



**HAL**  
open science

# The Mechanochemical Beckmann Rearrangement: An Eco-efficient “Cut-and-Paste” Strategy to Design the “Good Old Amide Bond”

Rita Mocci, Evelina Colacino, Lidia De Luca, Claudia Fattuoni, Andrea Porcheddu, Francesco Delogu

► **To cite this version:**

Rita Mocci, Evelina Colacino, Lidia De Luca, Claudia Fattuoni, Andrea Porcheddu, et al.. The Mechanochemical Beckmann Rearrangement: An Eco-efficient “Cut-and-Paste” Strategy to Design the “Good Old Amide Bond”. ACS Sustainable Chemistry & Engineering, 2021, 9 (5), pp.2100-2114. 10.1021/acssuschemeng.0c07254 . hal-03166332

**HAL Id: hal-03166332**

**<https://hal.umontpellier.fr/hal-03166332>**

Submitted on 30 May 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# The Mechanochemical Beckmann Rearrangement: An Eco-efficient “Cut-and-Paste” Strategy to Design the “Good Old Amide Bond”

Rita Mocci, Evelina Colacino, Lidia De Luca, Claudia Fattuoni, Andrea Porcheddu,\* and Francesco Delogu



Cite This: *ACS Sustainable Chem. Eng.* 2021, 9, 2100–2114



Read Online

ACCESS |



Metrics & More



Article Recommendations



Supporting Information

**ABSTRACT:** Discovered over a century ago, Beckmann rearrangement is still today fully compliant with all the green chemistry principles and consistent with the key aspects of sustainable development. Herein, we report on a sustainable mechanochemical procedure allowing the design of new amide frameworks via an eco-efficient “cut-and-paste” process of C–C and C–N bonds on the oxime backbone. We combined inexpensive and readily available reagents, such as *p*-tosyl imidazole (*p*-Ts-Im) and oxalic acid, to prepare smoothly and in good to high yields a library of structurally different amides, including value-added marketed compounds such as  $\epsilon$ -caprolactam and the active pharmaceutical ingredient (API) paracetamol. This solvent-free mechanochemical procedure has also been optimized and successfully extended to several ketones serving as oxime precursors.

**KEYWORDS:** Mechanochemistry, Beckmann rearrangement, Active pharmaceutical ingredients (APIs), *p*-Tosyl imidazole (*p*-Ts-Im), Amide, Oxime, Green metrics



## INTRODUCTION

Over the past few decades, organic synthesis has made great strides, revolutionizing many concepts often taken for granted.<sup>1–3</sup> Such advances are deeply rooted in classical reactions that are part of the cultural background learned by contemporary chemists in academia. Facilitated and supported in the daily work aiming at designing and developing new synthetic protocols by modern tools and resources, the chemist keeps drafting new strategies gaining inspiration from what is commonly referred to as “name organic reactions.”<sup>4</sup>

In 1886, the German chemist Ernst Otto Beckmann described the acid-induced conversion of an oxime into an amide (Scheme 1).<sup>5</sup> This reaction is presently known as the Beckmann rearrangement (BKR)<sup>6–10</sup> and even today plays a key role to obtain secondary amides in both industry and academia.<sup>11</sup> Several (sustainable) approaches have been reported to access the amide bond,<sup>12</sup> and its importance is witnessed by its presence in several marketed drugs and polymeric materials (Scheme 1).<sup>13,14</sup>

The industrial preparations of paracetamol<sup>15–18</sup> and  $\epsilon$ -caprolactam<sup>19</sup> (intermediate in the synthesis of nylon-6,6)<sup>20</sup> clearly prove how BKR is topical and crucial in many productive areas of modern society. Along this line, it is worth mentioning that secondary amides attract special interest because of their occurrence as the main structural component in many natural products, agrochemicals and pharmaceuticals,<sup>21,22</sup> detergents and lubricants,<sup>23,24</sup> and functional materials<sup>25</sup> (Scheme 1).

In addition, the wide availability of structurally different and inexpensive ketones enables easy access to the corresponding ketoximes as the starting materials of BKR, making it very attractive even from an atom-economy point of view (Scheme 2).<sup>26</sup>

In BKR, the initial protonation at the ketoxime oxygen gives a suitable leaving oxonium cation triggering the departure of the hydroxy group and the concomitant migration of a substituent (alkyl or aryl fragment, anti to the leaving group) from the  $sp^2$  carbon atom to the nitrogen cation (Scheme 2).<sup>27–32</sup> The simultaneous cleavage of the C–C bond and formation of a new C–N bond provides the most straightforward and reliable approach to insert the nitrogen atom in linear, branched, and cyclic ketones, leading to amide bond. In its classical form, BKR involves the reaction of an oxime with strong acids and often requires harsh reaction conditions and hazardous reagents, restricting its general applicability.<sup>33</sup>

More recent advances have already addressed, at least in part, these limitations via catalysis with transition metals<sup>34–43</sup>

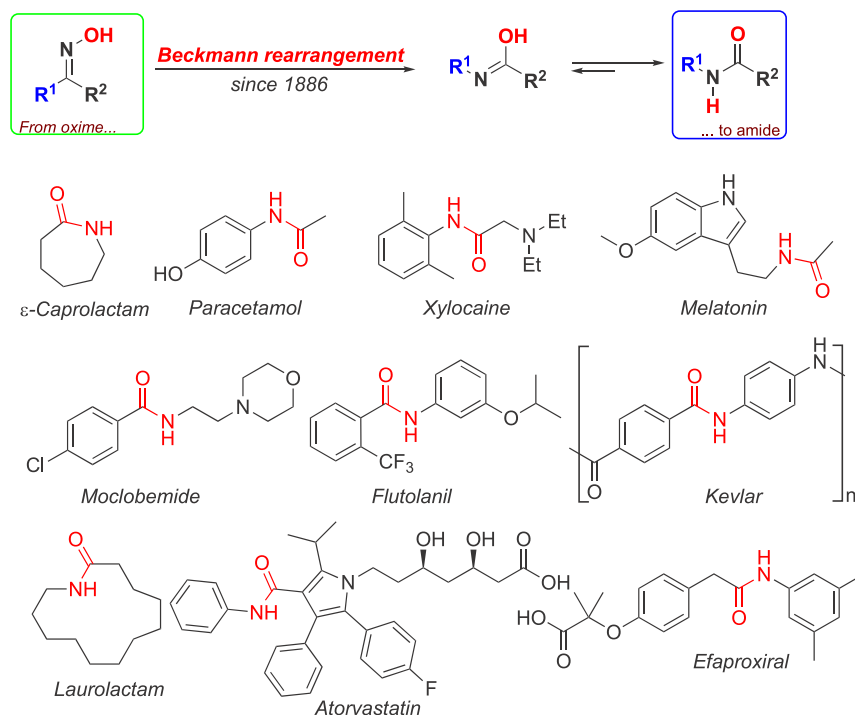
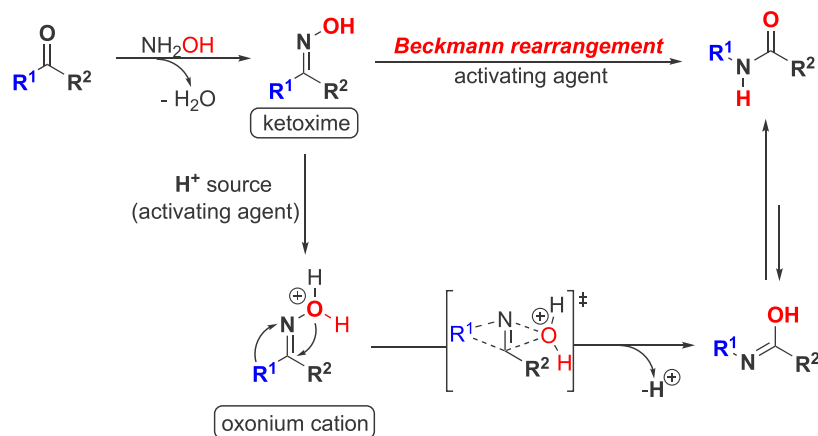
Received: October 1, 2020

Revised: December 19, 2020

Published: January 28, 2021



Scheme 1. BKR with Some Examples of Molecules Containing Secondary Amide Fragments

Scheme 2. Commonly Accepted Mechanism for BKR of Ketoximes<sup>156</sup>

or by employing a wide diversity of organic, often toxic, compounds serving as promoters,<sup>44–49</sup> such as cyanuric chloride,<sup>50,51</sup> propylphosphonic anhydride (T3P),<sup>52</sup> triphosphazene,<sup>53</sup> BOPCl,<sup>54</sup> CDI,<sup>55–57</sup> cyclopropenium salts,<sup>58</sup> calcium complexes,<sup>59</sup> sulfonic acid derivatives,<sup>60–66</sup> inorganic Lewis acids,<sup>67,68</sup> and boronic acids,<sup>67–69</sup> among others.<sup>70–74</sup> However effective and efficient they may be, most of these synthetic protocols require high temperatures and expensive, volatile, and toxic solvents (2,2,2-trifluoroethanol, hexafluoroisopropanol, CH<sub>3</sub>CN, and DMF) and/or excess of reagents to promote the activation of oximes. All of these concerns pose a serious threat to the application of these methodologies in industrial processes.<sup>75,76</sup>

For these reasons, the development of a simple, eco-efficient, cost-effective, and environmentally friendly BKR is highly desirable. It remains a significant challenge in this field, especially for the straightforward conversion from ketones to amides. Carrying out the process at room temperature, using eco-friendly reagents whenever possible and solvent-free

conditions, opens up new avenues for high-performance, scalable, sustainable, and economic BKR. These solutions would also have huge implications and direct benefits for industry, making a plethora of value-added compounds accessible.

The most important challenge arises in connection with solvent elimination. The solvent is, indeed, the major component of a process in solution and therefore significantly affects the production costs, especially if highly polluting.<sup>25,77–83</sup> As trivial as it may seem, developing a reaction without a solvent is not a simple algebraic operation in which one component, the solvent, is removed.<sup>84–88</sup> Rather, it involves exploiting the entire arsenal of expertise, methods, and resources available to modern chemists.

Within this context, mechanochemistry can effectively provide a more reliable and robust solution, allowing many classical processes to take place in the absence of solvent and making them more feasible/attractive for chemical industry.<sup>84–96</sup> In contrast to neat procedures, kinetic studies on

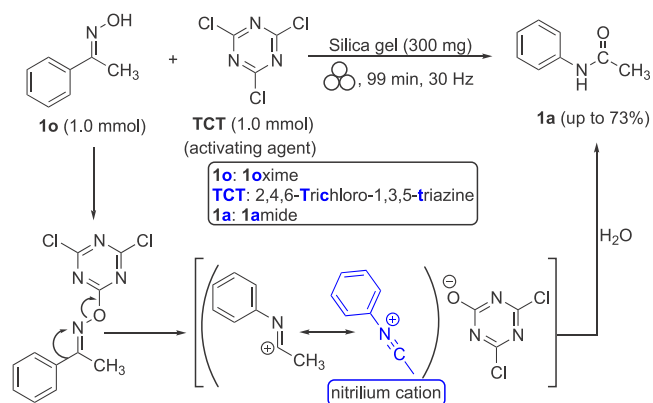
mechanochemical processes have highlighted that only a small fraction of reagents is involved in individual impacts.<sup>97–100</sup> Overall, the process works similarly to a highly diluted reaction (dispersion), while maintaining all the advantages of neat processes in solution. Since most oximes are solid and many of them also have high melting points,<sup>101</sup> mechanochemistry matches well with the BKR, thus paving the way to the preparation of amides along alternative reaction pathways, often foreclosed in a homogeneous phase.<sup>102–104</sup> Nowadays, the reaction between HCl NH<sub>2</sub>OH and a ketone is the most common, efficient, and inexpensive synthetic strategy for preparing ketoximes. In this procedure, the hydroxylamine hydrochloride salt requires a basic treatment, as sodium acetate, before use, to free NH<sub>2</sub>OH for reaction with ketones.<sup>105</sup> Unfortunately, HCl NH<sub>2</sub>OH is almost insoluble in most organic solvents, which is one of the significant drawbacks in using this readily available, inexpensive starting material. Furthermore, the oxime formation, especially those derived from more complex substrates, needs to be carried out under high temperature, and the resulting product has to be further purified by crystallization. Also, solvents and experimental conditions used to prepare oximes are often not consistent with BKR and should therefore be prepared before use. In mechanochemical processes, all challenges related to the reagent solubility and, in general, the solvent's choice are overcome. This fact has relevant implications in green chemistry since it allows the design of multistep *one-pot* reactions, cuts energy costs, and minimizes the operator's exposure to chemicals, making the process more cost-effective, and therefore more attractive for industry. Many of these issues have recently been well highlighted in a remarkable paper by Tobiszewsk.<sup>83</sup> Mechanochemistry could offer exhaustive answers to all these requirements and find new breaches into the walls that were difficult to overcome, breathing new life on organic synthesis. In this regard, this study aims to design and implement a sustainable and generally applicable mechanochemical BKR, using where possible, eco-friendly reagents and milder experimental conditions than those reported so far in the literature.

