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DOI: 10.1039/D6MR00053C

COMMUNICATION

# One-Sequence Mechanochemical Synthesis–Deracemisation of a Levetiracetam Intermediate.

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

**Starting from a racemic building block, we introduce a one-pot mechanochemical synthesis of enantioenriched 2-(benzylideneamino)butanamide, a key intermediate to the enantipure drug levetiracetam. Optimisation leads to an *ee* of up to 94% *ee* with an overall 80% isolated yield.**

## Introduction

From 2013 to 2022, 59% of all drugs approved by the Food and Drug Administration (FDA) were enantiopure, whereas only 3.6% were approved as racemates. Data from the European Medicines Agency (EMA) reveal a similar trend, with 52% of approvals for enantiopure compared to 2.2% for racemic compounds[1,2]. This clearly highlights the importance of being able to access enantiopure materials. Among the available strategies to obtain these, chiral resolution remains widely employed, including chromatographic separation[3–7] and diastereomeric crystallisation[8–12]. However, these approaches typically require large quantities of solvent, are costly[13,14], and intrinsically limited to a maximum theoretical yield of 50%, as the undesired enantiomer is often discarded.

Deracemisation offers a more sustainable strategy, as the undesired enantiomer (distomer) is converted into the desired enantiomer (eutomer), theoretically affording up to 100% of the latter[15,16]. This approach does impose the prerequisite of a racemisable target compound or intermediate. Deracemisation through abrasive grinding is one of the most recently introduced deracemisation methodologies. In this process, a suspension of the racemic solid in an organic solvent evolves over several days to afford an enantiopure solid. The supposed mechanism is a complex interplay between the racemisation reaction, enantioselective crystal growth and dissolution, as well as mechanical attrition[17–19]. Starting from a fully racemic mixture, the direction of enantiomeric enrichment is random; the direction of the deracemization (ultimate chirality obtained), can be controlled, however, by slightly enriching in the desired enantiomer [17,18].

We have recently transposed this process to a more sustainable setting, by introducing deracemisation through abrasive grinding by mechanochemistry. To emphasise the broader mechanochemical nature of the process, the terminology of mechanochemical deracemisation (MCDR) will be used from now on. We developed MCDR for various substrates, including ketones, isoindolinones, imines and esters, using either ball milling[20,21] or resonance acoustic mixing (RAM)[22]. In this process, the racemisation step is believed to occur within a mobile phase (MP), an amorphous phase generated by grinding in the presence of a small amount of liquid (LAG). The nature and amount of the MP is critical to the process as a larger amount of MP increases the proportion of racemic material and lowers the final enantiomeric excess (*ee*), whereas a smaller amount slows racemisation and thus implies longer reaction times[21].

Two substrates investigated in our previous studies are 2-(benzylideneamino)butanamide (**1a**) and 2-((2-methylbenzylidene)amino)butanamide (**1b**) for which the racemates were deracemised mechanochemically with a final *ee* of up to respectively 86% and 74% in a ball-milling process or respectively 88% and 83% in a RAM-based process[21,22]. Interestingly, this compound is an intermediate used for the deracemisation of 2-aminobutyramide (**2**)[23], a building block in the synthesis of levetiracetam and brivaracetam[24–27], two antiepileptic drugs[28,29] (Scheme ).

In the suggested process, the deracemisation of **1a** and **1b** involved two distinct steps: solution synthesis of the racemate starting from (*RS*)-**2**, followed by solution-based or

