Title: Metal-catalyzed organic reactions by Resonant Acoustic Mixing

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Abstract: We introduce catalytic organic synthesis by Resonant Acoustic Mixing (RAM): a mechanochemical methodology that does not require bulk solvent or milling media. Using as model reactions ruthenium-catalyzed ring-closing metathesis, ene-yne metathesis and copper-catalyzed sulfonamide-isocyanate coupling, we demonstrate RAM-based mechanochemical synthesis that is faster and operationally simpler than conventional ball milling. Moreover, the method can be readily scaled-up, as demonstrated by straightforward catalytic synthesis of the antidiabetic drug Tolbutamide from hundreds of milligrams to at least 10 grams, without any significant changes in reaction conditions.

Main text:

Mechanochemical reactions, conducted by mechanical agitation such as ball-milling, grinding, or extrusion have emerged as a uniquely versatile means to conduct synthesis without using bulk solvents.[1,2] Other than providing a highly general route to organic, organometallic, metal-organic and inorganic reactions,[3-6] and in particular greener synthesis of pharmaceutical molecules and materials,[7] mechanochemistry offers access to reactions and products that are difficult or have previously not been accessible by more conventional routes.[8,9] Resonant acoustic mixing (RAM, Figure 1a) is a blending technology[10] based on rapid mechanical agitation, which avoids the use of milling or crushing media (*e.g.* balls, screws) inherent to milling or extrusion, and was recently demonstrated as a route for the mechanosynthesis of cocrystals,[11] and even metal-organic frameworks (MOFs).[12] In principle, the ability to avoid milling media should provide an opportunity to considerably simplify mechanochemical reaction design, facilitate scale-up, and eliminate the currently-unavoidable contamination of products through wear and tear of the milling media.

We now demonstrate the first application of RAM for conducting organic transformations, and in particular metal-catalyzed reactions (Figure 1d-f). This proof-of-concept study presents RAM as a methodology for rapid and, high-to-excellent reactant conversions in several metal-catalyzed processes, such as ruthenium-catalyzed olefin ring closing metathesis (RCM),[13,14] ruthenium-catalyzed ene-yne metathesis (RCEYM),[15] and copper-catalyzed synthesis of sulfonylureas.[16] By using RAM, we demonstrate a significant simplification of mechanochemical RCM compared to the previously established ball-milling process,[13] notably, the elimination of the need for solid abrasives, reduction in catalyst amount, and significantly reduced reaction times. This work also pioneers a mechanochemical strategy for RCEYM, and confirms the unprecedented potential of RAM for mechanochemical reaction scale-up, by a direct two-fold increase in the scale of catalytic mechanosynthesis[16] of the active pharmaceutical ingredient (API) Tolbutamide, from hundreds of milligrams to ca. 10 grams.

