughput compared to standard milling devices. The new milling system uses a multiposition jar (variable sizes are possible), allowing to process up to 12 samples simultaneously, enabling the fast analysis of multiple experimental parameters at the same time. During milling, the variation of force intensity depends on the position of the vials over the time, according to a movement referred to as "lunar". The development of this new synthetic technology was applied to the high throughput mechanochemical preparation of 3,4-dihydro-2H-benzo[*e*][1,3]oxazine derivatives *via* a *one-pot* three-component reaction.

Graphical Abstract



Keywords. High Throughtput Mechanochemistry, Multiposition ball-mill, Multicomponent reactions (MCR), Mannich Reaction, Benzoxazines.

In the past decades, the search for cleaner and more sustainable approaches to chemical synthesis led to a reborn of mechanochemistry.[1, 2] Excellent and extensive reviews already highlighted the advantages of this enabling technology not only as a valid alternative to chemistry in solution for the preparation of molecules[3-10] and materials,[9-14] but also as a fully effective key strategy for new synthetic opportunities altering product selectivity[15] or leading access to products elsewhere impossible to be obtained by other methods.[16-21] Tools for real-time mechanistic studies (by X-ray powder diffraction or Raman spectroscopy techniques)[22-26] or the use of extruders for scale-up purposes[27, 28] were successfully achieved. While the investigation of kinetics and energetics[29, 30] involved in mechanochemical processes are still in infancy, with regard to synthetic chemistry, the main limitation on the use of ball mills concerns its low throughput. The development of advanced mechanochemical devices, where many samples are milled in parallel will increase time efficiency enabling the fast analysis of multiple experimental parameters at the same time. In addition, they might also improve throughput protocols for the preparation of samples for parallel sequencing.

A modified multisampling planetary mill[31] was successfully used some time ago for co-crystal screening[32, 33] or to prepare dispersions of carbon black pigments.[34] Besides these few examples, nothing is presently known about the use of this high throughput experimentation in mechanically activated organic reactions.

In this regard, we have developed an unprecedented "*parallel synthesis*" *via* a mechanochemical approach" to massive access molecules faster and more efficiently. In our ongoing research work on the development of in the field of medicinal mechanochemistry[35] for preparing Active Pharmaceutical Ingredients (APIs)[36, 37] or added value products for the industry,[37] we prepared a library of substituted 3,4-dihydro-2H-benzo[*e*][1,3]oxazines by "parallel mechanochemistry". 3,4-Dihydro-2H-benzo[*e*][1,3]oxazines are scaffolds of industrial relevance, which are widely used for preparing polymers, resins and cross-linking agents.[38] These substrates are also suitable building blocks for the design of biologically active compounds[39] from herbicides and fungicides to therapeutically usable drugs.[40]

The development of this new synthetic methodology will be set-up in two distinct phases. First, the main advantages and technical aspects of the new enabling device will be described, whereas later the high throughput mechanochemical preparation of 3,4-dihydro-2H-benzo[*e*][1,3]oxazine derivatives *via* a *one-pot* three-component reaction will be examined.

The synthesis were executed using a new planetary milling system where standard milling jar was modified to process up to 12 samples simultaneously,[31] depending on the size of the vial. Indeed, a 4-, 8- and 12-position laboratory mill could host vials with a capacity of 200 mL, 20 mL and 2 mL respectively (Figure 1). This upgraded version of the starting milling jar enables up to 48 samples to be milled in parallel (see Supporting Information, Figure S1). All this translates in a reduced effort and time for the screening of the optimized reaction conditions and higher productivity of molecules per unit of time.

The multisampling device offers other advantages, such as: i) no cleaning or cross contamination of the jars, since the reactants are milled directly into the vials, (in which the reaction mixture can be also stored or analyzed directly through the vial glass by Raman, avoiding loss of samples; ii) many small amounts of samples (only 10's of mg!) can be reacted at the same time; iii) the aluminum vial adapters serve as heat sinks, minimizing sample heating and iv) vials can be continuously loaded and unloaded, thus processing hundreds of samples per day.

For the experiments described in this study, 8- or 12-position vial adapters, to hold respectively 20 mL or 2 mL glass vials, were used (Figure 1b, c) and the effectiveness of the planetary milling system was investigated for the preparation of a library of substituted 3,4-

dihydro-2H-benzo[*e*][1,3]oxazines (Scheme 1). Hanusa's formalism was used to represent the reaction activated by mechanochemical energy.[5]

a) b)

c)

Figure 1. a) A multisampling planetary mill for more details visit http://www.automaxionltd.com/; b) 12 position jar hosting 2 mL GC/LC glass vials; c) 8 position jar hosting 20 mL glass vials.

