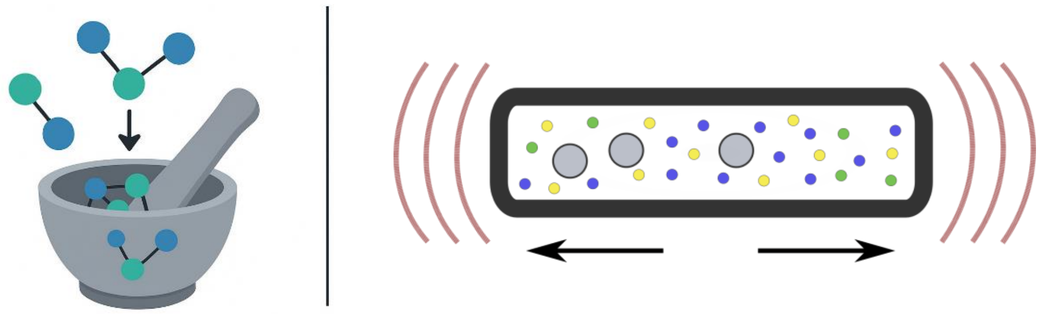
Mechanochemistry in Organic Synthesis: A Cleaner Path to Innovation

From mortar and pestle to Ball milling



Introduction

Over the last two decades, mechanochemistry has emerged as a powerful and sustainable alternative to traditional solution-based synthesis. Once considered a niche laboratory curiosity, this solid-state approach—where chemical transformations are driven by mechanical force—has rapidly gained traction across various fields of chemistry. In organic synthesis, mechanochemistry has proven to be a game-changer, enabling the development of cleaner, more efficient reactions while unlocking access to molecular structures and materials that are difficult, or even impossible, to obtain through conventional methods.

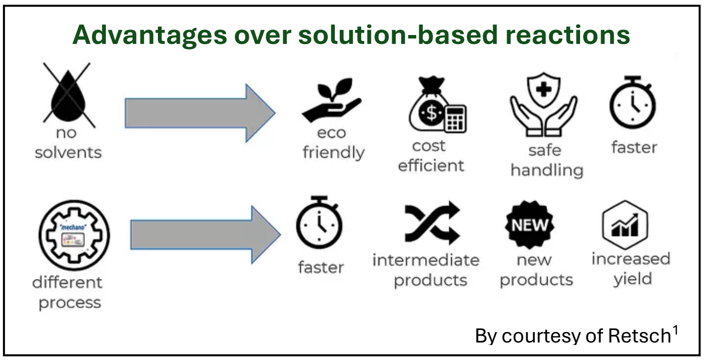
In this article, we explore the growing impact of mechanochemistry on organic synthesis, highlighting recent progress and applications, as well as its advantages over traditional methods. Professor Frédéric Lamaty (CNRS Research Director and Head of the Green Chemistry Team at the IBMM) shares insights into the field and his perspective on its future development and application.

Finally, several reactions carried out using mechanochemistry by Oxeltis scientists will be presented to illustrate the everyday applications of this powerful approach and the exciting possibilities it offers.

1. **Mechanochemistry: A Game-Changer in Organic Synthesis**

Mechanochemistry is a branch of chemistry that involves initiating and driving chemical reactions through mechanical force rather than traditional thermal or solution-based methods. It typically employs techniques such as ball milling, grinding, or shearing to break and form chemical bonds.

In ball milling, for example, powders are placed in a rotating or vibrating container with heavy balls. The kinetic energy from the collisions between the balls and the reactants provides the energy needed to drive chemical transformations—without the use of solvents or high temperatures.



Mechanochemistry stands out as a compelling alternative to traditional solvent-based synthesis, offering significant benefits in terms of speed, environmental impact, and synthetic versatility. By using mechanical force to drive chemical reactions, this method often achieves transformations more quickly and cleanly than those conducted in solution. Its minimal reliance on solvents not only reduces chemical waste but also makes the process more sustainable and cost-effective. Furthermore, mechanochemistry opens new pathways by bypassing solubility constraints, enabling the formation of products and materials that are otherwise challenging to obtain through conventional techniques. With its ability to facilitate selective reactions and access novel compounds, mechanochemistry is increasingly seen as a transformative tool in modern synthetic chemistry.

Mechanochemistry is gaining ground in pharmaceutical research due to its eco-friendly nature and unique reactivity profile. Key applications include:

- **Polymorph Screening**: Mechanochemistry can selectively produce different crystalline forms (polymorphs) of a drug, which may impact bioavailability and stability.[2]
- **Cocrystal Formation**: Used to develop pharmaceutical cocrystals that improve drug solubility and performance without altering the active compound.[3]
- **API Synthesis**: Mechanochemical methods have been applied in the synthesis of active pharmaceutical ingredients (APIs), reducing solvent use and simplifying processing.[4]
- **Late-Stage Functionalization (LSF)**: Mechanochemistry enables LSFs of complex pharmacological molecules to fine-tune properties such as potency, selectivity, metabolic stability, and solubility, while also generating analogues from existing scaffolds to support structure–activity relationship (SAR) studies.[5]
- **Green Chemistry Initiatives**: Companies and researchers are adopting mechanochemistry to meet sustainability goals, aligning with green chemistry principles.