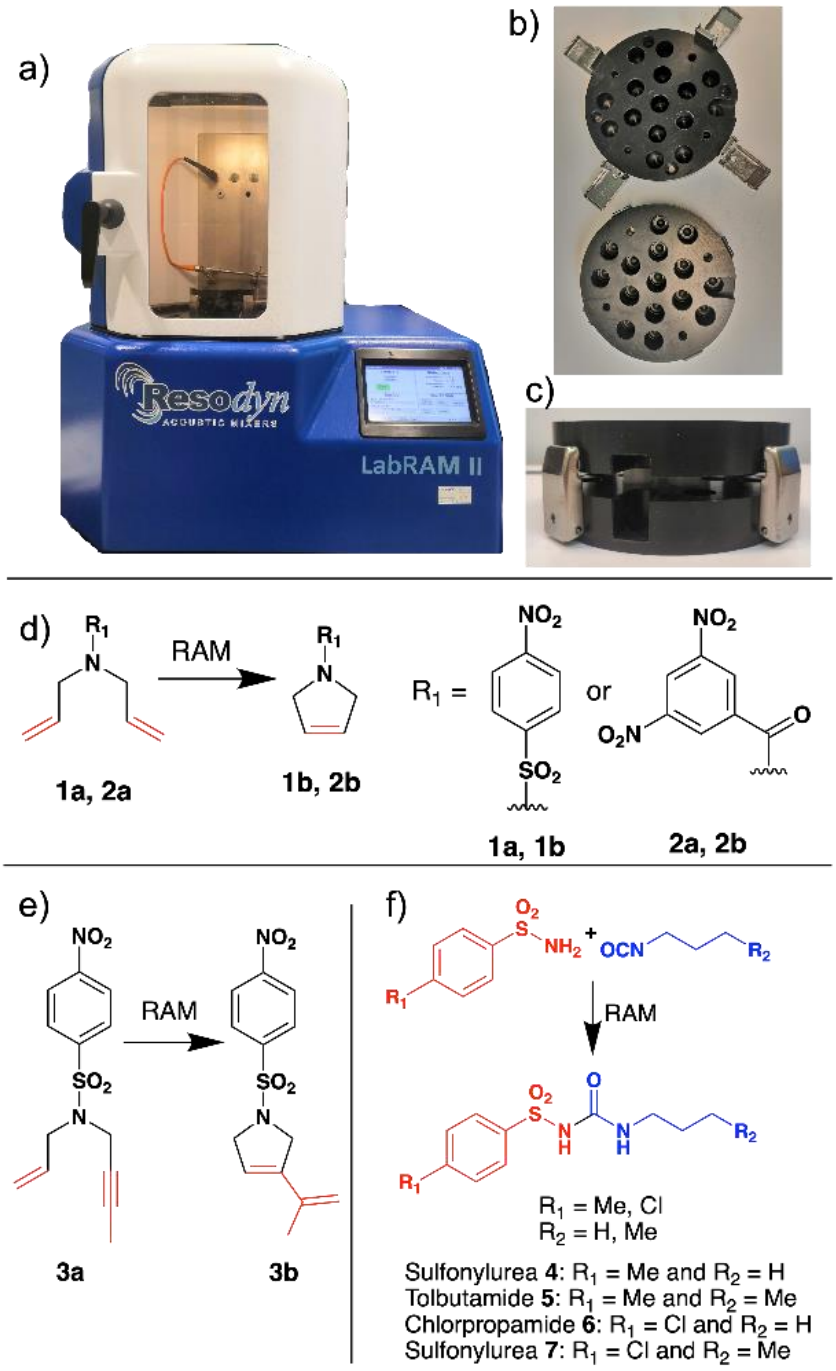

Figure 1. a) The LabRAM II instrument. Different views of the custom-designed RAM sample holder: b) top view and c) side view, with reaction vials mounted. Reaction schemes for explored reactions: d) ruthenium-catalyzed ring-closing metathesis (RCM), e) ruthenium-catalyzed ring-closing ene-yne metathesis (RCEYM), and f) copper-catalyzed coupling to produce sulfonylureas, including APIs Tolbutamide and Chlorpropamide.

As model systems for ruthenium-catalyzed RCM we focused on diolefins **1a** and **2a**, expected to form 3-pyrrolines **1b** and **2b**, respectively (Figure 1d). The same systems were previously used in developing a ball milling RCM strategy, which required simultaneous use of small amounts of liquid additives (as in liquid-assisted grinding, LAG[17,18]), large excess (150% by weight) of inert

solid abrasives (*e.g.*, K_2SO_4) to prevent clumping, and multiple additions of the catalyst (0.5 mol%) over 2-4 hours. Consequently, **1a** and **2a** are suitable systems to compare the performance of RAM to ball-milling, the most widely used mechanochemical synthesis strategy to date.

In developing RAM as a synthetic methodology, we recognized the possibility to vary the following parameters: *i*) acceleration (typically expressed in the acceleration of gravity: g = 9.81 m s^{-2}) *ii*) reaction time; *iii*) presence of a liquid, whose quantity is expressed by the liquid-to-solid ratio η (in μL/mg)[19] already used in LAG mechanochemistry; *iv*) temperature of the sample holder, as well as other conventional variables, such as the catalyst amount. Because this is the first time that RAM is employed in organic synthesis, all these parameters and variables were explored. To ensure reproducibility, each reaction was performed in triplicate, and sample analysis was performed by solution nuclear magnetic resonance (NMR) spectroscopy after suitably quenching and dissolving the entire reaction mixture.

As our first entry into exploring RCM by RAM, we agitated mixtures of **1a** with 0.1 or 0.5 mol% of either 1st or 2nd generation Grubbs, or 1st or 2nd generation Hoveyda-Grubbs (G-1, G-2, HG-1, HG-2, respectively) catalyst, using the commercially available LabRAM II instrument (Figure 1a).[20] Using this instrument, the samples are shaken at a set frequency of 60 Hz, and the intensity of the process is controlled by varying the vertical acceleration of the reaction vessel (0-90 g). To facilitate reaction screening, we have designed a custom sample holder suitable for holding up to 15 vials (Figure 1b,c). Acoustic mixing at 30, 60 or 90 g did not lead to any reaction, as evidenced by ^{1}H NMR analysis of the entire sample. Next, we turned to the RAM in the presence of small amounts of a liquid. This liquid-assisted (LA-RAM) technique was previously shown to promote or even enable the synthesis of MOFs.[12] The addition of ethyl acetate (EtOAc, η = 0.25 μL/mg) led to the formation of **1b** with each of the four catalysts, at a 0.1 mol% loading . Notably, HG-1 (85(2)% conversion by ^{1}H NMR) was found to be significantly more effective than the other catalysts (Table 1). The efficiency of HG-1 is unexpected, as this catalyst is anticipated to be more sensitive than HG-2, and marks a clear difference from ball-milling reactions where HG-2 performed significantly better than HG-1. Focusing on HG-1, we explored the role of different liquid additives, demonstrating that high conversions (>70%) are achievable with a range of liquids, with $CHCl_3$ and CH_3NO_2 producing values of 92(2)% and 95(1)%, respectively.