The motion of the vials differs from the motion of the vessel in a conventional planetary mill, where the jar is located in the center and it turns around its own axis and simultaneously counter-clockwise around the principal wheel axis. With a multi-position jar, the movement was referred to as 'lunar':[31] vials are distributed around the jar periphery and experiment a degree of rotation around an axis which is different from the vial axis, while keeping counter-clockwise motion around the same principal wheel axis (Figure 2a). The force on a bead in the vial *varies* during the rotation: when the vials are closer to the center of the sun wheel, the force is less, when closer to the outer edge, the force is greater and equal to those in a conventional planetary system where the beads are always towards the outer edge of the sun wheel and therefore experience *constant* force (Figure 2b).

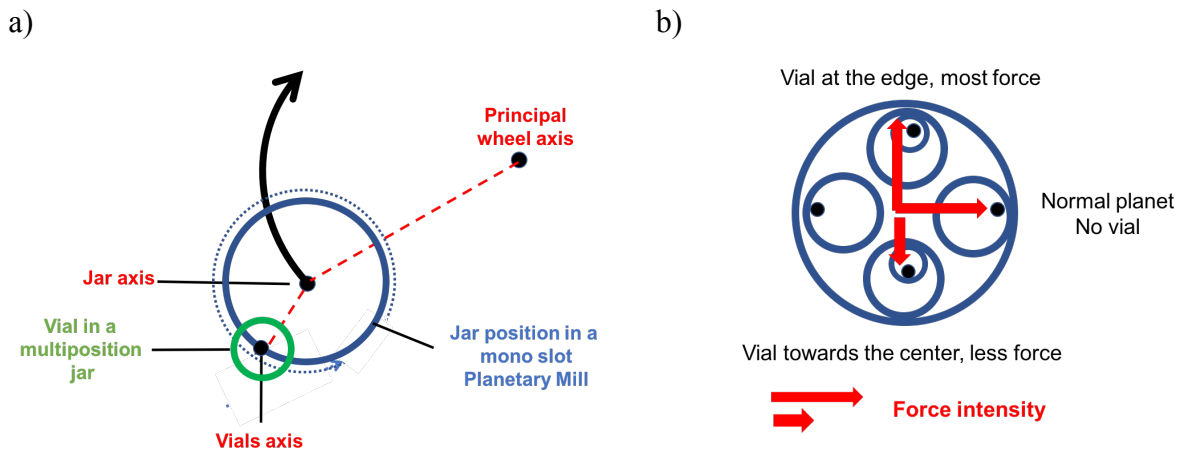
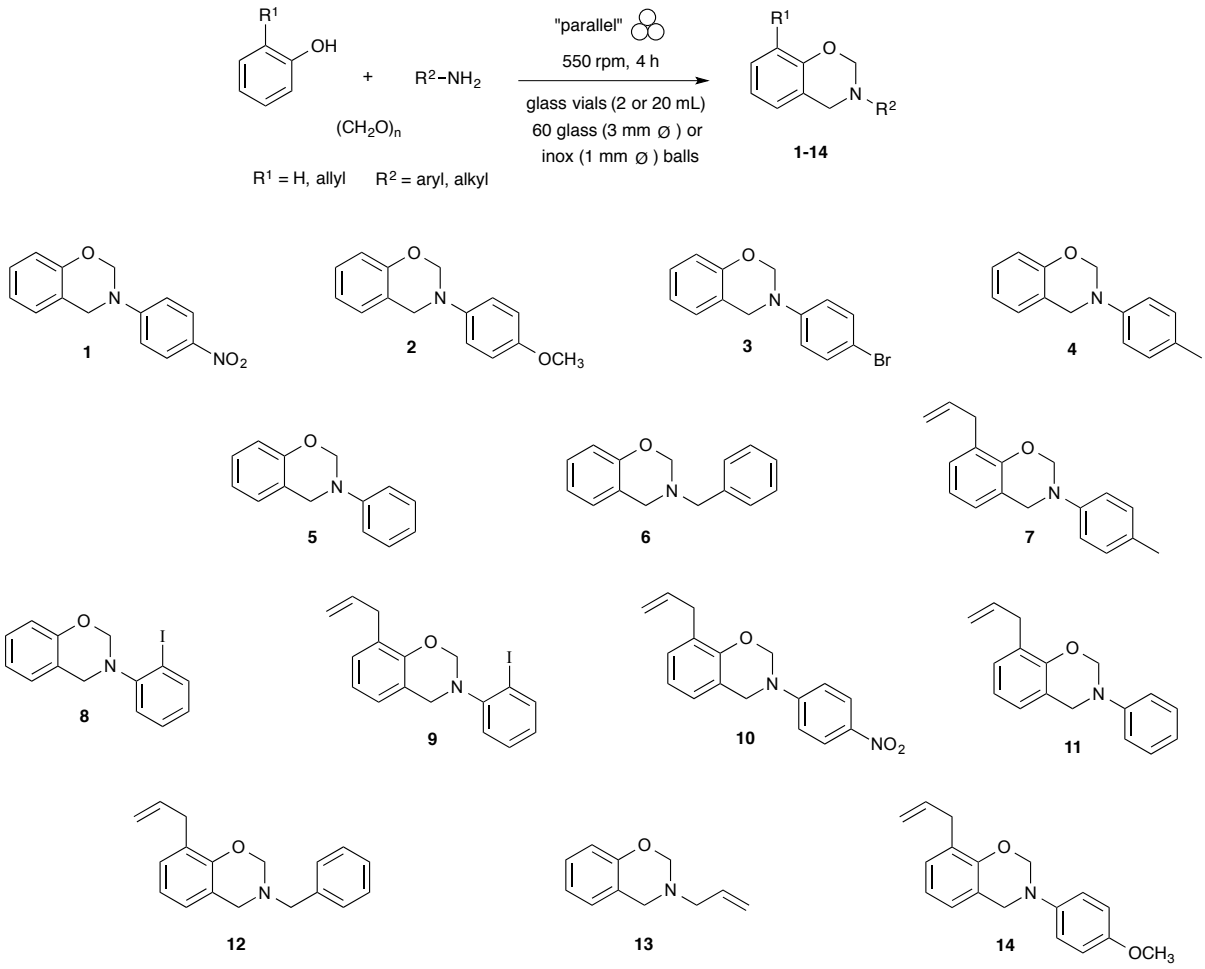


