Hes·so
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Master of Science HES-SO in Life Sciences

Mechanochemistry a Solvent Free & Eco-efficient Strategy to Synthesize API

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CHEMICAL DEVELOPMENT & PRODUCTION

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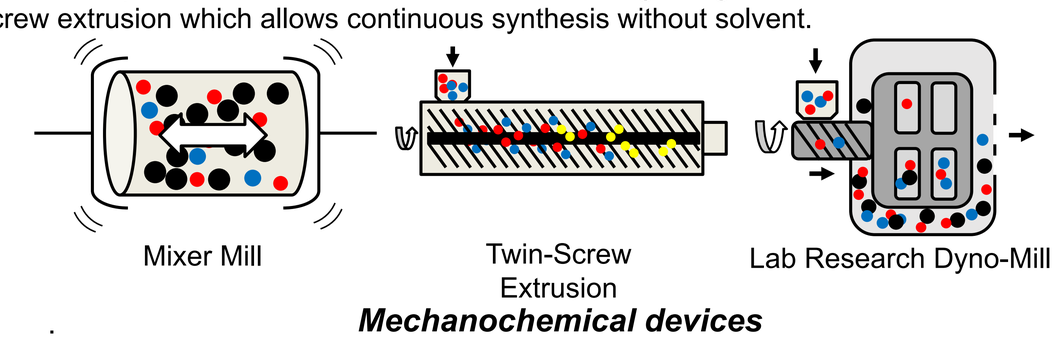
DESCRIPTION

Mechanochemistry is the activation of reaction by inducing a mechanical stress to a solid-state mixture. Because it is in solid state, the reaction proceeds in solvent-free manner and avoid treatment of large amounts of wastes. Mechanochemsitry does not only allow to reduce waste but also new reactivities, polymorphic forms and better reactivities. A particular interesting field is the synthesis of active ingredients, which generates for the most part huge quantities of waste due to solvents. This has led to the development of syntheses via mechanical activation of active ingredients, so-called medicinal mechanochemistry. A functional group of particular interest in this field is the amide. As the basis of the peptide bond, it is present in many pharmaceutical and biochemical molecules such as paracetamol, a painkiller, and Ethotoin, an anticonvulsant used for epilepsy.

Several devices exist bringing different advantages and disadvantages. The ball mills are the most represented in this field, but others are beginning to arouse interest such as the twin screw extrusion which allows continuous synthesis without solvent.



Mixer Mill | Twin-Screw Extrusion | Lab Research Dyno-Mill

Mechanochemical devices

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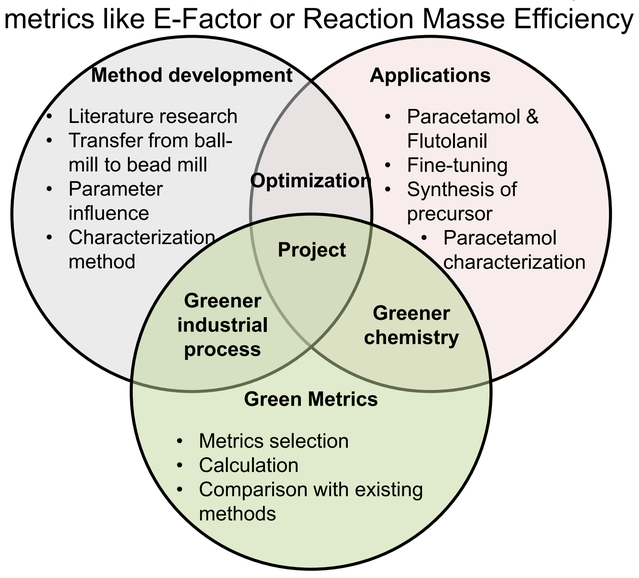
The aim was to study the feasibility and optimize the two-step mechanochemical Beckmann rearrangement starting from acetophenone and 4-hydroxyacetophenone to form acetanilide and paracetamol, respectively, with the Dyno-Mill.

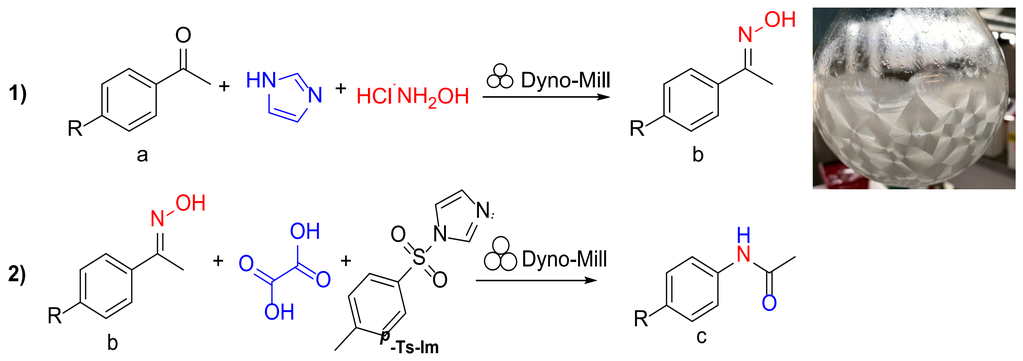
OBJECTIFS

First, the mechanochemical Beckmann rearrangement of acetanilide in two steps with Dyno-Mill should be optimized. Parameters of interest had to be determined and studied. Application of the optimized parameters to 4-hydroxyacetophenone, precursor of acetaminophen the pain-killer, had to be done and fine-tuning of them was done. Application to flutolanil, a crop protection molecule, had to be done. Precursor of flutolanil had to be synthesized first.