The ability to achieve a 91-95% conversion of **1a** within 30 minutes simply by LA-RAM with only 0.1 mol% catalyst loading, without any other additives or resorting to sequential catalyst addition, is a remarkable improvement over previously developed LAG process. Nevertheless, we were interested to further improve the conversion to **1b** with EtOAc as a liquid additive, due to its attractive environmental metrics.[21] For this purpose, we explored LA-RAM reaction kinetics by measuring conversions at reaction times of 10, 20 or 30 minutes, accelerations of 30, 60, or 90 g, with each reaction done in triplicate. At 90 g, an apparently linear increase of conversion with time up to 30 minutes was observed, whereas at 30 and 60 g the conversion remained steady at ca. 20% for 20 minutes, but rapidly increased to ~80% by the 30 min time point (Figure 2a).

Table 1. Screening catalysts and liquid additives in ruthenium-catalyzed RCM of **1a** to form **1b**.[a] All LA-RAM reactions were performed with $\eta^{19} = 0.25$ μL/mg.

Entry	Catalyst	Liquid additive	Conversion (%)[b,c]
1	HG-1	/	0(0)
2	G-1	EtOAc	45(3)
3	G-2	EtOAc	3(1)
4	HG-1	EtOAc	85(2)
5	HG-2	EtOAc	23(4)
6	HG-1	water	0(0)
7	HG-1	toluene	74(3)
8	HG-1	$CHCl_3$	92(2)
9	HG-1	MeOBz	72(4)
10	HG-1	acetone	85(2)
11	HG-1	CH_3NO_2	95(1)
12	HG-1 [c]	EtOAc	97(1)

[a] Reaction conditions: 0.7 mmol **1a**, 0.1 mol% catalyst, LA-RAM at 60 *g* for 30 minutes; [b] based on ^{1}H NMR analysis of the entire sample; [c] each reaction was done in triplicate and deviation from the mean is given in parentheses; [d] 0.5 mol% HG-1.

These differences in reaction kinetics suggests poorer mixing at lower g values, which was verified by a separate set of experiments in which **1a** and HG-1 were first pre-mixed, without any liquid additive, by RAM for 5 min at either 30 or 90 *g*, followed by addition of EtOAc and further agitation for 10, 20 or 30 min. Under such treatment, the reactions immediately presented higher conversions, which increased linearly with time (Figure 2b, c), corroborating the importance of efficient mixing, and the role that higher acceleration plays in ensuring it. Nevertheless, extending the reaction time past 30 min led to little increase in conversion, suggesting catalyst deactivation. Higher conversion of **1a** into **1b** by LA-RAM with EtOAc were subsequently achieved by two strategies. The first was simply increasing catalyst content to 0.5 mol%, which is the loading used previously in ball-milling RCM. This readily afforded a 97% conversion in 30 min. Alternatively, we exploited the ability to vary the temperature in the LabRAM II instrument, by flowing thermostated water around our in-house designed sample chamber.[22] Setting the thermostatic bath temperature (τ) to 45 , 55 or 70 °C was found to translate to reaction temperatures of 30 , 36 , and 45 °C, respectively. Using $\tau = 45$ °C led to remarkable improvement in reactivity, with conversions of 78(3) and 92(2)% observed after 5 and 10 min, respectively (Table 2). Assuming that conversion could be limited by evaporation of EtOAc, we explored RCM under identical conditions but using MeOBz as a liquid additive with a higher boiling point. This led to a 98(1)% conversion into **1b** in 10 minutes (Table 2). The significant improvement in conversion upon mild increase in

temperature is consistent with previous observations in ball milling reactions,[23] and implies that the RAM environment does not involve high temperatures.