Figure 2. Schematic representation of a) 'lunar movement'[31] and b) variation of force intensity depending on the position of the vials.

3,4-Dihydro-2H-benzo[*e*][1,3]oxazines were prepared in a *one-pot* cascade sequence by condensation/Mannich base ring-closure reactions involving stoichiometric quantity of phenol (or *o*-allyl phenol), paraformaldehyde and a primary amine (aromatic, allylic or benzylic).

The possibility to screen simultaneously four different parameters for the preparation of three different compounds (**1-3**, Scheme 1) significantly reduced the optimization time and costs associated therewith. Indeed, twelve experiments were performed at the same time, by milling the reactants at 550 rpm for 4 hours, using four different reaction conditions for preparing each benzoxazine **1-3** (Scheme 1).



Scheme 1. High-throughput parallel mechanochemical preparation of benzoxazines.

All the experiments were performed in a 12-position jar hosting 2 mL glass vials each one containing 60 stainless steel balls (Ø 1 mm) using: i) stoichiometric quantity of paraformaldehyde (2 equiv.); ii) an excess of paraformaldehyde (up to 4 equiv.); or in the presence of grinding additives such as iii) NaCl[41] (100 mg); or iv) polyethylene glycol[36, 42] (PEG) HO-PEG-2000-OH (450 mg/mmol of substrate). Full conversion of starting materials was observed after 4 hour milling at 550 rpm and using a two-fold excess of paraformaldehyde. Lower rotation speeds or shorter reaction times were detrimental, leading to partial conversion of the reactants and uncomplete intramolecular cyclization reactions. '*Diluted solid solutions*' of reactants, in the presence of NaCl, required longer reaction times (6-8 hours) to achieve a full conversion of substrates, while the conversion, reaction time and yields were not affected or improved when HO-PEG-2000-OH was used as additive, except for benzoxazine **3**, obtained in traces in the absence of PEG polymer.

Table 1. Comparative data for mechanochemical and solution synthesis of 3,4-dihydro-2H-benzo[*e*][1,3]oxazines **1-14**.

Compound	Yield (%)[a]		Compound	Yield (%)[a]	
	Multiposition Ball-milling	In solution		Multiposition Ball-milling	In solution
1	45	56[43]	**8**	77	n.d.[c]
2	65	74[44]	**9**	43	n.d.[c]
3	67[b]	32[44]	**10**	23	n.d.[c]
4	65	63[45]	**11**	58	72[46]
5	73	62[45]	**12**	50	n.d.[c]
6	75	52	**13**	45	62[47]
7	50	51	**14**	37	35

[a] Isolated yield. The reaction scale was: a) for 2 mL glass vials (each vial containing with 60 stainless steel balls of Ø 1 mm): alcohol (0.53 mmol), paraformaldehyde (2.12 mmol), amine (0.53 mmol), b) for 20 mL glass vials (each vial containing 60 glass balls of Ø 3 mm): alcohol (3.19 mmol), paraformaldehyde (12.74 mmol), amine (3.19 mmol); [b] HO-PEG-2000-OH (450 mg/mmol of substrate) was used; [c] n.d. = never described.