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Supplementary Information available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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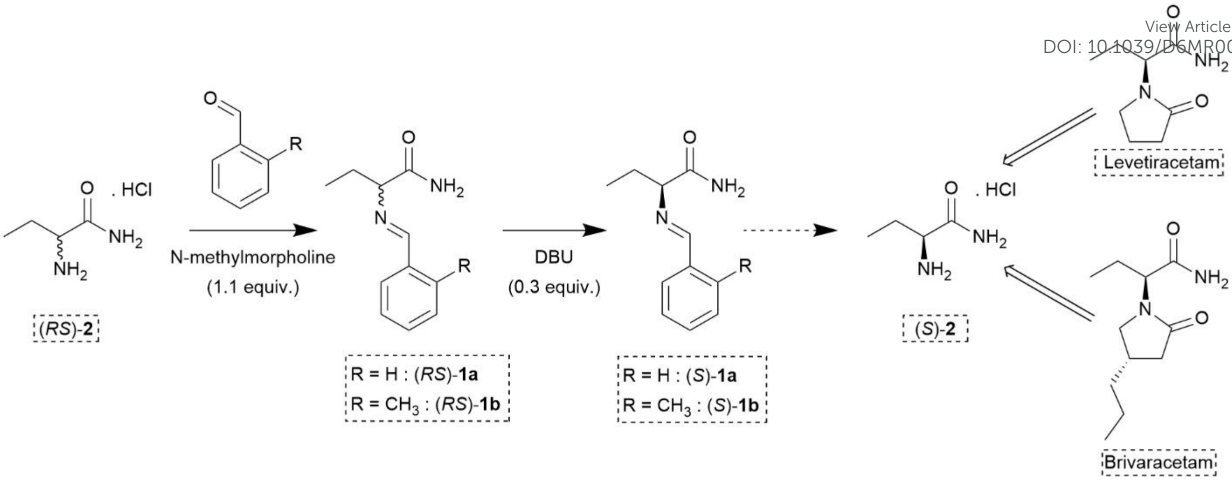
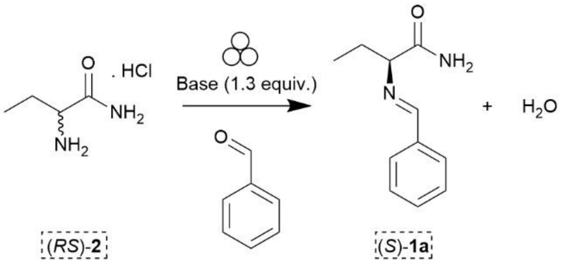


Scheme 1 : Access to (*S*)-**2**, a key building block of levetiracetam and brivaracetam, from (*RS*)-**2** via formation and subsequent deracemisation of **1a**/**1b**.



Scheme 2 : One-pot mechanochemical process comprising a base-catalysed condensation (Schiff base formation) between (*RS*)-2-aminobutyramide hydrochloride ((*RS*)-**2**) and benzaldehyde under ball-milling conditions, generating the imine (*RS*)-2-(benzylideneamino)butanamide ((*RS*)-**1a**) with concomitant formation of water ($H_2O$). Continued milling induces deracemization of the imine to afford enantiomerically enriched (*S*)-2-(benzylideneamino)butanamide ((*S*)-**1a**).

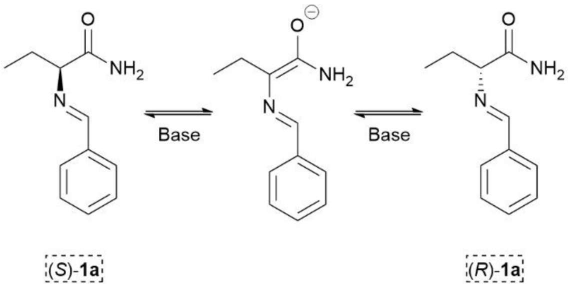
mechanochemical deracemisation [21,23]. In the present study, we aim to push the potential of mechanochemistry, highlighting how the synthesis and deracemisation processes can be successfully combined into a single mechanochemical – process (Scheme ).

## Results and discussion

Exact conditions of each experiment and analytical characterisation ($^1$H-Nuclear Magnetic Resonance ($^1$H-NMR) and chiral High-Performance Liquid Chromatography (cHPLC)) are available in the SI.

### Mechanochemical synthesis of the racemate

To validate our approach, we first examined whether **1a** could be synthesised mechanochemically by a condensation between **2** and tolualdehyde which, to the best of our knowledge, has not yet been reported. A base is required to neutralise the hydrochloride salt ((*RS*)-**2**) and enable imine formation. Three bases were evaluated for this purpose: N-methylmorpholine (NMM, used in the solution-phase synthesis)[23], 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, employed previously for the deracemisation step)[21,23], and NaOH as it is a solid inorganic base. As the subsequent deracemisation process requires some filling agent to limit the proportion of MP and thereby prevent racemisation of the system[21], two such agents were also tested for the mechanochemical synthesis of compound (*RS*)-**1a**: NaCl (used in our previous work)[21] and $Na_2SO_4$. The latter was chosen as it can trap the water released during imine formation[30], thereby preventing an increase in the MP and minimizing the impact of water on the mixing of the reaction medium.