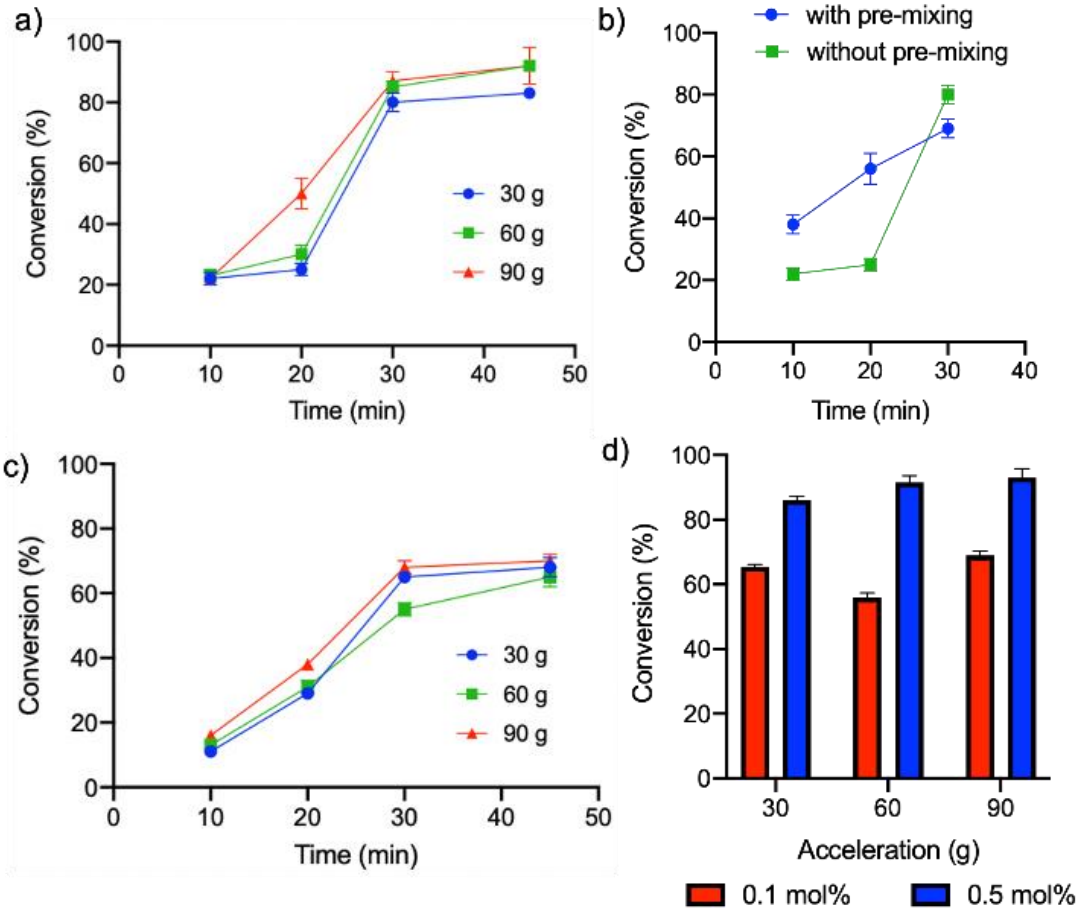

Figure 1. a) Conversion of **1a** to **1b** by LA-RAM with respect to different reaction times at 30, 60 and 90 *g*. b) Comparison of the conversion of **1a** to **1b** for LA-RAM reactions with (blue) and without (green) a brief pre-mixing period by dry RAM, at 30 *g* (for analogous experiment at 90 *g*, see SI). c) Conversion of **2a** to **2b** upon LA-RAM at different *t* and 30, 60 or 90 *g*. d) Conversion of **2a** to **2b** after 30 min LA-RAM with catalyst loadings of 0.1 (red) and 0.5 mol% (blue) at 30, 60 or 90 *g*. In all cases, the liquid additive was EtOAc (η = 0.25 µL/mg), and RCM catalyst was HG-1. Error bars are standard deviations from triplicate experiments, and data is provided in the SI.

With a set of LA-RAM strategies for RCM established, we turned to substrate **2a**, previously noted[14] to undergo RCM by ball-milling more slowly compared to **1a**. Indeed, LA-RAM of **2a** in the presence of 0.1 mol% of HG-1 and EtOAc led to no more than 68% conversion to **2b** after 30 min, independent of acceleration (Figure 2c). The conversion was readily improved by either of the two strategies established with **1a**: increasing the catalyst loading to 0.5 mol% gave conversions between 85% and 90% in 30 min (Figure 2d), while heating the system using a flow of water thermostated at 45 °C led to ~95% conversion in 5 min, using either EtOAc or MeOBz as the liquid additive and 0.1 mol% of HG-1 (Table 2).

Table 2. Conversion (in %)[a,b] of **1a** and **2a** to the corresponding RCM products **1b** and **2b**, upon LA-RAM in the presence of EtOAc or MeOBz (η = 0.25 μL/mg), at different times (*t*, in minutes), and with reaction systems thermostated using flowing water of temperature τ = 45 °C.[c]

Entry	Reactant	Liquid additive	Time (min)	Conversion (%)[a,b]
1	**1a**	EtOAc	5	78(3)
2	**1a**	EtOAc	10	92(2)
3	**1a**	MeOBz	5	89(1)
4	**1a**	MeOBz	10	98(1)
5	**2a**	EtOAc	5	95(1)
6	**2a**	MeOBz	5	95(1)

[a] based on ^{1}H NMR analysis of the entire sample; [b] each reaction was done in triplicate and deviation from mean is given in parentheses; [c] setting the thermostat to 45 °C corresponds to reaction mixture temperature of ~ 30 °C.

Next, we challenged LA-RAM with RCEYM, a catalytic metathesis transformation that has not yet been explored under mechanochemical conditions, with **3a** as the substrate (Figure 1e). While no conversion to the expected 3-pyrroline **3b** was observed upon RAM of **3a** with 0.1 mol% of HG-1, screening of liquid additives (η = 0.25 μL/mg) gave conversions between 6 (with *p*-cymene) and 37% (with $CHCl_3$) over a period of 30 minutes, at 60 *g* (Table 3). Overall, this screen revealed that *p*-cymene and dimethylcarbonate, both popular solvents for RCM in solution,[24] gave low conversions, while the highest was observed with $CHCl_3$. To verify if the high conversion in the presence of $CHCl_3$ might be related to inherent acidity of the liquid, we also explored LA-RAM in the presence of EtOAc and 0.2% (v/v) HCl, which led to poorer conversion. Focusing on $CHCl_3$ as the liquid additive, we explored a range of strategies to increase reaction conversion, including changes to *t*, *g*, and multiple catalyst additions (Table 3).