2. Expert Insights: Frédéric Lamaty, *Ph.D*, Director of Research CNRS, Head of Green Chemistry Team IBMM

Biography :

Frédéric Lamaty is a French chemist and Research Director at the Centre National de la Recherche Scientifique (CNRS), based at the Institut des Biomolécules Max Mousseron (IBMM) in Montpellier. He leads the Green Chemistry and Enabling Technologies team, focusing on sustainable and solvent-free synthetic methods, particularly mechanochemistry. Frédéric earned his chemical engineering degree in 1988 from the École Supérieure de Chimie Industrielle de Lyon. In 1992, he completed his Ph.D. at Purdue University under Professor Eichi Negishi (Nobel Laureate in Chemistry, 2010), specializing in palladium-catalyzed cyclizations.

Since joining CNRS in 1994, Frédéric has advanced research in organic and green chemistry, focusing on synthesizing amino acids, peptides, heterocycles, and organometallic compounds. His work emphasizes the use of alternative solvents (e.g., PEG, glycerol, water) and innovative technologies like microwave activation, flow chemistry, ball-milling, and reactive extrusion. In 2011, he received the ADEME-Pollutec Prize for Innovative Environmental Techniques for his solvent-free peptide mechanosynthesis.

Frédéric Lamaty continues to contribute to sustainable pharmaceutical synthesis, notably through reactive extrusion methods recognized by the International Union of Pure and Applied Chemistry (IUPAC) as transformative for green chemistry.

- What sparked your interest in mechanochemistry ?

At the end of the 80s, a solid-state chemist from Oldenburg, Professor Gerd Kaupp, published studies on successful solvent-free organic reactions using ball-milling, involving exclusively solid starting materials and reagents. As a member of the Laboratory of Aminoacids, Peptides and Proteins (which later became a department of IBMM), and wishing to develop a more sustainable synthesis than the existing solid-phase peptide synthesis (SPPS), the idea came up to develop a mechanosynthesis of peptides, using solid amino acid derivatives such as Urethane protected amino acid N-Carboxy Anhydrides. The classical SPPS is highly efficient but consumes large quantities of CMR solvents such as DMF and the new approach could alleviate this problem. This project marked the starting point of many methodological developments in solvent-free organic synthesis using mechanochemistry.

- How do you see mechanochemistry transforming organic synthesis, particularly in Pharmaceuticals?

Mechanochemistry will transform organic synthesis, including in pharmaceuticals: why should one use a solvent in a reaction if you do not need it? This will still take some time because performing a solvent-free organic reaction is still considered by synthetic chemists either a curiosity or leading to an impractical procedure.

- What are the biggest challenges and opportunities in scaling up mechanochemical processes?

Technological developments such as reactive extrusion or the use of resonant acoustic mixing exist and have proven their effectiveness on a small but relatively easily extrapolated scale. When process chemists begin to consider, for example, an extruder as a fully-fledged reactor for scaling up a continuous solvent-free synthesis, a major advancement will have been made. In fact, this approach is already being explored (but not advertised) by a number of companies throughout the world, particularly in the pharmaceutical industry. One of the biggest hurdles at *present is investment, since switching to mechanochemistry means changing the production tools. This again will take some time to develop.*

- What are some recent breakthroughs or exciting developments in the field?

I am not sure we can talk about recent breakthroughs but rather of developments at a rapid pace, in all areas of chemistry, sign of a more sustained interest of scientists in mechanochemistry. One can cite the development of mechanocatalysis or in-situ analysis of mechanochemical reactions. New reactivities in solvent-free conditions are discovered regularly and are of great interest. These are not results that are sought, but results brought about by serendipity.

One area that has boomed in recent years is pollution control concerning polymers. In this case, this is not considered as mechanosynthesis, but rather as destructive action, which, if controlled, can close the loop of a circular economy with the regeneration of monomers. Significant advances have been made in managing the fate of persistent compounds such as PFAS.

- What advice would you give to researchers or companies looking to adopt mechanochemistry?

Start by acquiring a ball mill and the necessary accessories. This is a low-cost investment, worth trying on your chemistry. You need a minimum of know-how to find the correct reaction conditions, so be patient, persistent, and learn. Finally, why not hire a collaborator who has experience in mechanochemistry?