Scheme 3 : Base-catalysed racemisation of **1a** through an enolate intermediate.

Based on previous published conditions[21], milling was performed in a 14 ml polytetrafluoroethylene (PTFE) jar containing three 10 mm $ZrO_2$ balls, filling the vessel with 280 mg of (*RS*)-**2**, 1.1 equiv. of base, 5.0 mL of bulk material and 1.0 equiv of liquid aldehyde. $^1$H-NMR analysis of the crude showed successful mechanochemical formation of **1a** under all tested conditions (Table S1). Signals corresponding to the reactants benzaldehyde and (*RS*)-**2** are no longer present (or in minor amount), with the 1.8 and 1.6 ppm multiplets confirming imine formation (Figures S1-12). cHPLC analysis confirms no deracemisation occurred with the obtained imines being racemic (Figures S22-27).

### Integrated synthesis-deracemisation process

Following the successful mechanochemical synthesis of (*RS*)-**1a**, we examined the feasibility of pushing the reaction mixture through to the next step of the overall process, by deracemizing the obtained racemate of the imine. Accordingly, the milling time was extended to 24 h and the base loading increased to 1.3 equiv. (1.0 equiv. for HCl neutralisation and 0.3 equiv. required for the racemisation process).

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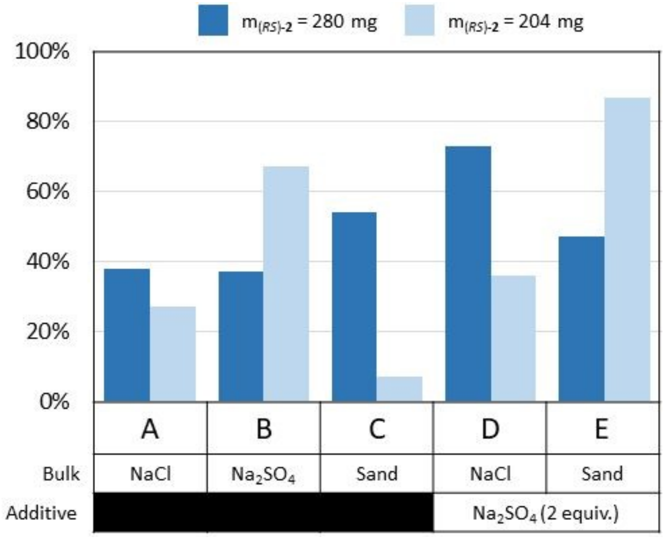

Figure 1 : Impact of milling material and mass of (*RS*)-**2** on the one-step synthesis/deracemisation process of **1a**. Table below lists (from top to bottom) the nature of the filling material, the potential additive. The process runs by filling a 14 mL PTFE jar with (*RS*)-**2**, 5.0 mL of bulk material, three $ZrO_2$ balls of 10 mm of diameter, 1.3 equiv. of DBU and 1.0 equiv. of benzaldehyde. The system is milled at 30 Hz for 24 h.

We first investigated the influence of the base (DBU or NMM), the nature of the bulk material, and the initial amount of (*RS*)-**2**. Two initial loadings were evaluated. A first set of experiments employed 280 mg of (*RS*)-**2**, mirroring the mass of solid used in our previously reported MCDR paper, where 280 mg of (*RS*)-**1a** was used[21]. However, as imine formation also requires the addition of one equivalent of benzaldehyde, this led to a higher final mass of (*RS*)-**1a** (384 mg). To ensure direct comparability with our previous results, we also investigated a second loading of 204 mg of (*RS*)-**2**, corresponding to a theoretical final mass of 280 mg of (*RS*)-**1a** after reaction. NaOH was not evaluated beyond 1.0 equiv. in order to avoid potential side reactions arising from the hydroxyl nucleophilicity.