## RESULTS AND DISCUSSION

Drawing on decades of experience using 1,3,5-trichlorotriazine (TCT)<sup>106–119</sup> as activating agent, we attempted to demonstrate that a similar rearrangement could take place upon a mechanochemical approach. With this aim, preliminary tests were performed by milling acetophenone oxime (1.0 mmol) and TCT (1.0 mmol) in a stainless-steel jar (15 mL) in the presence of one ball ( $f = 8$  mm) of the same material. However, a black tar was obtained that was difficult to handle during workup. To overcome this problem, 300 mg of silica gel was added during the milling step. Indeed, the complete conversion of oxime **1o** to amide **1a** made acetanilide recovery (from the crude reaction) more straightforward (Scheme 3). Upon completion (99 min), the resulting solid was extracted with ethyl acetate for compound isolation. The residue was subjected to silica gel chromatography to remove any TCT byproducts to afford amide **1a** in an overall 66% yield.

To simplify this procedure further, the solid was scratched out of the jar, loaded on a short silica gel pad (short plug), and then eluted with AcOEt to give a final amide yield of 73%. Unfortunately, we were unable to reduce the amount of TCT or to use only catalytic amounts (10 mol %), even in the presence of ZnCl<sub>2</sub> (10 mol %). The result was the incomplete

### Scheme 3. Mechanochemical-Assisted Synthesis of Acetanilide **1a** by Using TCT



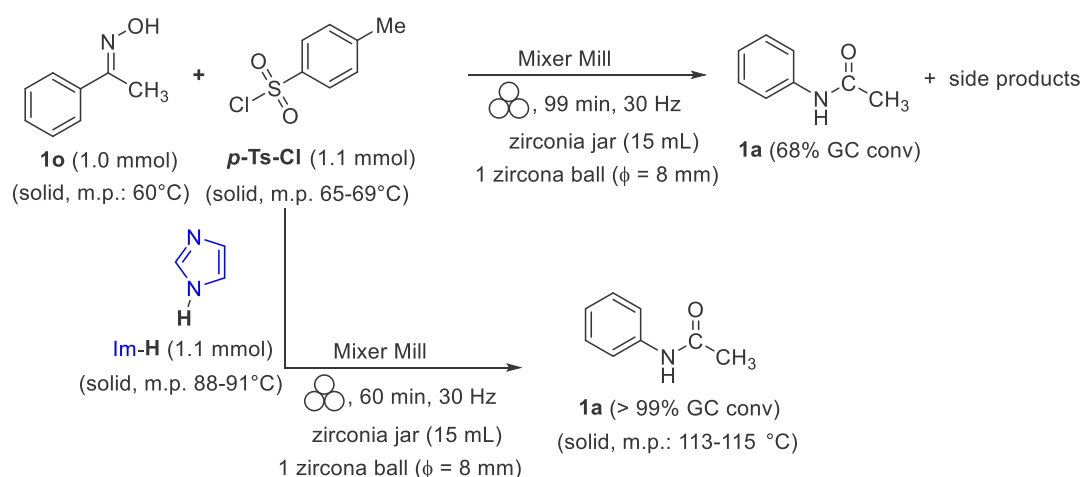
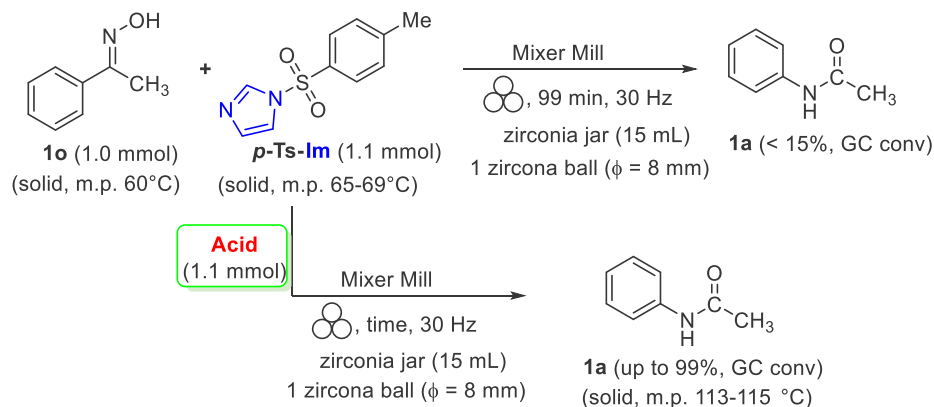
conversion of the acetophenone oxime to amide **1a**. The procedure developed using an equimolar amount of TCT, although efficient and effective, turned out to be difficult to adopt for industrial scale-up applications. In addition, from the environmental point of view, the reaction suffers from poor atom economy, but the need for workup procedures based on a liquid–liquid extraction followed by a chromatographic purification heavily impacts on the sustainability of the process.

Taking inspiration from some recently published papers,<sup>120,121</sup> we directed our attention to *p*-toluenesulfonyl chloride (*p*-TsCl), a low-value byproduct of the saccharine industrial production (and other food additives) by the Remsen–Fahlberg process,<sup>122,123</sup> and recently used for a less environmentally wasteful preparation of isocyanides.<sup>124</sup> *p*-TsCl is an inexpensive solid reagent that is much easier to handle and less toxic than other established activating agents for BKR. On the basis of the above considerations, *p*-TsCl appeared to be suitable for scaling up to an industrial process.

To achieve this goal, the acetophenone oxime (1.0 mmol) and *p*-TsCl (1.1 mmol) were milled in zirconia milling jars (15 mL) with a grinding ball of the same material ( $f = 8$  mm) for 30, 60, and 99 min at 30 Hz. Unfortunately, BKR of the referral oxime failed to go to completion after prolonged reaction periods (99 min). On a further increase in reaction time up to 2 h, we observed a significant rise in side products, mainly derived from the decomposition of oxime **1o**.<sup>125</sup> Keeping constant all other experimental conditions, we added into the jar a stoichiometric amount of imidazole, which promoted the complete conversion of oxime **1o** into acetanilide and reduced the reaction time of the BKR to 60 min (Scheme 4).

The pivotal BKR was subsequently monitored *ex situ* by withdrawing aliquots at different time intervals (15 min) and analyzing them using GC-MS<sup>126,127</sup> and thin-layer chromatography (TLC) until the peak/spot corresponding to the oxime disappeared (60 min). The analyses were performed by re-preparing the sample from scratch (*ex novo*) and prolonging the overall reaction time between one analysis and the next (15, 30, and 45 min, etc.). Noteworthy, GC-MS analysis showed the rapid formation, after only 15 min, of a significant amount of 1-(*p*-toluenesulfonyl)imidazole (*p*-Ts-Im), which is consumed in the course of the reaction with kinetics comparable to those of amide product formation.

Intrigued by these findings, a stoichiometric amount of acetophenone oxime (1.0 mmol) and *p*-Ts-Im (1.1 mmol, commercially available) were milled in a zirconia grinding jar

Scheme 4. Screening of the Reaction Parameters for the Maximization of the Degree of Conversion of Ketoxime **1o** to Amide **1a**Scheme 5. Influence of an Acid Reagent in the BKR Promoted by 1-(*p*-Toluenesulfonyl)imidazole (*p*-Ts-Im, CAS No. 2232-08-8)

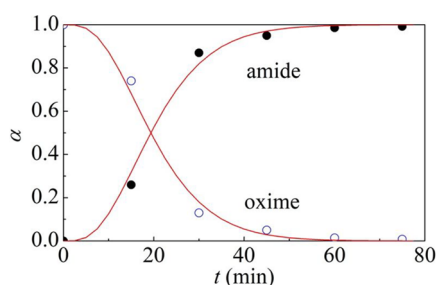
Entry	Acid	Time	pKa	GC Conv (%)
1	PTSA	< 75 min	-2.8	> 99
2	Citric acid	99 min	3.09	49
3	Tartaric acid	99 min	2.99	85
4	Boric acid	99 min	9.24	15
5	Oxalic acid	15 min	1.23	> 99

(15 mL) with a zirconia grinding ball ( $f = 8$  mm) for 99 min, during which we observed negligible conversion (<15%) of oxime **1o** to amide **1a** (Scheme 5). This suggests that the hydrochloric acid developed during the reaction using *p*-TsCl (Scheme 4) plays a key role both in promoting the initial activation of *p*-Ts-Im generated *in situ* and the subsequent BKR, as highlighted in Scheme 5.

Hence, the model reaction was repeated once again using the same conditions, but in the presence of an equimolar amount of *p*-toluenesulfonic acid (PTSA, 1.1 mmol) to ensure complete conversion of the substrates. To our great pleasure, BKR was completed in less than 75 min (GC-MS and TLC analyses), confirming our initial hypothesis (Scheme 5, entry 1). Additionally, we characterized the experimental conversion curve (GC-MS data). The relative amounts of initial oxime **1o**

and final amide **1a**,  $\alpha$ , are shown in Figure 1 as a function of the milling time,  $t$ . It can be seen that the conversion curves have a sigmoidal shape. The mechanochemical transformation is quite fast, with the conversion degree of the oxime in amide as high as 0.87 after 30 min.

We carried out a preliminary kinetic analysis to provide additional information on the transformation rate. To this aim, we used a kinetic model that properly accounts for the statistical nature of the mechanical processing of solids by ball milling.<sup>98-100</sup> Specifically, in a first approximation, we assumed that the product forms abruptly in a fraction of the solid mixture that has undergone at least three impacts. While the assumption is seemingly rough, it allows deriving the relatively simple kinetic equations (eqs 1a and 1b):



**Figure 1.** Relative amounts of initial oxime and final amide,  $\alpha$ , as a function of the milling time,  $t$ . Best-fitted curves are shown.

$$\alpha_{\text{oxime}} = [1 + kt + (kt)^2/2 + (kt)^3/6] \exp(-kt) \quad (1a)$$

$$\alpha_{\text{amide}} = 1 - [1 + kt + (kt)^2/2 + (kt)^3/6] \exp(-kt) \quad (1b)$$

where  $\alpha$  is the mass fraction of initial oxime or final amide,  $k$  is the apparent rate constant of the mechanochemical transformation, and  $t$  is the milling time. Despite the rough assumptions, eq 1a satisfactorily best fits the experimental data. Therefore, we can infer that it captures the fundamental features of the transformation kinetics. The best-fitting equation yields a  $k$  value approximately equal to  $0.18 \text{ min}^{-1}$ . On the basis of previous work,<sup>98–100</sup> the apparent rate constant

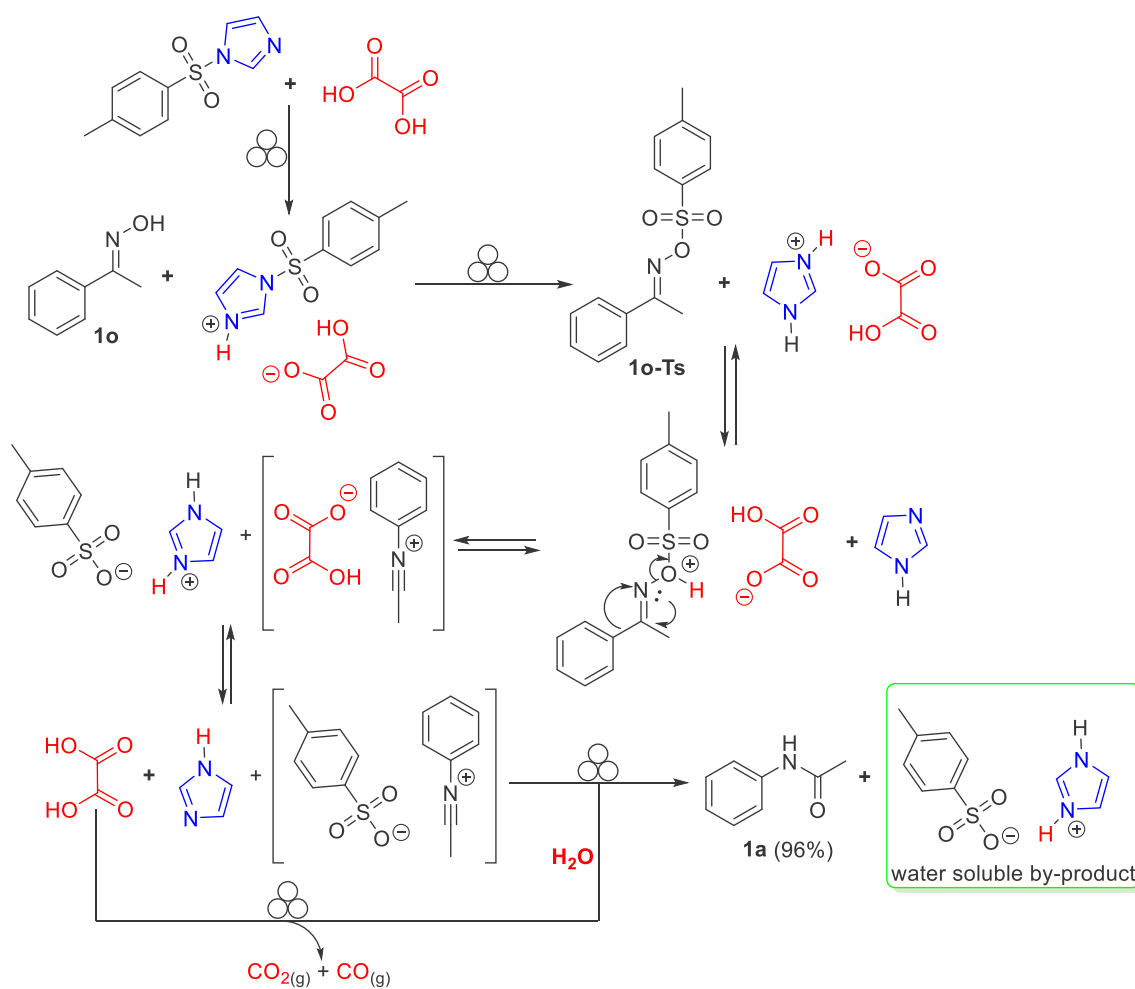
measures the mass fraction of reactants involved in the product formation per time unit. Thus, we can suppose that approximately 24 mg of oxime is effectively converted into amide per time unit.