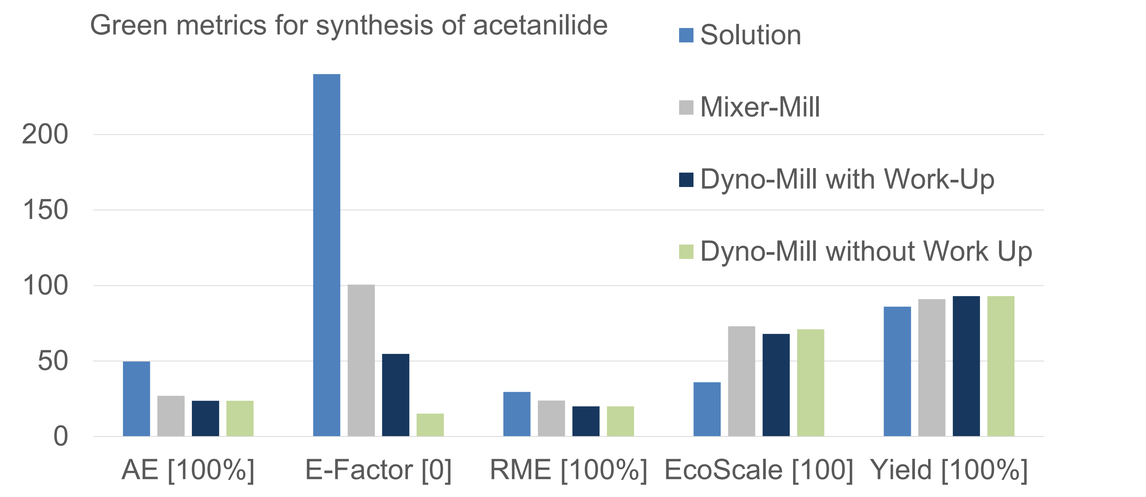
Finally, the method had to be compared to solution-based synthesis of those industrial compounds. Green metrics like E-Factor or Reaction Masse Efficiency had to be used.



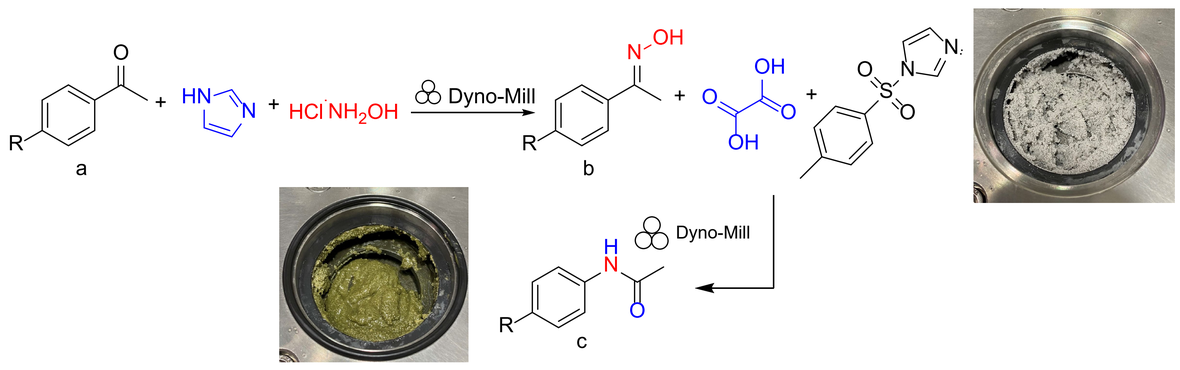
RESULTS



Step	*R*	*Rotation speed [rpm]*	*Equivalents to a/b*	*Time [min]*	*Yield [%]*
1	-	4000	1.05	20	96
2	-	6000	1.20	30	97 (93)
1	-OH	4000	1.06	30	96
2	-OH	6000	1.00	45	93 (89)



Comparison of the green metrics



Entry	*R*	*Rotation speed [rpm]*	*Equivalents to a*	*Time [min]*	*Yield [%]*
1	-	4000 – 6000	1.05 – 1.20	20 - 90	55 (91)
2	-OH	4000 - 6000	1.05 – 1.20	45 - 60	63 (84)

CONCLUSION

Most of the objectives were achieved with success. The device Dyno-Mill showed to be efficient for the mechanochemical Beckmann rearrangement with yields and green metrics better than in literature. Bead milling appears to be a good technology to synthesize organic compound. Advantages are a commercially available apparatus with larger scale options for scale-up, high energy input, and potentially a continuous mode. It can already run solid state reactions in fed batch or batch mode with little adjustments. Some improvement in the design can be done to facilitate the manipulations or downstream process. Also, some analytical features would be beneficial for following and optimizing any mechanochemical synthesis. Raman or FT-IR probes could be fixed on the reaction chamber.

The method developed here could be processed in a larger device to assess the scalability but before a downstream process for the isolation of amide should be found. Since it is now practicable to open and scratch the Dyno-Mill at larger scale, an extraction method with solvent should be found. It can be done via solubility curves of the reactant and product. With this done, the method could be applied to any ketone to get the desired amide in short times with good to excellent yields.

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