Optimizing Aldol Reactions via Mechanochemistry: Study the potential of Dyno-Mill Technology

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The need for a more sustainable and greener chemistry is becoming more and more important, and implementing mechanochemistry on an industrial scale could help to decrease the ecological impact by considerably reducing the amount of solvents used. To date there is little data highlighting the benefits of these mechanical technologies with regards to process scale-up. Bead-mill technology (Dyno®-Mill) was used for the first time for the sustainable mechanochemical synthesis of Acetaminophen (known as Paracetamol) using Beckmann rearrangement. The optimized solvent-free method was able to deliver around ten grams on a laboratory scale, and gave better yields compared with solvent-based (89 vs. 74 %). [1] Since C-C bond formation is a key reaction in pharmaceutical chemistry, an asymmetric organocatalysis with an amine acid (L-proline) between a ketone and an aldehyde (aldol reaction) was carried out to study which variables mainly influence the responses (yield, conversion, diastereoselectivity, and Space-Time-Yield). After optimization, similar yields were obtained compared to solvent-based processes (96–99%), with a Space-Time-Yield at least five times higher and attractive green metrics due to a one-third reduction in waste (including work-up).

[1] Geib, R.; Colacino, E.; Gremaud, L. Sustainable Beckmann Rearrangement Using Bead-Milling Technology: The Route to Paracetamol. *ChemSusChem* **2024**, 17 (12), e202301921.