The milling experiments have been carried out using a single zirconia ball. If we assume that its collisions with the jar are partially inelastic, then we can reasonably expect that the impact frequency is approximate twice the milling frequency. Since we performed milling at 30 Hz, we can expect that impacts occur at a frequency of 60 Hz. It follows that, in 1 min, the zirconia ball undergoes about 3600 impacts. In turn, we can surmise that approximately  $6.6 \mu\text{g}$  of oxime is effectively processed during each individual impact.

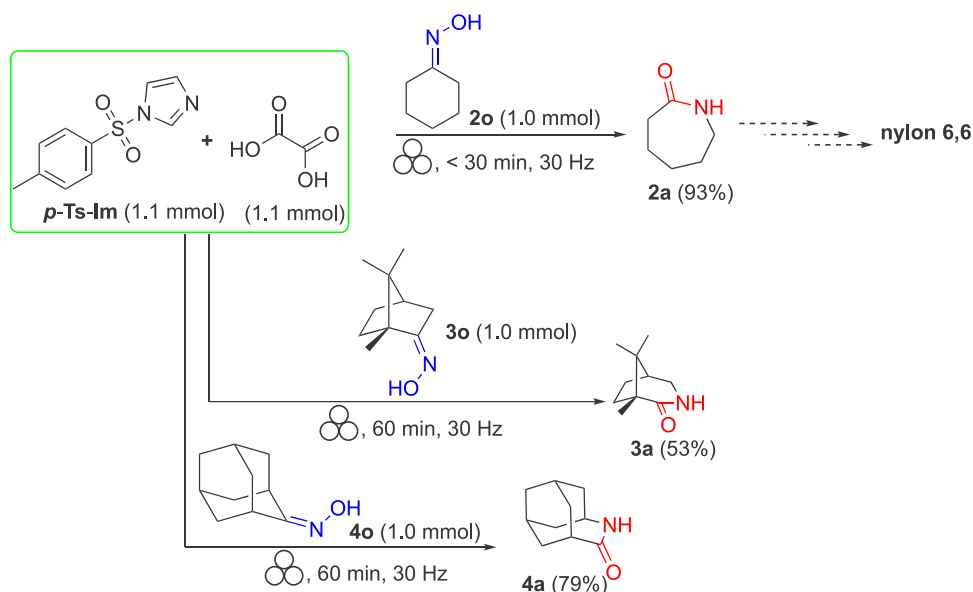
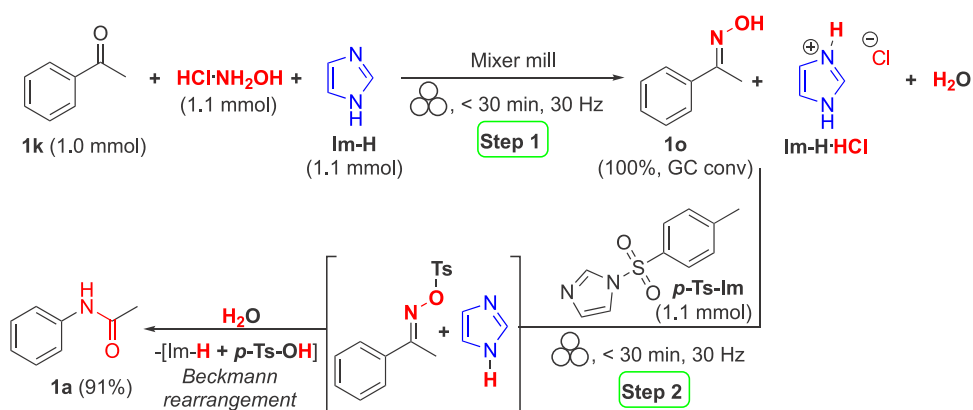
This value is not far from those typically observed in mechanochemical transformations.<sup>98–100</sup> We recognize that this is an interesting issue, but further discussion is out of the present work scope. We will deepen our insight into this interesting issue in a future study.

We then carried out additional experiments, reacting oxime **1o** (1.0 mmol), imidazole (1.1 mmol), and *p*-toluenesulfonic acid (1.1 mmol) to clearly rule out the role of the acid in this mechanochemical 1,2-rearrangement. In the absence of the activating agent *p*-Ts-Im, we only observed the formation of negligible amount (7%, GC-MS analysis) of amide **1a**, even after prolonged grinding (99 min).

#### Scheme 6. Combination of *p*-Ts-Im and Oxalic Acid Promotes a Rapid Conversion of Oxime **1o**



Scheme 7. Assessment of Robustness of the Mechanochemical BKR

Scheme 8. Optimization of the Process Parameters for the BKR of Oxime 1o Generated *In Situ* from Acetophenone 1k

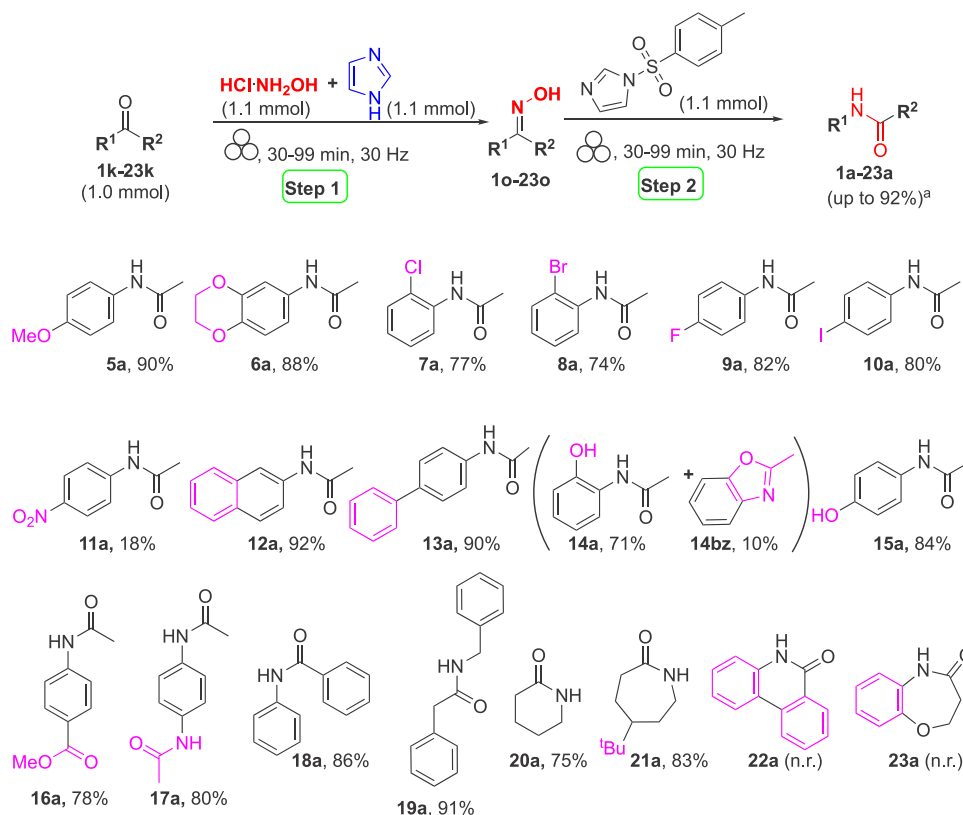
Although *p*-Ts-Im is cheap and commercially available, the use of freshly prepared reagent gave better results in our hands.<sup>128</sup> It can be directly prepared from *p*-toluenesulfonic acid by reaction with 1,1'-carbonyldiimidazole (CDI).<sup>128–135</sup> The latter synthesis is particularly effective and avoids the use of harmful chlorinating agents reducing hazardous waste collection. Compared to other reagents widely used in the BKR, *p*-Ts-Im combines at best the need for a reagent with easy-handle properties, effective, and inexpensive to use in macroscale applications.

Starting from these findings, we screened other green acids instead of PTSA to tailor a more eco-efficient procedure, and the results are summarized in Scheme 5. The scenario changes again, for the better, using oxalic acid: The whole experiment was completed in approximately 15 min (as assessed by GC-MS and TLC analyses). IR and NMR analyses on reaction crude further confirmed these results showing that the GC-MS was sensitive, precise, and accurate for the quantitative determination of oxime to amide conversion. We assumed that during the milling process, a proton was transferred from oxalic acid to the imidazole ring of *p*-Ts-Im, promoting the formation of tosyl ester (1o-Ts) on the oxime (Scheme 6).<sup>136</sup> The activation of the oxime with *p*-Ts-Im in an acidic environment triggered the subsequent BKR, as shown in

Scheme 6. Besides, the combination of *p*-Ts-Im and oxalic acid not only promotes a rapid conversion of oxime 1o but also facilitates the purification steps of the target amide from the resulting crude reaction. Trituration of the postreaction solid with water, 10% citric acid solution, and 10% K<sub>2</sub>CO<sub>3</sub> solution provided the acetanilide in high yields (96%) and with a good degree of purity (Scheme 6). Most byproducts are present in the reaction crude as salts. A similar pathway where imidazole acts as a “proton carrier” in mechanochemical activated reactions has been previously described for CDI-based transformations.<sup>137</sup>

To validate these findings, other oximes were used as substrates. The mechanochemical BKR of cyclohexanone oxime (1.0 mmol) with *p*-Ts-Im (1.1 mmol) and oxalic acid (1.1 mmol) in the same processing conditions as above (zirconia jar 15 mL, a zirconia ball *f* = 8 mm) at 30 Hz was complete in 30 min (Scheme 7). It provided ε-caprolactam 2a in high yields (93%), opening promising prospects for future industrial applications to the sustainable production of nylon-6,6. The good experimental results on structurally more complex substrates, such as (1*R*)-camphor oxime 3o and 2-adamantanone oxime 4o, also confirmed the robustness of the proposed method also on sterically hindered substrates (Scheme 7).<sup>138</sup>

## Scheme 9. Reaction Scope of Mechanochemical BKR



<sup>a</sup>Isolated yields

With these results in hand, we planned to go further starting directly from ketones, which are even cheaper and widely available than the corresponding oximes. Unfortunately, and despite several attempts, the preparation of ketoxime **1o** by milling equimolar amounts of acetophenone (1.0 mmol) and hydroxylamine hydrochloride (1.1 mmol) failed to go to completion, even after prolonged reaction periods (>99 min). Subsequent investigations revealed that the addition of imidazole (1.1 mmol) favors the complete conversion of acetophenone (**1k**) into its corresponding oxime (**1o**) in just 30 min. In this optimized procedure, imidazole works both as a base and grinding agent (Scheme 8).<sup>137</sup>

Finally, the addition of fresh *p*-Ts-Im (1.1 mmol) promotes in ca. 30 min a rapid rearrangement of the oxime previously generated *in situ* to give the target amide **1a** in high yield (91%) and purity. In this one-pot/two-step reaction, the presence of imidazole hydrochloride (Im·H·HCl, generated in the first step) was sufficient to trigger the Beckmann rearrangement (Scheme 8). Further control testing highlighted that Im·H·HCl (1.1 mmol), ground together with acetophenone oxime (1.0 mmol), is not able to induce a BKR response (<10%) even after prolonged grinding (99 min).