Table 3. RCEYM conversion of **3a** to **3b** catalyzed by HG-1 (0.1 mol%) upon neat RAM or by LA-RAM in the presence of different liquid additives (η = 0.25 μL/mg).[a]

Entry	Liquid additive	Conversion (%) [b]
1	/	0(0)
2	EtOAc	19(4)
3	EtOAc + 0.2% HCl(aq)	10(2)
4	CH_3NO_2	31(3)
5	$CHCl_3$	37(2)
6	chlorobenzene	28(2)
7	*p*-cymene	6(1)
8	dimethylcarbonate	15(2)

[a] Reactions conducted for 30 min, at 60 *g*. [b] result of triplicate experiment, with deviation from the mean in parentheses.

A two-fold increase in either time (to 60 min) or HG-1 amount (to 1 mol%) led to less than two-fold increases in conversion, from 37% to ca. 54%. No significant difference was observed when conducting the reaction at 30 or 90 *g*. A notable improvement in conversion was observed, however, if HG-1 was introduced to the reaction mixture in either two or three portions, in 0.5 mol% quantity each time. With a LA-RAM time of 30 min after each addition, such a procedure led to conversions of ca. 75%. The conversion was further augmented to >80% by either extending the LA-RAM time to 60 min after each catalyst addition or, in order to counter the evaporative loss of liquid additive taking place upon each catalyst addition, by introducing an additional 50 μL of $CHCl_3$. The maximum conversion obtained so far by using either of these strategies was 86%. Increasing the temperature during LA-RAM by thermostating with water set at 45 ^oC (corresponding to reaction mixture temperature of ~30 ^oC) led to a significant improvement in conversion at 0.5 mol% catalyst loading: 58% after 30 minutes, and 66% after 60 minutes at 60 *g*. Higher temperatures, however, led to poorer conversions (~40%), indicating either catalyst thermal sensitivity, or the loss of volatile liquid additive. Ultimately, almost quantitative conversion (95%) of **3a** to **3b** within 90-120 minutes was achieved by combining mild heating with two or three catalyst additions (Table 4). This achievement demonstrates LA-RAM as a platform to adapt and optimize a transformation not yet explored under mechanochemical conditions.

Table 4. Overview of the RCEYM conversion (in %) of enyne **3a** to **3b** by LA-RAM, with respect to the thermostat temperature (τ, in ^oC), reaction time (*t*, in minutes), HG-1 catalyst addition strategy and loading (in mol%), $CHCl_3$ addition strategy and volume (*V*, in μL).

Entry	τ (°C)[a]	HG-1 (mol %)	*t* (min)	*V* (μL)	conversion (%)[b]
1	45	0.5	30	50	58(2)
2	55	0.5	30	50	44(3)
3	70	0.5	30	50	40(2)
4	45	0.5	60	50	66(3)
5	45	2 x 0.5	2 x 30	2 x 50	85(2)
6	45	2 x 0.5	2 x 60	2 x 50	95(1)
7	45	3 x 0.5	3 x 30	3 x 50	95(1)

[a] Temperature of the water thermostat; [b] result of triplicate experiment, with deviation from the mean given in parentheses.

Our final targets were the catalytic syntheses of sulfonylureas by copper-catalyzed coupling of a sulfonamide and an isocyanate (Figure 1f). This reaction is an archetypal example of mechanochemical API synthesis, introduced for 1st and 2nd generation antidiabetic drugs Tolbutamide (**5**), Chlorpropamide (**6**), and Glibenclamide (Figure 1f). Our main focus was on the reaction of *p*-toluenesulfonamide with *n*-butylisocyanate to produce Tolbutamide, catalyzed by CuCl (Table 5). When using ball-milling in the presence of 5 mol% CuCl, this reaction was

reported to give **5** in 90% yield after 2 hours of LAG with CH_3NO_2 (η = 0.25 μL/g), and was previously scaled to ~1 gram.[16]

After 30 min at an acceleration of 60 *g*, RAM of a neat mixture of *p*-toluenesulfonamide, *n*-butylisocyanate and 5 mol% CuCl gave low (10%) conversion to **5**. The addition of a liquid (η = 0.25 μL/mg) led to different results, as using EtOAc, MeOBz, acetone, 2-butanone, and CH_3NO_2 led to noticeable increases in conversion (Table 5).

Table 5. Overview of conversions in Tolbutamide (**5**) synthesis by CuCl-catalyzed coupling of *p*-toluenesulfonamide with *n*-butylisocyanate by RAM, or LA-RAM with different liquid additives.

Entry	Liquid additive[a]	Conversion (%)[b]
1	/	10(1)
2	toluene	0(0)
3	$CHCl_3$	0(0)
4	MeOBz	26(2)
5	EtOAc	63(2)
6	acetone	61(3)
7	nitromethane	74(2)
8	2-butanone	31(3)

[a] LA-RAM with η = 0.25 μL/mg. [b] Based on ^{1}H NMR. Reaction conditions: *p*-toluenesulfonamide (0.5 mmol), *n*-butyl isocyanate (0.5 mmol), CuCl (5 mol%), 60 *g*, and reaction time of 30 min. Each reaction was performed in triplicate, and deviation from the mean is given in parentheses.