When NMM was used, the product **1a** was successfully formed but remained racemic under all tested conditions, regardless of the filling material or the initial amount of (*RS*)-**2** used (Table S2, entries A1-4). In contrast, the use of DBU consistently led to formation of enantioenriched **1a** with the final *ee* ranging from 27% to 67% after 24 h of milling (Figure , entries A-B). Given that NMM is less basic than DBU[31,32], it is likely not strong enough to promote formation of the achiral intermediate required for deracemisation (Scheme ).

cHPLC analysis shows that all MCDR experiments are enriched in (*R*)-**1a**. This is due to a slight excess of (*R*)-**2** in the commercial bottle. Although (*S*)-**1a** is the enantiomer required for levetiracetam synthesis, this does not impact our study, as the objective here is to demonstrate that one-pot deracemisation is feasible. If the final objective were the synthesis of levetiracetam, one would instead start from a slight excess of (*S*)-**2** by seeding the commercial powder with this enantiomer. Enantiomeric assignments were made by comparison of the cHPLC peaks with enantiopure reference samples of **1a** (Figures S18-21).

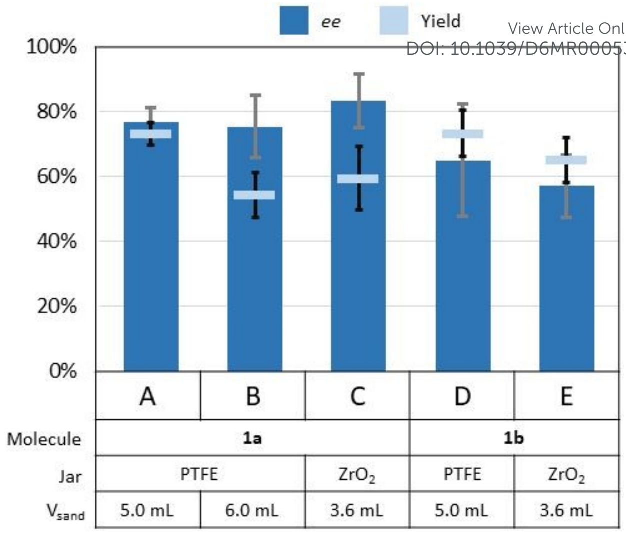

Figure 2: Reproducibility of the one-step synthesis/deracemisation of **1a/1b**. Table below lists the imine, the material of the jar and the volume of sand. The heights of the chart represent the mean of *ee* (dark blue) and yield (light blue). The vertical bars represent the standard error of the *ee* (grey) and of the yield (black). 14 mL PTFE jar was filled with (*RS*)-**2**, sand, 2.0 equiv. of $Na_2SO_4$, three $ZrO_2$ balls of 10 mm of diameter, 1.3 equiv. of DBU and 1.0 equiv. of aldehyde. 10 mL $ZrO_2$ jar was filled with (*RS*)-**2**, sand, 2.0 equiv. of $Na_2SO_4$, two $ZrO_2$ balls of 10 mm of diameter, 1.3 equiv. of DBU and 1.0 equiv. of aldehyde. The system is milled at 30 Hz for 24 h.

The main limitation associated with the use of DBU is the unfavourable rheology of the reaction mixture, which results in reduced powder flowability of the reaction mixture. The powder indeed tends to adhere to the walls of the jar, particularly when $Na_2SO_4$ was used as the bulk material, thereby preventing efficient mixing. Several strategies were explored to address this issue.

First, to decrease the volume of DBU, we attempted to combine two bases, using 0.3 equiv. of DBU for deracemisation and 1.0 equiv. of NaOH for neutralisation of the chloride salt. Although **1a** is properly synthesised, no significant enantioenrichment was observed (Table S2, entries A9-10).

Second, sand was evaluated as alternative filling material (Figure , entry C). Even though the rheology remained poor deracemisation occurs, reaching 54% when 280 mg of (*RS*)-**2** was used.

Finally, a combination of filling agents was tempted, using only two equivalents of $Na_2SO_4$ to sequester water, while NaCl and sand were used as the primary bulk components (Figure , entries D-E). With this approach, and using 204 mg of starting material and sand as bulk, an *ee* of 89% was reached.