Pleasingly, the reaction worked well with acetophenone derivatives bearing substituents of different nature on the aromatic ring and at different positions, albeit to a less degree with electron-poor groups (amides **5a**–**17a** in Scheme 9). The reactions of substrates **7a**–**10a** containing chlorine, bromine, or fluorine on the benzene moiety gave different yields of the corresponding BKR products, depending on the halide's nature (Scheme 9).<sup>139</sup> Under optimal ball-milling conditions, 4-phenylacetophenone and 2-acetonaphthone were also compat-

ible with this 1,2-rearrangement providing amides **12a** and **13a** in good yields (92 and 90%, respectively, Scheme 9).

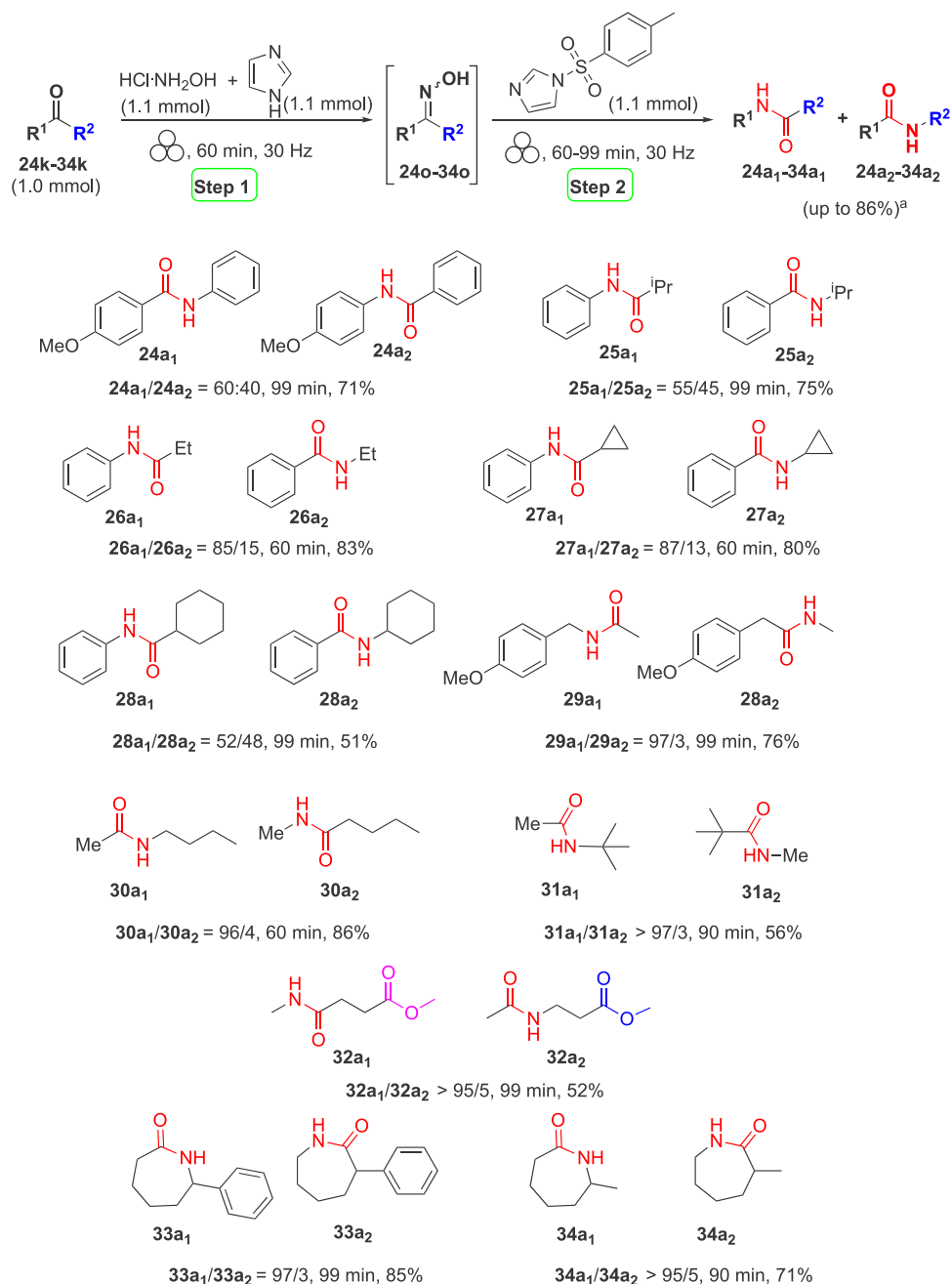
The rearrangement of oxime **14o**, prepared *in situ* by 2-hydroxyacetophenone **14k**, led to target amide **14a** together with minor amounts of benzoxazole **14bz**. The formation of the benzoxazole ring with *o*-hydroxyacetophenone is a consecutive reaction, resulting from the attack of the hydroxyl group in 2-position on the intermediate nitrilium cation. The *in situ* generation of the benzoxazole ring confirms the reaction pathway running through a nitrilium cation intermediate, according to previous reports for BKR in solution (Scheme 3, bottom).<sup>140</sup>

Even more interestingly, we envisioned that the mechanochemical strategy could also be applied to 4'-hydroxyacetophenone **15k**, which is a key intermediate of paramount importance in the synthesis of paracetamol (Scheme 9, amide **15a**).<sup>141</sup> The reaction proceeded smoothly and provided desired rearrangement product **15a** in an overall yield of 84%. This protocol opened a novel route for paracetamol mechanochemical synthesis and pointed out the robustness and great potential for future industrial applications.<sup>142</sup> In this regard, the preparation of active pharmaceutical ingredients (APIs) by mechanochemistry is a recent area of investigation referred to as "medicinal mechanochemistry",<sup>143–147</sup> which paves the way for a sustainable pharmaceutical development. Since the pioneering mechanochemical preparation of Pepto-Bismol metallo-drug,<sup>148</sup> other APIs were prepared at both laboratory and large scale.<sup>149–153</sup>

Notably, this procedure tolerated the presence of ester and amide moieties on the molecular structure, and the rearrangement of oximes **16o** and **17o**, generated *in situ* from methyl 4-



Scheme 10. Reaction Scope of Mechanochemical BKR by Using Unsymmetrical Ketones



<sup>a</sup>Isolated yields.

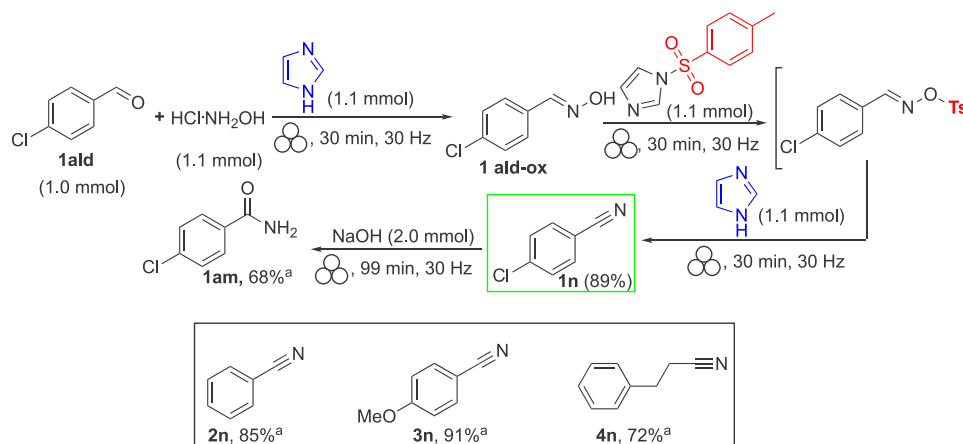
acetylbenzoate (**16k**) and 4'-acetylacetanilide (**17k**) have also been successful under the same reaction conditions.

Benzophenone (Scheme 9) also worked well and gave good yields (86%) of diarylated amide product **18a**, although BKR took longer to complete (99 min). Concerning this last reaction, there have been substantial improvements compared to what is already known in the literature for solution-based procedures. Although several published mechanochemical protocols provide practical and straightforward access to aldoximes and nitrones,<sup>154</sup> ketoxime synthesis is always a challenging process requiring the use of a special heated jar.<sup>101,155</sup> In this regard, the ball milling of benzophenone,  $HCl \cdot NH_2OH$ , and  $K_2CO_3$  provides good conversions into benzophenone oxime only if grinding occurs at 140 °C for 90

min.<sup>103</sup> On the contrary, using imidazole instead of  $K_2CO_3$ , the reaction proceeds smoothly and efficiently at room temperature, making the present process even more energetically efficient both from an economic and sustainable point of view.

Next, we turned our attention to aliphatic ketones to validate the scope and limitation of the optimized mechanochemical BKR methodology (Scheme 9, amides **19a**–**23a**). Under the optimized reaction conditions, 5- and 6-membered-cyclic ketones oxime (prepared *in situ*) reacted undergoing ring expansion to corresponding lactams **20a** and **21a** in good to excellent yields. Generally speaking, the BKR of cyclic ketones proceeded smoothly, giving the corresponding lactams in good yields, although the 1,2-migration process was susceptible to ring strain, easily overcome by mechanochemical activation.<sup>155</sup>

Scheme 11. Preparation of an Array of Nitriles



<sup>a</sup>Isolated yields.

As expected, and in accordance with many other studies in solution reported in the literature,<sup>156,157</sup> the reaction of ketones **22k** and **23k** failed to provide the rearrangement of corresponding amides **22a** and **23a** (Scheme 9).

The application of this mechanochemical protocol to unsymmetrical ketones bearing different ligands ( $R^1COR^2$ ) could lead to the formation of two amides ( $R^1NHCOR^2$  and  $R^1CONHR^2$ , Scheme 10). Generally speaking, the migration selectivity of BKR depends on the configuration (cis or trans with respect to the  $-OH$ ) and type of the substituents  $R^1$  and  $R^2$ , attached to the carbonyl carbon on ketoxime. As shown in Scheme 10, we observed that the aryl moieties underwent 1,2-migration comparatively faster than aliphatic residues. Contrary to what is generally reported in the literature for similar reactions in solutions,<sup>33,34</sup> the 1,2-migratory aptitude of the aryl ring (on the oxime) containing electron-donating groups appears to be slightly poorer than that of the phenyl ring (Scheme 10, **24a<sub>1</sub>** and **24a<sub>2</sub>**).<sup>158</sup> BKR of phenylisopropyl ketone **25k** provided a mixture (around 1:1) of the two corresponding amides, **25a<sub>1</sub>** and **25a<sub>2</sub>**, while the rearrangement of propiophenone gave amide **26a<sub>1</sub>** as the main compound. Similar results were also obtained with the cyclopropyl phenyl ketone, which afforded amide **27a<sub>1</sub>** in good overall yield and in high selectivity.

GC-MS and NMR analyses of the crude reaction mixture highlighted that the structure of the amide formed, and as results, the ratio of the two compounds, was not significantly affected by the stereochemical identity ( $E/Z$ ) of the ketoxime. Presumably, one isomer interconverts in the other under the acid reaction condition. The ratio of the two amides is strictly related both to the kinetic profiles of BKR and oxime ( $E/Z$ )-isomerization during the milling. Whenever the BKR of  $E$ -oxime to the corresponding amide was slower than the  $E$ - to  $Z$ -oxime conversion, the other isomer ( $Z$ -oxime) underwent geometric isomerization later, resulting in a mixture of amide compounds.<sup>102</sup>

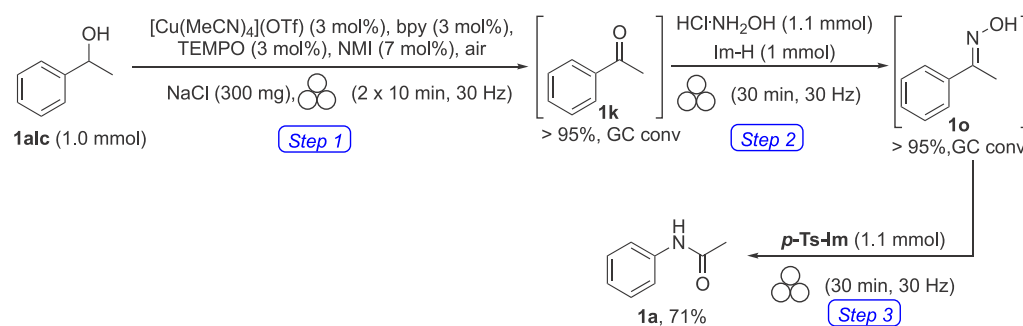
Next, we applied the developed mechanochemical procedure to other nonsymmetrical ketones bearing both linear and branched aliphatic residues (Scheme 10). In general, the longest alkyl chain moves toward the nitrogen atom of the *in situ* generated oxime, providing the corresponding amide in good yields and excellent selectivity (Scheme 10, amides **30a<sub>1</sub>** and **30a<sub>2</sub>**). The presence of a bulky alkyl group on the ketone significantly promotes the reaction chemoselectivity in

preparing oxime **31k<sub>1</sub>**, with the isomer bearing the  $-OH$  group, in the anti-position to the branched/longer chain, as the major product (>95%). Amide **31a<sub>1</sub>** was isolated as the sole product (Scheme 10). Conversely, an ester group in unsymmetrical ketone framework **32k** stabilizes the *syn*-oxime, promoting the selective migration of the methyl fragment in the subsequent BKR. Along the same lines, BKR of 2-phenyl- and 2-methyl- cyclohexanone (Scheme 10, ketones **33** and **34**) led to the 1,2-migration of the more highly substituted linker ( $R^1$  or  $R^2$ ) on the oxime derivative, giving the corresponding phenyl or methyl-migrated product with excellent chemoselectivity.