With CH_3NO_2 identified as the liquid additive producing the highest conversion in 30 min, we explored how Tolbutamide synthesis is affected by other LA-RAM parameters: time, acceleration, temperature, and η. As in other reactions studied so far, changes in *g* had little or no effect. Increasing *t* to 60 min, however, led to >80% conversion to **5**.

Similar behavior was also observed upon extending our screen to analogous reactions of *p*-toluenesulfonamide with *n*-propylisocyanate to give compound **4**, as well as of *p*-chlorosulfonamide with *n*-propyl- and *n*-butylisocyanates to produce Chlorpropamide (**6**) and compound **7**, respectively (Figure 3a, b). In all cases, conversion was more affected by time than by acceleration, reaching 80-85% for **4**-**7**, and ca. 70% for **6** after 60 min. The absence of acceleration-related effects suggests efficient mixing of reactants and the catalyst. Conversely, more significant effects related to acceleration should be observable at lower catalyst loadings, where improved mixing would be needed for reaction progress. To verify this reasoning, we explored the synthesis of Tolbutamide (**5**) at lower CuCl contents of 1 and 0.5 mol% (Figure 3c). A difference in reaction progress dependent on acceleration became evident at the CuCl loading of 0.5 mol%.

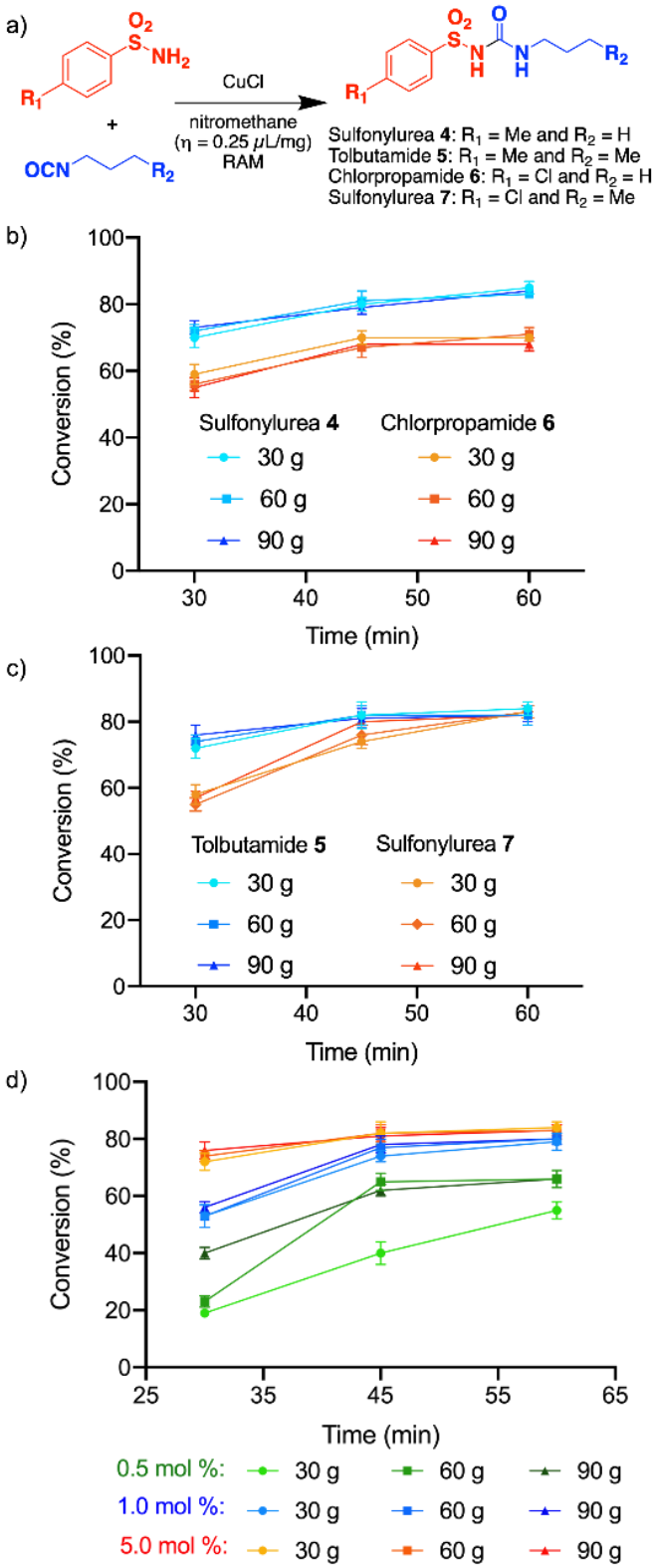

Figure 3. The influence of sample acceleration on conversion in CuCl-catalyzed LA-RAM synthesis of sulfonylureas **4**-**7**: a) reaction scheme; b) reactions with *n*-propylisocyanate; c) reactions with *n*-butylisocyanate, and d) synthesis of Tolbutamide (**5**) at catalyst loadings of 5.0, 1.0 and 0.5 mol%. Data is provided in the SI.