In addition to the excellent *ee* values, comparable to those previously obtained for the MCDR of (*RS*)-**1a**, the one-pot reaction/deracemisation strategy led to a significant improvement in overall efficiency. Whereas the combination of solution-phase synthesis followed by deracemisation (either solution-based or mechanochemical) led to an overall yield of only 55%[21], our one-pot mechanochemical approach provides enantioenriched **1a** in a 80% isolated yield (Table S2, entry A16-1). This result highlights the synthetic advantage of merging synthesis and deracemisation into a single mechanochemical operation.

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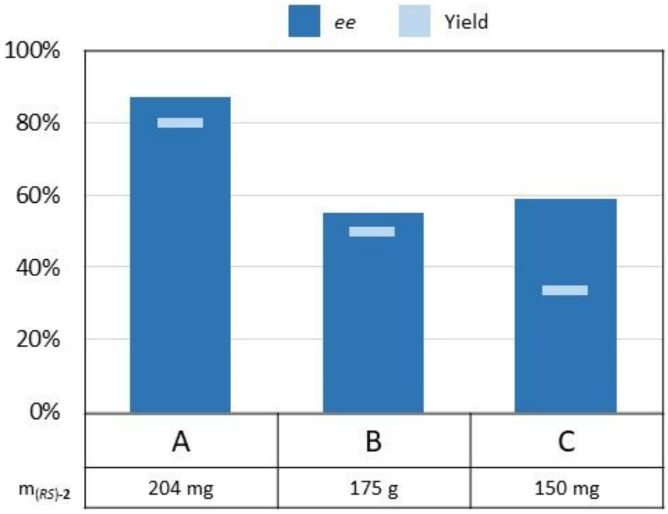

Figure 3 : Mass of (*RS*)-**2** influence for the one-step synthesis/deracemisation of **1a**. Table below lists the mass of (*RS*)-**2.** 14 mL PTFE jar was filled with (*RS*)-**2**, 5.0 mL of sand, 2.0 equiv. of $Na_2SO_4$, three $ZrO_2$ balls of 10 mm of diameter, 1.3 equiv. of DBU and 1.0 equiv. of benzaldehyde. The system is milled at 30 Hz for 24 h.

Figure 4 : Rheology after the milling of **1a** with 5.0 mL (*left*) and 6.0 mL (*right*) of sand. 14 mL PTFE jar was filled with (*RS*)-**2**, sand, 2.0 equiv. of $Na_2SO_4$, three $ZrO_2$ balls of 10 mm of diameter, 1.3 equiv. of DBU and 1.0 equiv. of benzaldehyde.

To evaluate reproducibility of the process the optimal conditions were repeated three additional times leading to an average *ee* of 77% and standard error of 5% together with a reproducible yield of 73% and standard error of 3% (Figure , entry A). Some variability in *ee* can be expected and is attributed to the kinetics of the deracemisation process. The evolution of *ee* follows a sigmoidal curve where, initially, the mixture remains racemic for a variable period of time. Once a slight stochastic crystal size difference between enantiomers occurs, the *ee* increases drastically until a plateau is reached.[20] The variability results from both the variable latency time preceding the onset of deracemisation and the rheology of the medium. After 24 h of milling, the reaction mixture systematically formed a compact mass strongly adhered to the walls of the jar, at which point efficient mixing was no longer maintained. The deracemisation therefore stops once this mechanical state is reached, and the final *ee* reflects the level of chiral amplification attained at this stage. The system may still be in the amplification stage, or the plateau may already have been reached. Prolonging the milling is thus unlikely to provide further improvement.