The developed synthetic protocol could easily be scaled-up to 1 g, laying the foundations for potential industrial-scale applications. The methodology was tested and validated on acetophenone and acetophenone oxime (1 g) without any loss of reaction efficiency.

To gain a better understanding of the effectiveness of this mechanochemical protocol, the proposed procedure was subsequently validated against an array of aldehydes **1ald–3ald** (Scheme 11). 4-Chlorobenzaldehyde (1.0 mmol),  $HCl \cdot NH_2OH$  (1.1 mmol), and imidazole (1.1 mmol) were milled together in a zirconia jar (15 mL) with one ball ( $f = 8$  mm) of the same material until the aldehyde was completely consumed (30 min). The subsequent addition of *p*-Ts-Im (1.1 mmol), which activates the aldoxime (Scheme 11), was followed 30 min later by the further addition of imidazole (1.1 mmol). The base significantly sped up the subsequent elimination reaction, promoting the conversion of the *O*-tosyl-oxime into desired nitrile **1n** (89%, Scheme 11). Solid nitriles (**1n** and **3n**, Scheme 11) were purified by treating the resulting crude reaction with 10% aqueous solution of citric acid and  $K_2CO_3$ . The purification of liquid nitriles required extraction of reaction crude with AcOEt, followed by an aqueous work up (10% citric acid and 10%  $K_2CO_3$ ).

Interestingly, 4-chlorobenzonitrile **1n** was subsequently hydrolyzed with solid NaOH (2 equiv) to provide corresponding primary amide **1am** in overall good yields over three steps, paving the way for a practical synthesis of amides starting from aldehydes.<sup>159</sup> As a general trend, this optimized mechanochemical methodology opens up the possibility for a wider range of structurally different primary and secondary amides, starting from various inexpensive and commercially available substrates (aldehydes and ketones).

Scheme 12. Preparation of Amide **1a** Starting from 1-Phenylethanol **1alc** via a One-Pot/Three-Step Mechanochemical Approach

The development of solvent-free processes also makes the design of multistep one-pot mechanochemical reactions possible, thus reducing the need for tedious purifications that often characterize traditional organic procedures. In this context, we have investigated the BKR by using more eco-friendly alcohols, which often derived from biobased sources, as substitutes for ketones serving as key precursors to prepare oximes. We first prepared the copper-based catalyst by grinding together  $[\text{Cu}(\text{MeCN})_4]\text{OTf}$  (3 mol %), 2,2'-bipyridyl (3 mol %), and 1-methylimidazole (NMI, 7 mol %) in a zirconia milling jar (15 mL) equipped with one ball ( $f = 8$  mm) of the same material for 2 min, adapting oxidation procedure previously reported by us (Scheme 12).<sup>160</sup>

Next, 1-phenylethanol (1.0 mmol) and the co-oxidant agent 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 3 mol %) adsorbed on NaCl (300 mg)<sup>161</sup> were added to the previously prepared metal catalyst, and the jar was shaken at 30 Hz for 10 min. To increase the surface area exposed to air, the resulting solid material was peeled off the jar walls with a spatula, continuously turned upside down and left open to the air for about 5 min (open-jar).<sup>162</sup> Finally, the reaction mixture was ground until the complete conversion of the starting material (monitored by TLC and GC-MS analysis), running open-jar grinding cycles. The resulting acetophenone was first converted into corresponding oxime **1o** by treatment with HCl  $\text{NH}_2\text{OH}$  and imidazole, followed by grinding with *p*-Ts-Im to give acetanilide **1a** in satisfactory overall yields (71%) over three synthetic steps according to the method previously described (Scheme 12).<sup>163</sup>

Finally, we turned our attention to green chemistry metrics, aware that many advantages of this mechanochemical process (compared to its analog in solution) cannot be summarized in simple numerical calculations, although these are useful. These include high energy savings, short reaction times, rapid and efficient access to complex molecules via one-pot multistep reactions (including BKR) from renewable raw materials (alcohols), and finally, the use of *p*-Ts-Im in mechanochemistry reactions under not anhydrous conditions. In any case, the green chemistry calculation highlights that the *E*-factor ( $E = 101$  and 3, with and without aqueous crude trituration, respectively) for the pivotal BKR of **1k** into **1a**, performed under ball-mill conditions, is far better (reducing waste more than half) than those of similar processes performed in solution<sup>120</sup> ( $E \gg 243$  and 12,<sup>164</sup> Figure 2). These good results are further confirmed by comparing ball-milling/solution eco-scales where the data are all broadly in support of mechanochemical processes (eco-scale score: 73 milled and 32 solution, Figure 2).

## Green Chemistry Metrics

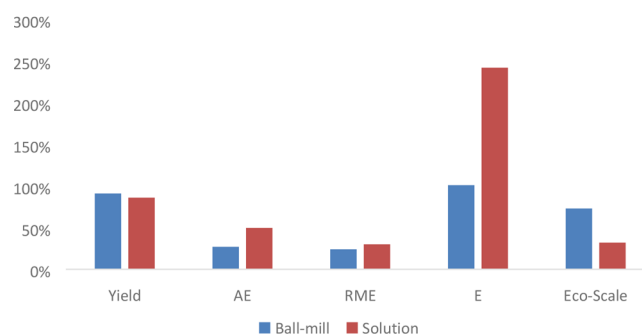


Figure 2. Comparative graphical plot of green chemistry metrics calculated for the preparation of acetanilide **1a** from acetophenone **1k**.

## CONCLUSION

In summary, BKR discovered over a century ago, has, still today, all the hallmarks of any other modern reaction. BKR is fully compliant with all the requirements of green chemistry and is consistent with the principles of sustainable development. Despite its ubiquity in the literature, Beckmann rearrangement still remains the subject of an ongoing challenge to prepare amides from easily available and affordable building blocks: alcohols and ketones. This reaction allowed us to draw new amide frameworks through an eco-efficient process of “cut-and-paste” of C–C and C–N bonds in the backbone of an oxime. Herein, we developed an eco-sustainable mechanochemical procedure that allows us to rearrange, like a Rubik’s cube, the broken bonds in mild conditions, avoiding and/or reducing solvents, and potentially toxic reagents. The combination of inexpensive and eco-friendly reagents such as *p*-Ts-Im and oxalic acid was successful to smoothly prepare in good to high yields a structurally different amide library, including caprolactam and paracetamol. This solvent-free mechanochemical procedure has also been optimized and successfully extended to several ketones serving as oxime precursors. The absence of solvents during the synthesis of the target amides allowed us to validate the BKR via a one-pot/multistep process starting directly from eco-friendly secondary alcohols. Finally, the mechanochemically activated Beckmann rearrangement expands the toolbox of organic chemistry rearrangements already performed by milling.<sup>152,165,166</sup>

## ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.0c07254>.

Experimental procedures, green metrics,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and spectral data of compounds (PDF)

## AUTHOR INFORMATION

### Corresponding Author

**Andrea Porcheddu** – Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Cagliari, Italy; [orcid.org/0000-0001-7367-1102](https://orcid.org/0000-0001-7367-1102); Phone: +39 070 675 4410; Email: [porcheddu@unica.it](mailto:porcheddu@unica.it)

### Authors

**Rita Mocchi** – Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Cagliari, Italy

**Evelina Colacino** – ICGM, Univ. Montpellier, CNRS, ENSCM, Montpellier 34296, France; [orcid.org/0000-0002-1179-4913](https://orcid.org/0000-0002-1179-4913)

**Lidia De Luca** – Dipartimento di Chimica e Farmacia, Università degli Studi di Sassari, 07100 Sassari, Italy; [orcid.org/0000-0001-7211-9076](https://orcid.org/0000-0001-7211-9076)

**Claudia Fattuoni** – Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Cagliari, Italy

**Francesco Delogu** – Dipartimento di Ingegneria Meccanica, Chimica, e dei Materiali, Università degli Studi di Cagliari, 09123 Cagliari, Italy

Complete contact information is available at: <https://pubs.acs.org/10.1021/acssuschemeng.0c07254>

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Funding

PRIN project: Multi-Functional polymeric Composites based on grown materials, no. 2017B7MMJ5\_001. Progetto Fondazione di Sardegna, Grant CUP F72F20000230007 (A.P.).

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This article is based upon work from COST Action CA18112,<sup>167–170</sup> supported by COST (European Cooperation in Science and Technology).<sup>171</sup> The manuscript was written during the worldwide lockdown due to COVID-19 pandemic disease.

## REFERENCES

- (1) Holth, T. A. D.; Hutt, O. E.; Georg, G. I.; Rojas, C. M. In *Molecular Rearrangements in Organic Synthesis*; Rojas, C. M., Ed.; Wiley: New York, 2015; pp 111–150.
- (2) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1999.
- (3) Smith, M. B. *March's Advanced Organic Chemistry - Reactions, Mechanisms, and Structure*, 8th ed.; John Wiley & Sons, Inc., Hoboken, NJ, 2020.
- (4) Li, J. J. *Name Reactions, A Collection of Detailed Mechanism and Synthetic Applications*; Springer International Publishing, 2020.
- (5) Beckmann, E. Zur Kenntniss der Isonitrosoverbindungen" ([Contribution] to our knowledge of isonitroso compounds). *Ber. Dtsch. Chem. Ges.* **1886**, 19, 988–993.

(6) Blatt, A. H. The Beckmann Rearrangement. *Chem. Rev.* **1933**, 12, 215–260.

(7) Gawley, R. E. Beckmann Reactions: Rearrangements, Elimination-Additions, Fragmentations, and Rearrangement-Cyclizations. *Org. React.* **1988**, 35, 1–420. and references cited therein.

(8) Kumar, R. R.; Vanithan, K. A.; Balasubramanian, M. *Name Reactions for Homologation: Part 2*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2009; pp 274–292.

(9) Chandrasekhar, S. The Beckmann and Related Reactions. *Comprehensive Organic Synthesis II* **2014**, 7, 770.

(10) Srivastava, S.; Kaur, K. Beckmann Rearrangement Catalysis: A Review of Recent Advances. *New J. Chem.* **2020**, 44, 18530–18572.

(11) Johansson, I. Amides, Fatty Acid. In *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons: New York, 2004; Vol. 2, pp 442–463.

(12) De Figueiredo, R. M.; Suppo, J. S.; Campagne, J. M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, 116, 12029–12122.

(13) Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D. A Green Chemistry Perspective on Catalytic Amide Bond Formation. *Nat. Catal.* **2019**, 2, 10–17.

(14) Santos, A. S.; Silva, A. M. S.; Marques, M. M. B. Sustainable Amidation Reactions - Recent Advances. *Eur. J. Org. Chem.* **2020**, 2020, 2501–2516.

(15) Reddy, G. P.; Reddy, N. A process for synthesis of paracetamol. WO2017/154024, 2017.

(16) Davenport, K. G.; Hilton, C. B. Process for producing *N*-acetylhydroxy aromatic amines. US4524217, 18 June 1985.

(17) Fritch, J. R.; Fruchey, O. S.; Horlenko, T. Production of acetaminophen. US4954652A, 1988. <https://www.freepatentsonline.com/4954652.html>.

(18) Fritch, J. R.; Fruchey, O. S.; Horlenko, T.; Aguilar, D. A.; Hilton, C. B.; Snyder, P. S.; Seeliger, W. J. Production of acetaminophen. US5155273A, 1990.

(19) Ritz, J.; Fuchs, H.; Kieczka, H.; Moran, W. C. Caprolactam. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH, Weinheim, 2011. [https://doi.org/10.1002/14356007.a05\\_031.pub2](https://doi.org/10.1002/14356007.a05_031.pub2).

(20) Kohan, M. I.; Mestemacher, S. A.; Pagilagan, R. U.; Redmond, K., Polyamides. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2003. [https://doi.org/10.1002/14356007.a21\\_179.pub2](https://doi.org/10.1002/14356007.a21_179.pub2).