Improved conversions (Table 6) were also achievable by thermostating the sample holder with water set at τ = 70 °C, corresponding to a reaction mixture temperature of ~45 °C, which produced 81-87% conversions within 30 min, at 60 *g* and η = 0.25 μL/mg. Conversions of 80-90% across all four reactions were also obtained at a lower τ = 45 °C, but after 60 min.

Table 6. Influence of thermostat temperature (τ , in °C) and time (*t*, in min) on the conversion in LA-RAM synthesis of sulfonyl-ureas **4**-**7**.[a-c]

τ (°C)[d]	*t* (min)	**4**	**5**	**6**	**7**
22	30	72(2)	74(2)	56(2)	55(2)
45	30	78(3)	85(3)	63(2)	73(3)
70	30	85(2)	87(2)	81(2)	84(2)
22	45	81(3)	82(3)	67(3)	76(3)
45	45	89(2)	86(2)	79(3)	85(1)
22	60	83(1)	82(3)	71(2)	83(2)
45	60	90(1)	87(2)	80(2)	86(2)

[a] Based on ^{1}H NMR spectroscopy of the entire sample. [b] Each reaction was performed in triplicate and the deviation from the mean is given in parentheses. [c] Reaction conditions: sulfonamide (0.5 mmol), isocyanate (0.5 mmol), CuCl (5.0 mol%), 60 *g*, CH_3NO_2 (η = 0.25 μL/mg). [d] Temperature of thermostatic bath.

Reaction conversion was also improved by varying η (Figure 4a). Notably, screening all four CuCl-catalyzed reactions over a 30 min LA-RAM period, with η values between 0 and 1.5 μL/mg, revealed a maximum of conversion at η = 0.5 μL/mg. Consequently, high conversions were accessible for all four compounds **4** (90%), **5** (Tolbutamide, 88%), **6** (Chlorpropamide, 72%) and **7** (84%) by using t = 60 minutes, and η = 0.5 μL/mg.

The observed maximum in conversion with respect to η has not been described in mechanosynthesis, and can be rationalized by a balance between two opposing effects: increase in molecular mobility at low η is expected to promote reactions, while increased dilution at higher η is expected to reduce conversions. To verify such behavior in other mechanochemical approaches, we also conducted a systematic screen of Tolbutamide synthesis by ball-milling at different η values. The results showed a similar maximum in the conversion vs η profile of the reaction, although with overall lower conversions compared to LA-RAM (Figure 4b).

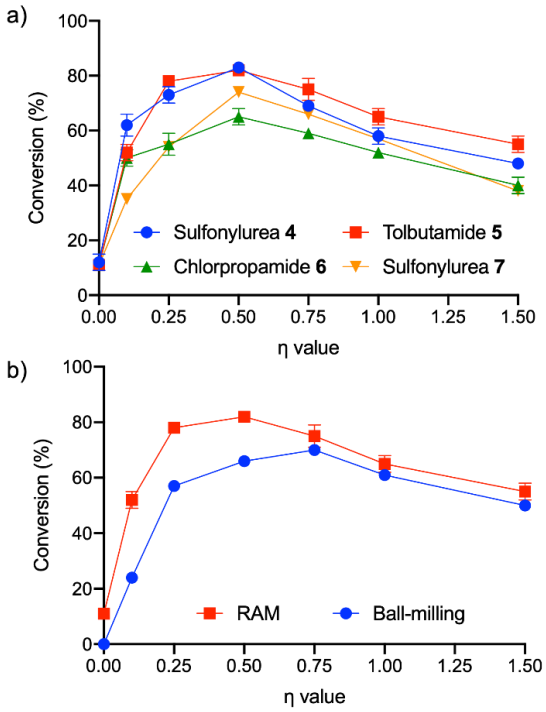

Figure 4. a) Conversion to sulfonyl-ureas **4-7** by LA-RAM with respect to the η value, with CH_3NO_2 as the liquid additive. Reactions were performed in triplicate, with 5 mol% CuCl catalyst, for 30 min at 60 *g*; b) Comparison of the η-dependent conversion to Tolbutamide (**5**) upon LA-RAM (red, at 60 *g*) and LAG (blue, at 30 Hz) in the presence of CH_3NO_2 as the liquid additive and 5 mol% CuCl, after 30 min. Data is provided in the SI.

With optimized LA-RAM conditions for the synthesis of Tolbutamide at hand, we explored the potential for scale-up by investigating the conversion at scales between 0.14 g and 1.38 g, without changing the volume (2.5 mL) of the vessel. The increase in reaction scale was associated with the filling degree, *i.e.*, the fraction of reaction vessel volume occupied by the reactants.[25] The filling degree was estimated by the ratio of the height of the reaction mixture in the RAM vessel and the vessel height. Overall, these results revealed a slight increase in the conversion of Tolbutamide (from 84% to 90%) upon increasing the filling ratio from 13% (0.14 g reaction) to 88% (1.38 g reaction) (Figure 5).