In a second set of experiments, the preparation of benzoxazines **1-3** was investigated using an 8-position jar hosting 20 mL glass vials, with 60 glass balls (Ø 3 mm), milling at 550 rpm for 4 h. The aim was to study not only the scalability of the reaction, but also its outcome as a function of the size and the nature of material used (stainless steel or glass) for the milling balls and the geometry of the milling jars. As a result, the same yields were obtained for benzoxazines **1-3,** independently on the process parameters used to achieve the condensation/Mannich base ring-closure reactions. The multisampling planetary mill allowed the optimization of the reaction conditions by processing more than 60 experiments in less than one week compared to 6-8 weeks expected if using a conventional mill. Later on, once the general protocol was disclosed, it was extended to other substrates allowing faster and more efficient preparation of a library of diverse benzoxazines **1-14** (Scheme 1). Worthy of note is the *N*-allylbenzozaxine **13,** an attractive scaffold used as starting material for the preparation of polybenzoxazines, which are interesting polymers with excellent mechanical properties and high thermal stability.[46, 48] Contrarily to methods in solution,[49] by mechanochemistry the reaction yield is not influenced by the effect of the electronic or steric nature of R^2 substituents on the primary amine, for both series having R^1 = H (Table 1, compounds **1-6**, **8** and **13**) or R^1 = allyl group (Table 1, compounds **7**, **9-12** and **14**), with the exception of benzoxazines **1** and **10**. In the last case, the modest yields in both series are likely due to the presence of electron withdrawing nitro group, reducing the nucleophilicity of the

nitrogen atom of the substituted aniline, involved in the first step of the mechanism, where a condensation reaction with the aldehyde occurs. Nevertheless, for the same R^2 substituents, yields depended of the nature of R^1 *ortho*-substitution on starting phenol (R^1 = H or allyl), leading to better yields when R^1 = H (compounds **1**, **2**, **4**, **6** and **8** *vs* compounds **7**, **9**, **10, 12** and **14**). This is in agreement with previous reports on the synthesis of benzoxazines in solution, highlighting the key role played by both the reactivity of phenolic hydroxyl as well as the electron density of the aromatic carbon atom at the free *ortho*-position in the phenol ring.[50, 51]

Considering that the type of forces generated during milling and the total mechanical energy transferred to the powder influence the outcome of a mechanochemical reaction,[52-56] benzoxazines **1** and **2** were also prepared by milling the reactants for 4 hours in a vibrational (VBM, at 30 Hz) or in a classic planetary mill (PBM, at 550 rpm). Stainless steel or zirconia jars were used and the results were compared with those obtained when the reactant were milled in 20 mL glass vials, using the multiposition mill (Table 2). In a VBM or classic PBM, full conversion of the starting materials was observed in both cases. Benzoxazine **1** was recovered in 88% after precipitation in water, while benzoxazine **2** was obtained in 20% after extraction and purification on column chromatography. In the last case, yield was hampered by the formation of many polar unidentified by-products, never observed when using glass vials which produce cleaner reaction profiles, even with glass or stainless steel balls (Table 2).

Table 2. Influence of the technical parameters for the preparation of benzoxazines **1** and **2**.

	Yield (%)[a]		
	Planetary Ball Mill (PBM)		**Vibrating Ball Mill (VBM)**
	Multiposition	Classic	
Compound	Glass vials[b]	ZrO_2 jar[c]	Stainless steel jars[d]
1	45	0	88
2	65	0	20

[a] Isolated yield; [b,c,d] The reaction was performed for 4 hours in: [b] 20 mL jars containing 60 glass balls (Ø 3 mm) each at 550 rpm [c] 45 mL jar with 11 balls (Ø 12 mm) at 550 rpm; [d] 10 mL jar containing 6 balls (Ø 5 mm) at 30 Hz.

Benzoxazines **1** and **2** could not be obtained when the milling was performed in a zirconia jar, despite the full conversion of substrates, maybe due to the formation of polybenzoxazine network *via* a thermally induced ring-opening polymerization side-reaction.[57-59] The reversible heterolytic scission of the cyclic *N,O*-acetal moiety is thermally or catalytically induced,

leading to phenolic structures by a Mannich base bridge [-CH_2-N(R^2)-CH_2-], very similar to traditional phenolic resin network polymer.[60]

It is also worth noticing that diverse procedures (choice of the solvent, reaction time, temperature) were reported for the preparation of benzoxazines in solution, depending on the nature of the product to be obtained. Attempts to prepare benzoxazines by solventless methods upon heating,[61] by microwaves [45] or using more eco-friendly procedures in alternative solvents such as PEG[62] (yields were not given) were also described, but no examples of mechanochemical activation were reported so far.

We strongly hope that our contribution will stimulate the development of this high-throughput device enabling a time-efficient approach for data gathering and a higher productivity for the preparation of libraries, compared to classic planetary mills.

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