(21) Lamberth, C.; Dinges, J. Different Roles of Carboxylic Functions in Pharmaceuticals and Agrochemicals. *Bioact. Carboxylic Compd. Classes Pharm. Agrochem.* **2016**, 1–11.

(22) Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **2020**, 63, 12290–12358.

(23) Sakai, K.; Shitara, Y. Influence of Physical States of Amide Type Gel-Lubricants on Their Tribological and Rheological Properties. *Tribologia* **2014**, 32, 20–28.

(24) Hoong, S. S.; Armiza, M. Z.; Mariam, N. M. D. N. S.; Armylisas, A. H. N.; Ishak, S. A.; Ismail, T. N. M. T.; Yeong, S. K. Synthesis of Estolide Ester and Amide from Acetylated Polyhydroxy Estolide for Lubricant Base Oil. *Eur. J. Lipid Sci. Technol.* **2020**, 122, 2000098.

(25) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds.; Wiley: New York, 2000.

(26) Tisserand, R.; Young, R. Essential Oil Composition. *Essential Oil Safety* **2014**, 5–22.

(27) An, N.; Tian, B. X.; Pi, H. J.; Eriksson, L. A.; Deng, W. P. Mechanistic Insight into Self-Propagation of Organo-Mediated Beckmann Rearrangement: A Combined Experimental and Computational Study. *J. Org. Chem.* **2013**, 78, 4297–4302.

(28) Grob, C. A.; Fischer, H. P.; Raudenbusch, W.; Zergenyi, J. Beckmann-Umlagerung Und Fragmentierung. 1. Teil. Mechanismus Sowie Nachweis Der Zwischenstufen Fragmentierungsreaktionen. 7. Mitteilung. *Helv. Chim. Acta* **1964**, 47, 1003–1021.

- (29) Hilmey, D. G.; Paquette, L. A. Promoter-Dependent Course of the Beckmann Rearrangement of Stereoisomeric Spiro[4.4]Nonane-1,6-Dione Monoximes. *Org. Lett.* **2005**, *7*, 2067–2069.
- (30) Marcus, R. A. Spiers Memorial Lecture: Interplay of Theory and Computation in Chemistry - Examples from on-Water Organic Catalysis, Enzyme Catalysis, and Single-Molecule Fluctuations. *Faraday Discuss.* **2010**, *145*, 9–14.
- (31) Yamabe, S.; Tsuchida, N.; Yamazaki, S. Is the Beckmann Rearrangement a Concerted or Stepwise Reaction? A Computational Study. *J. Org. Chem.* **2005**, *70*, 10638–10644.
- (32) Yamamoto, Y.; Hasegawa, H.; Yamataka, H. Dynamic Path Bifurcation in the Beckmann Reaction: Support from Kinetic Analyses. *J. Org. Chem.* **2011**, *76*, 4652–4660.
- (33) Kalia, J.; Raines, R. T. Hydrolytic stability of hydrazones and oximes. *Angew. Chem., Int. Ed.* **2008**, *47*, 7523–7526.
- (34) Jain, P. U.; Samant, S. D. A Facile One-Pot Transformation of Aromatic Aldehydes/Ketones to Amides: Fe<sub>2</sub>O<sub>3</sub>@SiO<sub>2</sub> as an Environmentally Benign Core-Shell Catalyst. *Chemistry Select* **2018**, *3*, 1967–1975.
- (35) Jefferies, L. R.; Weber, S. R.; Cook, S. P. Iron-Catalyzed C-N Bond Formation via the Beckmann Rearrangement. *Synlett* **2015**, *26*, 331–334.
- (36) KarimKoshteh, M.; Bagheri, M. Nano Fe<sub>3</sub>O<sub>4</sub> as Green Catalyst for Beckmann Rearrangement under Ultrasound Irradiation. *J. Mex. Chem. Soc.* **2017**, *61*, 28–34.
- (37) Khodaei, M. M.; Meybodi, F. A.; Rezai, N.; Salehi, P. Solvent Free Beckmann Rearrangement of Ketoximes by Anhydrous Ferric Chloride. *Synth. Commun.* **2001**, *31*, 2047–2050.
- (38) Munnuri, S.; Verma, S.; Chandra, D.; Anug, R. R.; Falck, J. R.; Jat, J. L. Cu(OTf)<sub>2</sub>-Catalyzed Beckmann Rearrangement of Ketones Using Hydroxylamine-O-Sulfonic Acid (HOSA). *Synthesis* **2019**, *51*, 3709–3714.
- (39) Owston, N. A.; Parker, A. J.; Williams, J. M. J. Iridium-Catalyzed Conversion of Alcohols into Amides via Oximes. *Org. Lett.* **2007**, *9*, 73–75.
- (40) Owston, N. A.; Parker, A. J.; Williams, J. M. J. Highly Efficient Ruthenium-Catalyzed Oxime to Amide Rearrangement. *Org. Lett.* **2007**, *9*, 3599–3601.
- (41) Park, S.; Choi, Y.-a.; Han, H.; Ha Yang, S.; Chang, S. Rh-Catalyzed One-Pot and Practical Transformation of Aldoximes to Amides. *Chem. Commun.* **2003**, *3*, 1936–1937.
- (42) Sharma, S. K.; Bishopp, S. D.; Liana Allen, C.; Lawrence, R.; Bamford, M. J.; Lapkin, A. A.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. Copper-Catalyzed Rearrangement of Oximes into Primary Amides. *Tetrahedron Lett.* **2011**, *52*, 4252–4255.
- (43) Verma, S.; Kumar, P.; Khatana, A. K.; Chandra, D.; Yadav, A. K.; Tiwari, B.; Jat, J. L. Zinc(II)-Catalyzed Synthesis of Secondary Amides from Ketones via Beckmann Rearrangement Using Hydroxylamine-O-Sulfonic Acid in Aqueous Media. *Synthesis* **2020**, *52*, 3272–3276.
- (44) Ganguly, N. C.; Mondal, P. Efficient Iodine-Mediated Beckmann Rearrangement of Ketoximes to Amides under Mild Neutral Conditions. *Synthesis* **2010**, *2010*, 3705–3709.
- (45) Hu, H.; Cai, X.; Xu, Z.; Yan, X.; Zhao, S. Beckmann Rearrangement of Ketoxime Catalyzed by N-Methyl-Imidazolium Hydrosulfate. *Molecules* **2018**, *23*, 1764.
- (46) Hyodo, K.; Hasegawa, G.; Oishi, N.; Kuroda, K.; Uchida, K. Direct and Catalytic Amide Synthesis from Ketones via Trans-oximation and Beckmann Rearrangement under Mild Conditions. *J. Org. Chem.* **2018**, *83*, 13080–13087.
- (47) Kuo, C. W.; Hsieh, M. T.; Gao, S.; Shao, Y. M.; Yao, C. F.; Shia, K. S. Beckmann Rearrangement of Ketoximes Induced by Phenyl Dichlorophosphate at Ambient Temperature. *Molecules* **2012**, *17*, 13662–13672.
- (48) Wang, Y.; Chen, Q.; He, M.; Wang, L. Polystyrene-Supported Phosphine Oxide-Catalyzed Beckmann Rearrangement of Ketoximes in 1,1,1,3,3,3-Hexafluoro-2-Propanol. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 210–214.
- (49) Xu, F.; Wang, N. G.; Tian, Y. P.; Chen, Y. M.; Liu, W. C. Ph<sub>3</sub>P/I<sub>2</sub>-Catalyzed Beckmann Rearrangement of Ketoximes into Amides. *Synth. Commun.* **2012**, *42*, 3532–3539.
- (50) Duangkamol, C.; Jaita, S.; Wangngae, S.; Phakhodee, W.; Pattarawarapan, M. An Efficient Mechanochemical Synthesis of Amides and Dipeptides Using 2,4,6-Trichloro-1,3,5-Triazine and PPh<sub>3</sub>. *RSC Adv.* **2015**, *5*, 52624–52628.
- (51) Furuya, Y.; Ishihara, K.; Yamamoto, H. Cyanuric Chloride as a Mild and Active Beckmann Rearrangement Catalyst. *J. Am. Chem. Soc.* **2005**, *127*, 11240–11241.
- (52) Augustine, J. K.; Kumar, R.; Bombrun, A.; Mandal, A. B. An Efficient Catalytic Method for the Beckmann Rearrangement of Ketoximes to Amides and Aldoximes to Nitriles Mediated by Propylphosphonic Anhydride (T<sub>3</sub>P<sub>2</sub>O). *Tetrahedron Lett.* **2011**, *52*, 1074–1077.
- (53) Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. Beckmann Rearrangement of Ketoximes to Lactams by Triphosphazene Catalyst. *J. Org. Chem.* **2008**, *73*, 2894–2897.
- (54) Zhu, M.; Cha, C.; Deng, W. P.; Shi, X. X. A Mild and Efficient Catalyst for the Beckmann Rearrangement, BOP-Cl. *Tetrahedron Lett.* **2006**, *47*, 4861–4863.
- (55) Foley, H. G.; Dalton, D. R. A General, Neutral Beckmann Rearrangement of Ketoximes. The Isolation of An Intermediate. *Synth. Commun.* **1974**, *4*, 251–253.
- (56) Kamijo, T.; Harada, H.; Iizuka, K. A Useful Reagent for the Beckmann Rearrangement and the Synthesis of Nitrile from Carboxamides: N,N'-Carbonyldiimidazole and Reactive Halides. *Chem. Pharm. Bull.* **1984**, *32*, 2560–2564.
- (57) Usachova, N.; Leitis, G.; Jirgensons, A.; Kalvinsh, I. Synthesis of Hydroxamic Acids by Activation of Carboxylic Acids with N,N'-Carbonyldiimidazole: Exploring the Efficiency of the Method. *Synth. Commun.* **2010**, *40*, 927–935.
- (58) Vanos, C. M.; Lambert, T. H. Cyclopropenium-Activated Beckmann Rearrangement. Catalysis versus Self-Propagation in Reported Organocatalytic Beckmann Rearrangements. *Chem. Sci.* **2010**, *1*, 705–708.
- (59) Kiely-Collins, H. J.; Sechi, I.; Brennan, P. E.; McLaughlin, M. G. Mild, Calcium Catalyzed Beckmann Rearrangements. *Chem. Commun.* **2018**, *54*, 654–657.
- (60) Chandra, D.; Verma, S.; Pandey, C. B.; Yadav, A. K.; Kumar, P.; Tiwari, B.; Jat, J. L. Direct Synthesis of Secondary Amides from Ketones through Beckmann Rearrangement Using O-(Mesitylsulfonyl)Hydroxylamine. *Tetrahedron Lett.* **2020**, *61*, 151822.
- (61) Kotha, S.; Ravikumar, O.; Majhi, J. Synthesis of a Tricyclic Lactam via Beckmann Rearrangement and Ring-Rearrangement Metathesis as Key Steps. *Beilstein J. Org. Chem.* **2015**, *11*, 1503–1508.
- (62) Nagesh, H. N.; Suresh, N.; Mahalakshmi Naidu, K.; Arun, B.; Padma Sridevi, J.; Sriram, D.; Yogeewari, P.; Chandra Sekhar, K. V. G. Synthesis and Evaluation of Anti-Tubercular Activity of 6-(4-Substitutedpiperazin-1-Yl) Phenanthridine Analogues. *Eur. J. Med. Chem.* **2014**, *74*, 333–339.
- (63) Rad, M. N. S.; Khalafi-Nezhad, A.; Behrouz, S.; Amini, Z.; Behrouz, M. A. Simple and Highly Efficient One-Pot Procedure for the Synthesis of Amides via Beckmann Rearrangements Using 1-Tosylimidazole (TsIm). *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 1658–1671.
- (64) Shirai, M.; Okamura, H. I-Line Sensitive Photoacid Generators for UV Curing. *Prog. Org. Coat.* **2009**, *64*, 175–181.
- (65) Takuwa, T.; Minowa, T.; Onishi, J. Y.; Mukaiyama, T. Facile One-Pot Syntheses of Amidines and Enamines from Oximes via Beckmann Rearrangement Using Trifluoromethanesulfonic Anhydride. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1717–1725.
- (66) Zhang, G.; Zhao, Y.; Xuan, L.; Ding, C. SO<sub>2</sub>F<sub>2</sub>-Activated Efficient Beckmann Rearrangement of Ketoximes for Accessing Amides and Lactams. *Eur. J. Org. Chem.* **2019**, *2019*, 4911–4915.
- (67) Gupta, P.; Paul, S. Solid Acids: Green Alternatives for Acid Catalysis. *Catal. Today* **2014**, *236*, 153–170.

- (68) Zicmanis, A.; Katkevica, S.; Mekss, P. Lewis Acid-Catalyzed Beckmann Rearrangement of Ketoximes in Ionic Liquids. *Catal. Commun.* **2009**, *10*, 614–619.
- (69) Mo, X.; Morgan, T. D. R.; Ang, H. T.; Hall, D. G. Scope and Mechanism of a True Organocatalytic Beckmann Rearrangement with a Boronic Acid/Perfluoropinacol System under Ambient Conditions. *J. Am. Chem. Soc.* **2018**, *140*, 5264–5271.
- (70) Crochet, P.; Cadierno, V. Catalytic Synthesis of Amides via Aldoximes Rearrangement. *Chem. Commun.* **2015**, *51*, 2495–2505.
- (71) Guo, S.; Deng, Y. Environmentally Friendly Beckmann Rearrangement of Oximes Catalyzed by Metaboric Acid in Ionic Liquids. *Catal. Commun.* **2005**, *6*, 225–228.
- (72) Hullio, A. A.; Mastoi, G. M. Preparation of Ionic Liquid-Based Vilsmier Reagent from Novel Multi-Purpose Dimethyl Formamide-like Ionic Liquid and Its Application. *Chin. J. Chem.* **2012**, *30*, 1647–1657.
- (73) Karimi, B.; Behzadnia, H. Novel Periodic Mesoporous Silica Chlorides (PMSCL) with 2D P 6 Mm Hexagonal Structures: Efficient Catalysts for the Beckmann Rearrangement. *Synlett* **2010**, *2010*, 2019–2023.
- (74) Mahajan, P. S.; Humne, V. T.; Tanpure, S. D.; Mhaske, S. B. Total Synthesis of Antimalarial Natural Product Isocryptolepine Via C-H Activation. *Org. Lett.* **2016**, *18*, 3450–3453.
- (75) Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; et al. Key Green Chemistry Research Areas from a Pharmaceutical Manufacturers' Perspective Revisited. *Green Chem.* **2018**, *20*, 5082–5103.
- (76) Roschangar, F.; Sheldon, R. A.; Senanayake, C. H. Overcoming Barriers to Green Chemistry in the Pharmaceutical Industry—the Green Aspiration Level™ Concept. *Green Chem.* **2015**, *17*, 752–768.
- (77) Clarke, C. J.; Tu, W. C.; Levers, O.; Bröhl, A.; Hallett, J. P. Green and Sustainable Solvents in Chemical Processes. *Chem. Rev.* **2018**, *118*, 747–800.
- (78) Ferrazzano, L.; Corbisiero, D.; Martelli, G.; Tolomelli, A.; Viola, A.; Ricci, A.; Cabri, W. Green Solvent Mixtures for Solid-Phase Peptide Synthesis: A Dimethylformamide-Free Highly Efficient Synthesis of Pharmaceutical-Grade Peptides. *ACS Sustainable Chem. Eng.* **2019**, *7*, 12867–12877.
- (79) Florindo, C.; Branco, L. C.; Marrucho, I. M. Quest for Green-Solvent Design: From Hydrophilic to Hydrophobic (Deep) Eutectic Solvents. *ChemSusChem* **2019**, *12*, 1549–1559.
- (80) Gao, F.; Bai, R.; Ferlin, F.; Vaccaro, L.; Li, M.; Gu, Y. Replacement Strategies for Non-Green Dipolar Aprotic Solvents. *Green Chem.* **2020**, *22*, 6240–6257.
- (81) Krishnakumar, V.; Vindhya, N. G.; Mandal, B. K.; Nawaz Khan, F. R. Green Chemical Approach: Low-Melting Mixture as a Green Solvent for Efficient Michael Addition of Homophthalimides with Chalcones. *Ind. Eng. Chem. Res.* **2014**, *53*, 10814–10819.
- (82) Obst, M.; König, B. Organic Synthesis without Conventional Solvents. *Eur. J. Org. Chem.* **2018**, *2018*, 4213–4232.
- (83) Tobiszewski, M.; Bystrzanowska, M. Monetary Values Estimates of Solvent Emissions. *Green Chem.* **2020**, *22*, 7983–7988.
- (84) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. Solvent-Free and Catalysts-Free Chemistry: A Benign Pathway to Sustainability. *ChemSusChem* **2014**, *7*, 24–44.
- (85) Baig RB, R. B. N.; Varma, R. S. Solvent-Free Synthesis. *An Introd. to Green Chem. Methods* **2013**, 18–38.
- (86) Rohokale, S. V.; Kote, S. R.; Deshmukh, S. R.; Thopate, S. R. Natural Organic Acids Promoted Beckmann Rearrangement: Green and Expedient Synthesis of Amides under Solvent-Free Conditions. *Chem. Pap.* **2014**, *68*, 575–578.
- (87) Sarkar, A.; Santra, S.; Kundu, S. K.; Hajra, A.; Zyryanov, G. V.; Chupakhin, O. N.; Charushin, V. N.; Majee, A. A Decade Update on Solvent and Catalyst-Free Neat Organic Reactions: A Step Forward towards Sustainability. *Green Chem.* **2016**, *18*, 4475–4525.
- (88) Zangade, S.; Patil, P. A Review on Solvent-free Methods in Organic Synthesis. *Curr. Org. Chem.* **2020**, *23*, 2295–2318.
- (89) Andersen, J.; Brunemann, J.; Mack, J. Exploring Stable, Sub-Ambient Temperatures in Mechanochemistry: Via a Diverse Set of Enantioselective Reactions. *React. Chem. Eng.* **2019**, *4*, 1229–1236.
- (90) Andersen, J.; Mack, J. Mechanochemistry and Organic Synthesis: From Mystical to Practical. *Green Chem.* **2018**, *20*, 1435–1443.
- (91) Friščić, T.; Mottillo, C.; Titi, H. M. Mechanochemistry for Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 1018–1029.
- (92) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an Emerging Tool for Molecular Synthesis: What Can It Offer? *Chem. Sci.* **2018**, *9*, 3080–3094.
- (93) Jones, W.; Eddleston, M. D. Introductory Lecture: Mechanochemistry, a Versatile Synthesis Strategy for New Materials. *Faraday Discuss.* **2014**, *170*, 9–34.
- (94) Margetić, D.; Štrukil, V. *Recent Advances in Mechanochemical Organic Synthesis*; IntechOpen, 2020. DOI: [10.5772/intechopen.90897](https://doi.org/10.5772/intechopen.90897).
- (95) Tan, D.; García, F. Main Group Mechanochemistry: From Curiosity to Established Protocols. *Chem. Soc. Rev.* **2019**, *48*, 2274–2292.
- (96) Colacino, E.; Ennas, G.; Halasz, I.; Porcheddu, A.; Scano, A., Eds. *Mechanochemistry. A Practical Introduction from Soft to Hard Materials*; De Gruyter STEM, 2021 <https://doi.org/10.1515/9783110608335>.
- (97) Carta, M.; Colacino, E.; Delogu, F.; Porcheddu, A. Kinetics of Mechanochemical Transformations. *Phys. Chem. Chem. Phys.* **2020**, *22*, 14489–14502.
- (98) Colacino, E.; Carta, M.; Pia, G.; Porcheddu, A.; Ricci, P. C.; Delogu, F. Processing and Investigation Methods in Mechanochemical Kinetics. *ACS Omega* **2018**, *3*, 9196–9209.
- (99) Torre, F.; Barra, P.; Pia, G.; Delogu, F.; Porcheddu, A. Microscopic Kinetic Information from Ag Oxalate Mechanochemistry in Ball Drop Experiments. *Mater. Lett.* **2020**, *267*, 127525.
- (100) Traversari, G.; Porcheddu, A.; Pia, G.; Delogu, F.; Cincotti, A. Coupling of mechanical deformation and reaction in mechanochemical transformations. *Phys. Chem. Chem. Phys.* **2021**, *23*, 229.
- (101) Bolotin, D. S.; Bokach, N. A.; Demakova, M. Y.; Kukushkin, V. Y. Metal-Involving Synthesis and Reactions of Oximes. *Chem. Rev.* **2017**, *117*, 13039–13122.
- (102) Aakeröy, C. B.; Sinha, A. S.; Epa, K. N.; Chopade, P. D.; Smith, M. M.; Desper, J. Structural Chemistry of Oximes. *Cryst. Growth Des.* **2013**, *13*, 2687–2695.
- (103) Mokhtari, J.; Naimi-Jamal, M. R.; Hamzeali, H.; Dekamin, M. G.; Kaupp, G. Kneading Ball-Milling and Stoichiometric Melts for the Quantitative Derivatization of Carbonyl Compounds with Gas-Solid Recovery. *ChemSusChem* **2009**, *2*, 248–254.
- (104) Setamdideh, D.; Khezri, B.; Esmaeilzadeh, S. Synthesis of Oximes with NH<sub>2</sub>OH·HCl/DOWEX(R) S0W x4 System. *J. Chin. Chem. Soc.* **2012**, *59*, 1119–1124.
- (105) Gao, Y.; Liu, J.; Li, Z.; Guo, T.; Xu, S.; Zhu, H.; Wei, F.; Chen, S.; Gebru, H.; Guo, K. Dichloroimidazolidinedione-Activated Beckmann Rearrangement of Ketoximes for Accessing Amides and Lactams. *J. Org. Chem.* **2018**, *83*, 2040–2049.
- (106) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. A Mild Procedure for the Preparation of 3-Aryl-4-Formylpyrazoles. *Synlett* **2004**, 2299–2302.
- (107) De Luca, L.; Giacomelli, G.; Porcheddu, A. A Simple Preparation of Ketones. N-Protected α-Amino Ketones from α-Amino Acids. *Org. Lett.* **2001**, *3*, 1519.
- (108) De Luca, L.; Giacomelli, G.; Porcheddu, A. Beckmann Rearrangement of Oximes under Very Mild Conditions. *J. Org. Chem.* **2002**, *67*, 6272–6274.
- (109) De Luca, L.; Giacomelli, G.; Porcheddu, A. An Efficient Route to Alkyl Chlorides from Alcohols Using the Complex TCT/DMF. *Org. Lett.* **2002**, *4*, 553–555.
- (110) De Luca, L.; Giacomelli, G.; Porcheddu, A. Mild and Highly Selective Formyl Protection of Primary Hydroxyl Groups. *J. Org. Chem.* **2002**, *67*, 5152–5155.

- (111) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. A New, Simple Procedure for the Synthesis of Formyl Amides. *Synlett* **2004**, *2004*, 2570–2572.
- (112) Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. 4-(4,6-Dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium Chloride (DMTMM): A Valuable Alternative to PyBOP for Solid Phase Peptide Synthesis. *Synlett* **2000**, *2000*, 275–277.
- (113) Giacomelli, G.; De Luca, L.; Porcheddu, A. A Method for Generating Nitrile Oxides from Nitroalkanes: A Microwave Assisted Route for Isoxazoles. *Tetrahedron* **2003**, *59*, 5437–5440.
- (114) Giacomelli, G.; Porcheddu, A.; Luca, L. [1,3,5]-Triazine: A Versatile Heterocycle in Current Applications of Organic Chemistry. *Curr. Org. Chem.* **2004**, *8*, 1497–1519.
- (115) Giacomelli, G.; Porcheddu, A.; Salaris, M. Simple One-Flask Method for the Preparation of Hydroxamic Acids. *Org. Lett.* **2003**, *5*, 2715–2717.
- (116) Porcheddu, A.; Cadoni, R.; De Luca, L. A Fast and Efficient One-Pot Microwave Assisted Synthesis of Various Di-Substituted 1,2,4-Oxadiazoles. *Org. Biomol. Chem.* **2011**, *9*, 7539–7546.
- (117) Porcheddu, A.; De Luca, L.; Giacomelli, G. A Mild and Inexpensive Procedure for the Synthesis of N, N' -Di-Boc-Protected Guanidines. *Synlett* **2009**, *2009*, 3368–3372.
- (118) Porcheddu, A.; Giacomelli, G.; Salaris, M. Microwave-Assisted Synthesis of Isonitriles. *J. Org. Chem.* **2005**, *70*, 2361–2363.
- (119) Stagi, L.; Chiriu, D.; Scholz, M.; Carbonaro, C. M.; Corpino, R.; Porcheddu, A.; Rajamaki, S.; Cappellini, G.; Cardia, R.; Ricci, P. C. Vibrational and Optical Characterization of S-Triazine Derivatives. *Spectrochim. Acta, Part A* **2017**, *183*, 348–355.
- (120) Pi, H. J.; Dong, J. D.; An, N.; Du, W.; Deng, W. P. Unexpected Results from the Re-Investigation of the Beckmann Rearrangement of Ketoximes into Amides by Using TsCl. *Tetrahedron* **2009**, *65*, 7790–7793.
- (121) Tian, B. X.; An, N.; Deng, W. P.; Eriksson, L. A. Catalysts or Initiators? Beckmann Rearrangement Revisited. *J. Org. Chem.* **2013**, *78*, 6782–6785.
- (122) Ager, D. J.; Pantaleone, D. P.; Henderson, S. A.; Katritzky, A. R.; Prakash, I.; Walters, D. E. Commercial, Synthetic Nonnutritive Sweeteners. *Angew. Chem., Int. Ed.* **1998**, *37*, 1802–1817.
- (123) Fahlberg, C.; Remsen, I. Ueber die Oxydation des Orthotoluolsulfamids. *Ber. Dtsch. Chem. Ges.* **1879**, *12*, 469–473.
- (124) Waibel, K. A.; Nickisch, R.; Möhl, N.; Seim, R.; Meier, M. A. R. A More Sustainable and Highly Practicable Synthesis of Aliphatic Isocyanides. *Green Chem.* **2020**, *22*, 933–941.
- (125) Sometimes, prolonged grinding overtime leads to breaking of the N–O bond of the oxime with the formation of the imine, which partially converts into the starting ketone.
- (126) Funke, P.; Das, K. G.; Bose, A. A. K. Mass Spectral Studies. II. Molecular Rearrangement Under Electron Impact. *J. Am. Chem. Soc.* **1964**, *86*, 2527–2528.
- (127) Patterson, S. D. Mass Spectrometry and Proteomics. *Physiol. Genomics* **2000**, *2*, 59–65.
- (128) The use of freshly prepared *p*-Ts-Im guarantees better reproducibility and higher yields (>7%) than those achieved with commercially available reagents.
- (129) Byun, H.-S.; Zhong, N.; Bittman, R. 6A-O-*p*-Toluenesulfonyl- $\beta$ -Cyclodextrin. *Org. Synth.* **2003**, *77*, 225.
- (130) Rad, M. N. S.; Khalafi-Nezhad, A.; Behrouz, S.; Amini, Z.; Behrouz, M. Simple and Highly Efficient Procedure for Conversion of Aldoximes to Nitriles Using N-(*p*-Toluenesulfonyl) Imidazole. *Synth. Commun.* **2010**, *40*, 2429–2440.
- (131) Soltani Rad, M. N.; Behrouz, S.; Faghihi, M. A.; Khalafi-Nezhad, A. A Simple Procedure for the Esterification of Alcohols with Sodium Carboxylate Salts Using 1-Tosylimidazole (TsIm). *Tetrahedron Lett.* **2008**, *49*, 1115–1120.
- (132) Soltani Rad, M. N.; Behrouz, S.; Khalafi-Nezhad, A. A Simple One-Pot Procedure for the Direct Conversion of Alcohols into Azides Using TsIm. *Tetrahedron Lett.* **2007**, *48*, 3445–3449.
- (133) Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A. A Simple One-Pot Procedure for the Direct Conversion of Alcohols into Alkyl Nitriles Using TsIm. *Tetrahedron Lett.* **2007**, *48*, 6779–6784.
- (134) Staab, A.; Wendel, K. Synthesen und Umsetzungen von Imidazoliden aromatischer Sulfonsäuren. *Chem. Ber.* **1960**, *93*, 2902–2915.
- (135) Staab, H. A. New Methods of Preparative Organic Chemistry IV. Synthesis Using Heterocyclic Amides (Azolides). *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351–367.
- (136) Konnert, L.; Gonnet, L.; Halasz, I.; Suppo, J.-S.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. Mechanochemical Preparation of 3,5-Disubstituted Hydantoins from Dipeptides and Unsymmetrical Ureas of Amino Acid Derivatives. *J. Org. Chem.* **2016**, *81*, 9802–9809.
- (137) Lanzillotto, M.; Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. Mechanochemical 1,1'-Carbonyldiimidazole-Mediated Synthesis of Carbamates. *ACS Sustainable Chem. Eng.* **2015**, *3*, 2882–2889.
- (138) The target reaction with acetophenone **1k** was also carried out in the presence of a solvent (acetonitrile) and stirred at room temperature for 96 h. Only negligible amounts of amide **1a** were detected (GC analysis).
- (139) Many of these comments could find a more detailed analysis in Ortiz-Trankina, L. N.; Crain, J.; Williams, C.; Mack, J. Developing Benign Syntheses Using Ion Pairs via solvent-Free Mechanochemistry. *Green Chem.* **2020**, *22*, 3638–3642.
- (140) Rancan, E.; Aricò, F.; Quartarone, G.; Ronchin, L.; Tundo, P.; Vavasori, A. Self-Catalyzed Direct Amidation of Ketones: A Sustainable Procedure for Acetaminophen Synthesis. *Catal. Commun.* **2014**, *54*, 11–16.
- (141) Do Prado, V. M.; De Queiroz, T. B.; Sá, P. M.; Seiceira, R. C.; Boechat, N.; Ferreira, F. F. Mechanochemistry for the Production of a Hybrid Salt Used in the Treatment of Malaria. *Green Chem.* **2020**, *22*, 54–61.
- (142) Portada, T.; Margetić, D.; Štrukil, V. Mechanochemical Catalytic Transfer Hydrogenation of Aromatic Nitro Derivatives. *Molecules* **2018**, *23*, 3163–3180.
- (143) Colacino, E.; Dayaker, G.; Morère, A.; Friščić, T. Introducing Students to Mechanochemistry via Environmentally Friendly Organic Synthesis Using a Solvent-Free Mechanochemical Preparation of the Antidiabetic Drug Tolbutamide. *J. Chem. Educ.* **2019**, *96*, 766–771.
- (144) Colacino, E.; Porcheddu, A.; Charnay, C.; Delogu, F. From enabling technologies to medicinal mechanochemistry: an eco-friendly access to hydantoin-based active pharmaceutical ingredients. *React. Chem. Eng.* **2019**, *4*, 1179–1188.
- (145) Pérez-Venegas, M.; Juaristi, E. Mechanochemical and Mechanoenzymatic Synthesis of Pharmacologically Active Compounds: A Green Perspective. *ACS Sustainable Chem. Eng.* **2020**, *8*, 8881–8893.
- (146) Sović, I.; Lukin, S.; Meštrović, E.; Halasz, I.; Porcheddu, A.; Delogu, F.; Ricci, P. C.; Caron, F.; Perilli, T.; Dogan, A.; Colacino, E. Mechanochemical Preparation of Active Pharmaceutical Ingredients Monitored by in Situ Raman Spectroscopy. *ACS Omega* **2020**, *5*, 28663–28672.
- (147) Tan, D.; Loots, L.; Friscic, T. Towards medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). *Chem. Commun.* **2016**, *52*, 7760–7781.
- (148) André, V.; Hardeman, A.; Halasz, I.; Stein, R. S.; Jackson, G. J.; Reid, D. G.; Duer, M. J.; Curfs, C.; Duarte, M. T.; Friščić, T. Mechanochemical Synthesis of the Metallo-drug Bismuth Subsalicylate from Bi<sub>2</sub>O<sub>3</sub> and Structure of Bismuth Salicylate without Auxiliary Organic Ligands. *Angew. Chem., Int. Ed.* **2011**, *50*, 7858–7861.
- (149) Colacino, E.; Porcheddu, A.; Halasz, I.; Charnay, C.; Delogu, F.; Guerra, R.; Fullenwarth, J. Mechanochemistry for “no solvent, no base” preparation of Hydantoin-based Active Pharmaceutical Ingredients: Nitrofurantoin and Dantrolene. *Green Chem.* **2018**, *20*, 2973–2977.
- (150) Crawford, D. E.; Porcheddu, A.; McCalmont, A. S.; Delogu, F.; James, S. L.; Colacino, E. Solvent-Free, Continuous Synthesis of

Hydrazone-Based Active Pharmaceutical Ingredients by Twin-Screw Extrusion. *ACS Sustainable Chem. Eng.* **2020**, *8*, 12230–12238. (highlighted in C&EN, 30 September, 2020, appeared in Volume 98, Issue 38). [https://cen.acs.org/pharmaceuticals/process-chemistry/Interlocking-screws-crank-pharmaceuticals/98/i38?utm\\_source=Synthesis=Synthesis=CENRSS](https://cen.acs.org/pharmaceuticals/process-chemistry/Interlocking-screws-crank-pharmaceuticals/98/i38?utm_source=Synthesis=Synthesis=CENRSS)

(151) Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. Mechanochemical Preparation of Hydantoins from Amino Esters: Application to the Synthesis of the Antiepileptic Drug Phenytoin. *J. Org. Chem.* **2014**, *79*, 10132–10142.

(152) Porcheddu, A.; Delogu, F.; De Luca, L.; Colacino, E. From Lossen Transposition to Solventless Medicinal Mechanochemistry. *ACS Sustainable Chem. Eng.* **2019**, *7*, 12044–12051.

(153) Tan, D.; štrukil, V.; Mottillo, C.; Frišćić, T. Mechanochemical synthesis of pharmaceutically relevant sulfonyl-(thio)ureas. *Chem. Commun.* **2014**, *50*, 5248–5250.

(154) Colacino, E.; Nun, P.; Colacino, F. M.; Martinez, J.; Lamaty, F. Solvent-Free Synthesis of Nitrones in a Ball-Mill. *Tetrahedron* **2008**, *64*, 5569–5576.

(155) In the face of quantitative oxime to amide conversions, we have experienced some trouble in recovering low molecular weight lactam derivatives.

(156) Lee, B. S.; Chi, D. Y. Beckmann Rearrangement of 1-indanone Oxime Using Aluminum Chloride. *Bull. Korean Chem. Soc.* **1998**, *19*, 1373–1375.

(157) Lee, B. S.; Chu, S.; Lee, I. Y.; Lee, B. S.; Song, J. U.; Ji, D. Y. Beckmann Rearrangements of 1-Indanone Oxime Derivatives Using Aluminum Chloride Anti Mechanistic Considerations. *Bull. Korean Chem. Soc.* **2000**, *21*, 860–866.

(158) Hernández, J. G.; Bolm, C. Altering Product Selectivity by Mechanochemistry. *J. Org. Chem.* **2017**, *82*, 4007–4019.

(159) Bolm, C.; Mocci, R.; Schumacher, C.; Turberg, M.; Puccetti, F.; Hernández, J. G. Mechanochemical Activation of Iron Cyano Complexes: A Prebiotic Impact Scenario for the Synthesis of  $\alpha$ -Amino Acid Derivatives. *Angew. Chem., Int. Ed.* **2018**, *57*, 2423–2426.

(160) Porcheddu, A.; Delogu, F.; De Luca, L.; Fattuoni, C.; Colacino, E. Metal-Free Mechanochemical Oxidations in Ertalyte® Jars. *Beilstein J. Org. Chem.* **2019**, *15*, 1786–1794.

(161) Konnert, L.; Gaudiard, A.; Lamaty, F.; Martinez, J.; Colacino, E. Solventless Synthesis of N-Protected Amino Acids in a Ball Mill. *ACS Sustainable Chem. Eng.* **2013**, *1*, 1186–1191.

(162) This step is critical for the success and reproducibility of the reaction.

(163) The reaction was monitored by GC-MS and TLC and ketone **1a** and oxime **1o** were used for the next step without being isolated (multistep one-pot reaction).

(164) No data about the amount of Na<sub>2</sub>SO<sub>4</sub>, solvents, and silica gel used during the purification step are provided.

(165) Ardila-Fierro, K. J.; Lukin, S.; Etter, M.; Uzarevic, K.; Halasz, I.; Bolm, C.; Hernandez, J. G. Direct Visualization of a Mechanochemically Induced Molecular Rearrangement. *Angew. Chem., Int. Ed.* **2020**, *59*, 13458–13462.

(166) Falencyk, C.; Poelloth, B.; Hilgers, P.; Koenig, B. Mechanochemically Initiated Achmatowicz Rearrangement. *Synth. Commun.* **2015**, *45*, 348–354.

(167) Hernández, J. G.; Halasz, I.; Crawford, D. E.; Krupička, M.; Baláž, M.; André, V.; Vella-Zarb, L.; Niidu, A.; García, F.; Maini, L.; Colacino, E. European Research in Focus: Mechanochemistry for Sustainable Industry (COST Action MechSustInd). *Eur. J. Org. Chem.* **2020**, *2020*, 8–9.

(168) Baláž, M.; Vella-Zarb, L.; Hernández, J. G.; Halasz, I.; Crawford, D. E.; Krupička, M.; André, V.; Niidu, A.; García, F.; Maini, L.; Colacino, E. Mechanochemistry: A Disruptive Innovation for the Industry of the Future. *Chemistry Today* **2019**, *37*, 32–34.

(169) For more information on COST Action CA18112, see Mechanochemistry for Sustainable Industry. <http://www.mechsustind.eu/> (accessed December 15, 2020).

(170) Mechanochemistry Pushes More Sustainable Processes. <https://www.cost.eu/stories/mechanochemistry-pushes-more-sustainable-processes/> (accessed December 15, 2020).

(171) For more information, see <http://www.cost.eu/> (accessed December 15, 2020).