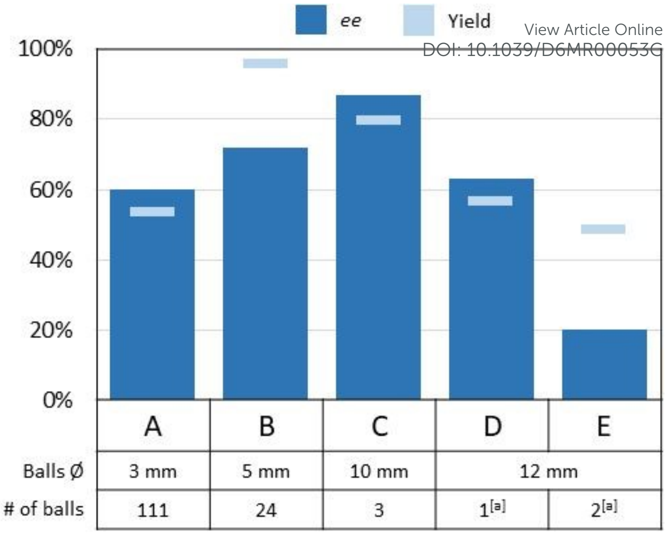

Figure 5 : Milling material influence for the one-step synthesis/deracemisation of **1a**. with 5.0 mL of sand as bulk. Table below lists the diameter and the number of balls. 14 mL PTFE jar was filled with 204 mg of (*RS*)-**2**, 5.0 mL of sand, 2.0 equiv. of $Na_2SO_4$, $ZrO_2$ balls, 1.3 equiv. of DBU and 1.0 equiv. of benzaldehyde. The system is milled at 30 Hz for 24 h. [a] To maintain a constant total volume of milling media, 1.7 balls of 12 mm diameter would be required. In practice, experiments were therefore performed using either one or two balls.

Although these results were highly encouraging, the rheology of the reaction mixture remained problematic. To further try and improve this aspect, following parameters expected to impact rheological behaviour were examined: the amount of (*RS*)-**2**, the quantity of sand, the milling media used, and the material of the jar.

Reducing the amount of (*RS*)-**2** (and associated volume of DBU), believed responsible for powder adherence to the vessel walls (Figure ) the rheology remained unfavourable. We decided to stick at this stage with the 204 mg loading which provides the highest combined *ee* and yield under the tested conditions.

Increasing the amount of sand did not resolve the rheological issue, as powder remained adhered to the jar walls (Figure ). We did, however, observe that the use of 6.0 mL of sand led to a final *ee* of 94%, the highest value obtained to date for the MCDR of **1a** (Table S2, entry A19-1). Nevertheless, the yield decreased significantly (46%), indicating that excessive dilution of the reactive phase negatively impacts the conversion rate. Due to the high *ee* observed, reproducibility was also studied under these conditions with two additional experiments. Compared to 5.0 mL of sand used, the 6.0 mL experiments exhibited stronger variability and consistently lower yields (Figure , entry B), making the use of 5.0 mL of sand a better compromise.

To probe the influence of mechanical parameters, the total milling volume was kept constant while varying the size (and number) of the $ZrO_2$ balls, focusing on systems containing 5.0 (Figure ) or 6.0 mL of sand (Figure ). Even though these changes were, however, systematically accompanied by a significant decrease in *ee*. In all cases, three 10 mm balls provided the highest enantioenrichment, confirming that this configuration offers the most favourable balance between impact energy and chiral amplification.

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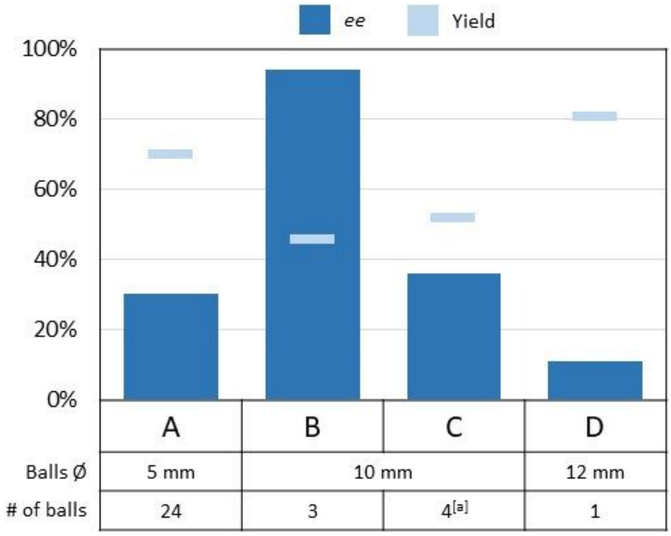

Figure 6 : Milling material influence for the one-step synthesis/deracemisation of **1a** with 6.0 mL of sand as bulk. Table below lists the diameter and the number of balls. 14 mL PTFE jar was filled with 204 mg of (*RS*)-**2**, 6.0 mL of sand, 2.0 equiv. of $Na_2SO_4$, $ZrO_2$ balls, 1.3 equiv. of DBU and 1.0 equiv. of benzaldehyde. The system is milled at 30 Hz for 24 h. [a] Although the total volume of milling media differs under these conditions, this experiment was conducted to assess whether the addition of an extra ball could improve mixing, given the increased volume of bulk material.