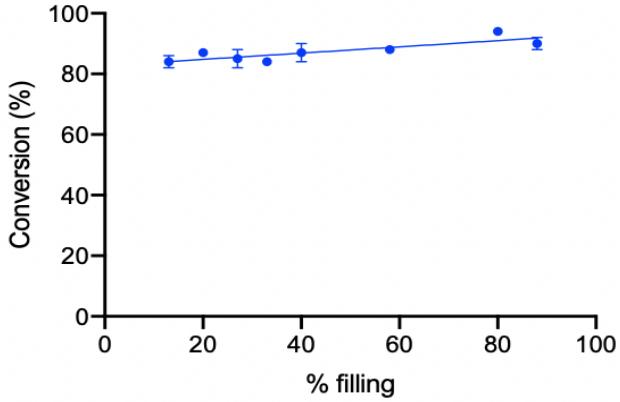

Figure 5. Change in conversion of LA-RAM Tolbutamide synthesis upon scaling from 0.14 g to 1.38 g in a reaction vessel of constant 2.5 mL volume, shown with respect to the filling degree. Reaction conditions: *p*-toluenesulfonamide (0.5 mmol), *n*-butylisocyanate (0.5 mmol), CuCl (5.0 mol%), 60 *g*, 1 hour, CH_3NO_2 (η = 0.50 µL/mg). Error bars are based on triplicate measurements. Individual data are given in the SI.

Switching to a larger reaction vessel of 30 mL volume enabled further scale-up (Table 7), with the highest herein explored reactant amount being 9.60 g. At that scale, the measured conversion was 95% after 60 min at 60 *g*. Importantly, we also explored reducing the amount of catalyst at the 9.60 g scale, which enabled the synthesis of Tolbutamide using only 2 mol% of CuCl, with a conversion of 90%. Product isolation, using a procedure similar to what was previously reported for ball-milling, *i.e.* by mixing the reaction mixture with an aqueous solution of disodium ethylenediaminetetraacetate (Na_2H_2EDTA) in RAM for 10 min and filtering, provided Tolbutamide in the isolated yield of 86%. Whereas the synthesis of APIs by mechanochemistry is a rapidly growing area, so far there are no studies on residual metal content resulting from metal-catalyzed reactions. The ability to rapidly synthesize a significant amount of Tolbutamide API, in the absence of any metal components except CuCl catalyst, provided an excellent opportunity to investigate the potential contamination with residual metal catalyst. Analysis of the raw Tolbutamide product by ICP-MS revealed a copper content of 370 ppm immediately after isolation, which was further reduced to 120 ppm upon recrystallization of crude Tolbutamide from ethanol. These results show the surprisingly simple, immediate and, in the context of mechanochemistry, unprecedented scale-up of the API synthesis by nearly 100-fold, from 0.14 g to almost 10 g, directly and without any modifications to the overall composition of the reaction mixture, or reaction conditions.[26]

Table 7. Conversion[a] and isolated yield upon scaling-up of LA-RAM Tolbutamide synthesis from 0.14 g to 9.60 g. Unless otherwise noted, all reactions have been conducted at η = 0.50 μL mg^{-1}, with CH_3NO_2 as the liquid additive, 5 mol% CuCl as the catalyst, after 60 min at 60 *g*, and in a 30 mL reaction vessel.

total weight (grams)	conversion (%)
0.14[a]	90
1.60	89, 84[b]
3.20	99
3.20[c]	93
9.60	95
9.60[c]	90, 86[b]

[a] In a vial of 2.5 mL volume. [b] Isolated yield. [c] Using 2 mol% CuCl.

In summary, this work shows that Resonant Acoustic Mixing, a methodology originally developed for sample blending and recently investigated in the assembly of cocrystals and MOFs, can be readily deployed for rapid, simple, high-yielding and readily scalable synthesis of organic molecules, including APIs. In particular, we have shown that this methodology enables a significant simplification of mechanochemical ruthenium-catalyzed ring-closing metathesis, the development of ruthenium-catalyzed ene-yne metathesis – a catalytic transformation not yet demonstrated under mechanochemical conditions – as well as rapid synthesis of sulfonylureas, including the antidiabetics Tolbutamide and Chlorpropamide. Importantly, the synthesis of Tolbutamide by acoustic mixing was found to be entirely independent on sample loading, and was directly, without any changes in the reaction protocol except using a larger volume vessel, scalable

by at least two orders of magnitude – from hundreds of milligrams to ca. 10 grams. These observations are unprecedented in mechanochemical synthesis, where changes in reaction scale typically require extensive re-optimization of reaction conditions. The herein observed simplicity of scaling up, ability to work with ruthenium catalysts that are often too sensitive for milling reactions, capability to work with sticky reaction mixtures, and the inherent capacity to modify the reaction temperature, make resonant acoustic mixing a uniquely versatile and simple approach to mechanosynthesis.

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