3. Applications of Mechanochemistry at Oxeltis

Oxeltis has been equipped with a mixer mill for 3 years. While the outcomes of the first reactions were rather modest compared to solution-based synthesis, mechanosynthesis has proved handy in numerous situations. These include the air-tolerant preparation and use of Grignard reagents[6] (Figure 1. a), as well as the formation of an O-alkylation isomer previously inaccessible in solution during difluoromethylation reactions (Figure 1. b). More recently, the mechanosynthesis of some Nitrosamine Drug Substance-Related Impurities (NDSRI) using mild reaction conditions[7] gave us fast, clean and good yielding reactions (Figure 1. c). It is worth noting that, while the use of peptide-based therapeutics is experiencing a surge of interest, DMF which is extensively used in SPPS has been identified as a Substance of Very High Concern. Mechanosynthesis has proven to be a viable and eco-friendly alternative,[8] and small peptides were synthesized in-house via this promising technique.

Mixer mill 400 available @Oxeltis

By courtesy of Retsch

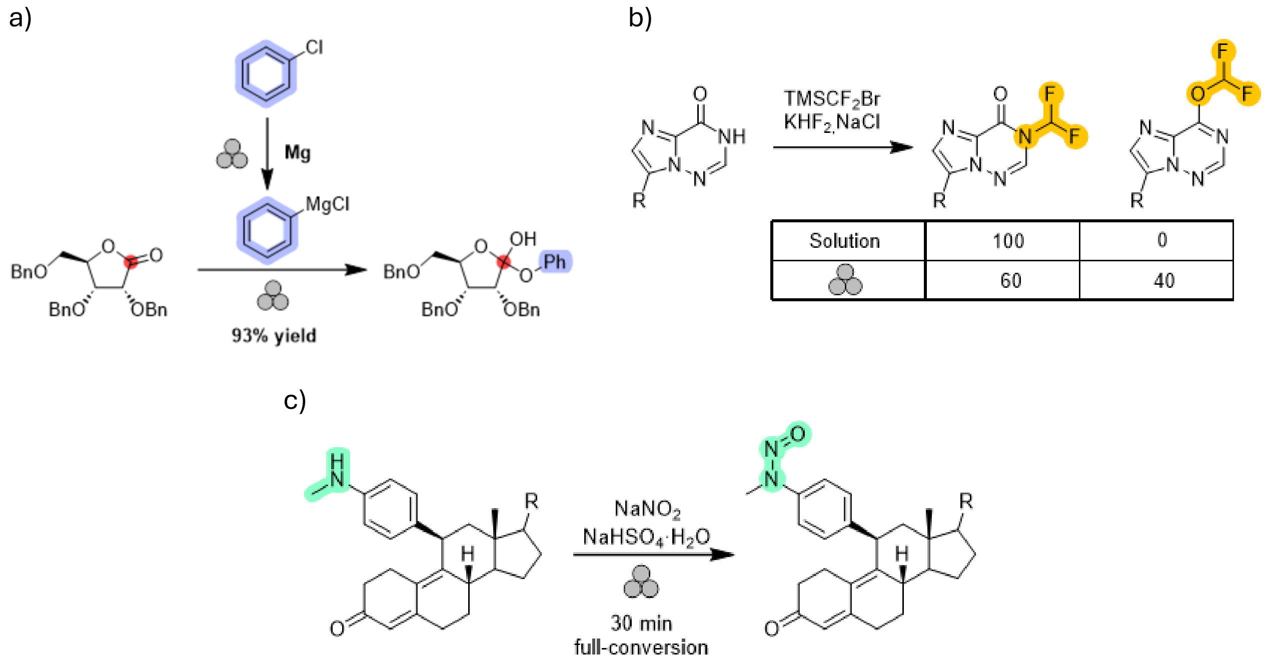


Figure 1. a) Preparation and use of Grignard reagents performed in air. b) O- & N-alkylation in solution Vs. by mechanochemistry. c) Mechanosynthesis of Nitrosamine Drug Substance-Related Impurities (NDSRI).

4. Conclusion

Mechanochemistry is transforming contemporary organic synthesis. With recent theoretical and practical breakthroughs, it provides viable solutions to challenges in sustainability and efficiency.

- It broadens the scope of green chemistry.
- It fosters academia-industry collaborations for broader deployment.
- **Call to action**: Oxeltis encourages the scientific community to explore mechanochemistry's full potential and co-develop cleaner, more efficient synthetic solutions. For more information on the subject or if you have any needs for mechanosynthesis please contact us at contact@oxeltis.com

[1] https://www.retsch.com/applications/mechanochemistry/
[2] *Adv. Drug Deliv. Rev.* **2017**, *117*, 147
[3] *Pharmaceutics* **2021**, *13*, 790
[4] *Chem. Commun.* **2016**, *52*, 7760
[5] *Angew. Chem. Int. Ed.* ***2025***, e202503061
[6] *Nat. Commun.* **2021**, *12*, 6691
[7] *ChemSusChem* **2024**, *17*, e202301034
[8] *Beilstein J. Org. Chem.* **2017,** *13,* 2087