To investigate the influence of the jar material, the optimised conditions (Figure , entry A) were transposed from a 14 mL PTFE jar to a 10 mL $ZrO_2$ jar, while maintaining a constant filling ratio (3.6 mL of sand). Under these conditions, the rheology improved markedly, as the reaction medium remained in a free-flowing powder state after 24 h of milling. Over three independent experiments, a mean *ee* of 83% was obtained, with one of the experiments even leading to almost enantiopure material (*ee* of 96%). The improvement of powder flowability was, however, accompanied by a decrease in yield (in the given timespan) as well as a higher experimental variability (8%), which can be attributed to stochastic differences in the latency time preceding the onset of deracemisation (Figure , entry C).

Finally, the optimised one-pot strategy was extended to derivative **1b**, previously reported to undergo deracemisation. The same conditions were applied, varying only the initial amount of (*RS*)-**2** and the jar material. As for **1a**, two initial loadings of (*RS*)-**2** were evaluated in a PTFE jar. Using 204 mg leads, after reaction with *o*-tolualdehyde, to a final mass of (*RS*)-**1b** higher than the 280 mg used in previously reported conditions. Alternatively, 190 mg of (*RS*)-**2** were employed to match a theoretical final mass of 280 mg of (*RS*)-**1b**. When 204 mg of (*RS*)-**2** were used an *ee* of 80% and a 55% yield was obtained (Table S3, entry B1). In contrast, starting from 190 mg led to excellent enantioenrichment (*ee* = 92%, yield = 86% ; Table S3, entry B2-1) surpassing previously reported values[22], although the rheological behaviour remained unfavourable in the PTFE jar.

Transposition of these conditions to a $ZrO_2$ jar, as performed for **1a**, significantly improved the rheology and promoted more efficient mixing. However, this was accompanied by a marked decrease in *ee* (40%, yield = 66%; Table S3, entry B3-1). The reproducibility of both conditions (PTFE and $ZrO_2$ jars) was then evaluated (Figure , entries D–E). Despite the less favourable rheology, the PTFE jar consistently afforded higher *ee* and yields than the $ZrO_2$ system.

Overall, these results demonstrate the efficiency of a one-pot mechanochemical synthesis of enantioenriched imines starting from racemic reactants. Our results highlight the delicate interplay between chemical parameters (base, water management) and mechanical factors (bulk material, impact regime, rheology). While the physical behaviour of the reaction medium remains challenging, the one-pot system consistently converges towards high levels of enantioenrichment with ultimately higher yields compared to a process, where the intermediate racemic imine is isolated.

## Conclusions

In summary, we are the first to highlight the potential of using a one-pot mechanochemical strategy combining synthesis and deracemisation. We applied this approach for the synthesis of enantioenriched 2-(benzylideneamino)butanamide (**1a**), an essential building block in the synthesis of levetiracetam and brivaracetam. Compared to the conventional two-steps protocol, this approach increases the overall yield from 55% to 80% while maintaining high enantiomeric excesses, reaching up to 94% *ee*.

This study, furthermore, highlights that both composition as well as rheology of the reaction medium is important for the outcome. Extension to derivative **1b** further confirms the robustness of the protocol. Overall, this work successfully establishes the potential of combining mechanochemical synthesis and deracemisation as an efficient strategy toward enantioenriched pharmaceutical building blocks.

## Author contributions

G. W. led the experimental work, analysed the reactions and wrote the manuscript. T. L. assisted in writing the manuscript. All authors participated in the discussion and interpretation of the data and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

All data allowing the findings of this study are available within the article and its supplementary information (SI). Supplementary information is available. See DOI:

## Acknowledgement

The authors would like to thank the FNRS for financial support in the context of project PDR T.0185.25.

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DOI: 10.1039/D6MR00053C

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## Data availability

All data allowing the findings of this study are available within the article and its supplementary information (SI). Supplementary information is available. See DOI: