The Mechanochemical Beckmann Rearrangement: An Eco-efficient "cut-and-Paste" Strategy to Design the "good Old Amide Bond"

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Research Article

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

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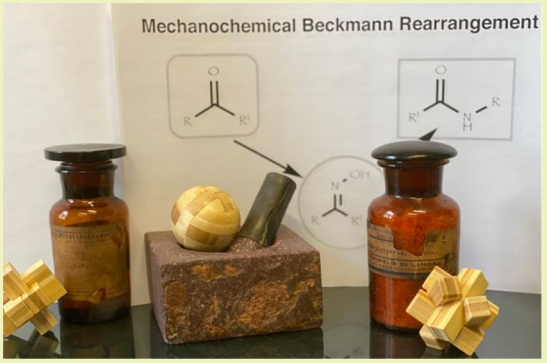
ABSTRACT: Discovered over a century ago, Beckmann rearrangement is still today fully compliant with all the green chemistry principles and consistent with the key aspects of sustainable development. Herein, we report on a sustainable mechanochemical procedure allowing the design of new amide frameworks 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 ε-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.[1−3] 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.*"[4]

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

The industrial preparations of paracetamol[15−18] and ε-caprolactam[19] (intermediate in the synthesis of nylon-6,6)[20] 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,[21,22] detergents and lubricants,[23,24] and functional materials[25] (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).[26]

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).[27−32] 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.[33]

More recent advances have already addressed, at least in part, these limitations via catalysis with transition metals[34−43]

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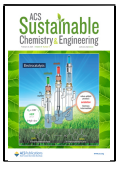
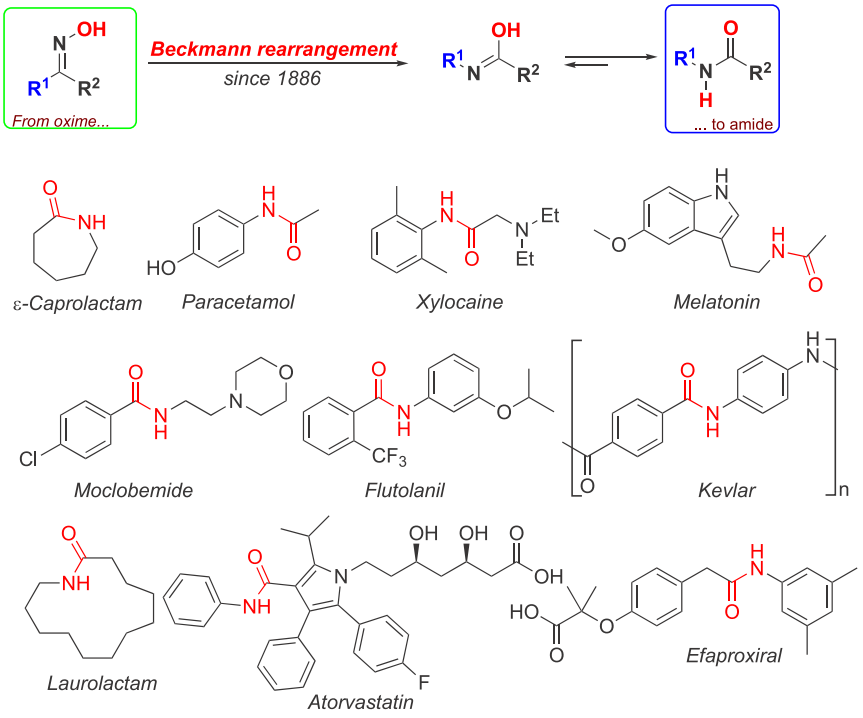
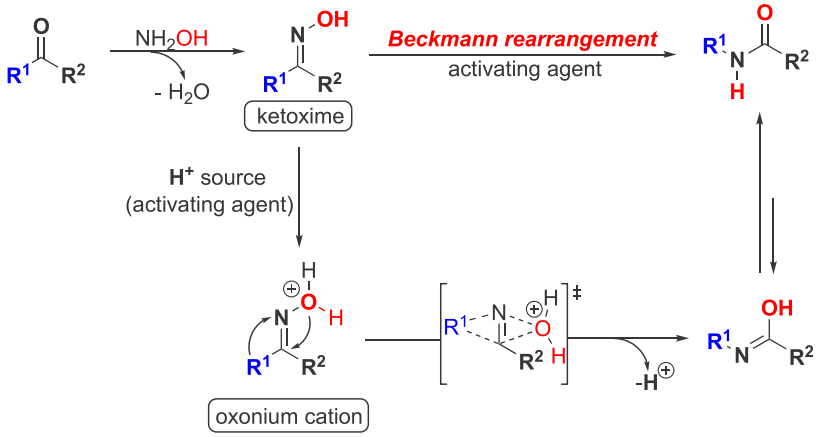


Scheme 1. BKR with Some Examples of Molecules Containing Secondary Amide Fragments



Scheme 2. Commonly Accepted Mechanism for BKR of Ketoximes[156]



or by employing a wide diversity of organic, often toxic, compounds serving as promoters,[44−49] such as cyanuric chloride,[50,51] propylphosphonic anhydride (T3P),[52] triphosphazene,[53] BOPCl,[54] CDI,[55−57] cyclopropenium salts,[58] calcium complexes,[59] sulfonic acid derivatives,[60−66] inorganic Lewis acids,[67,68] and boronic acids,[67−69] among others.[70−74] 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_3CN, 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.[75,76]

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 BKRs. 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.[25,77−83] 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.[84−88] 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.[84−96] In contrast to neat procedures, kinetic studies on

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ACS Sustainable Chem. Eng. 2021, 9, 2100−2114

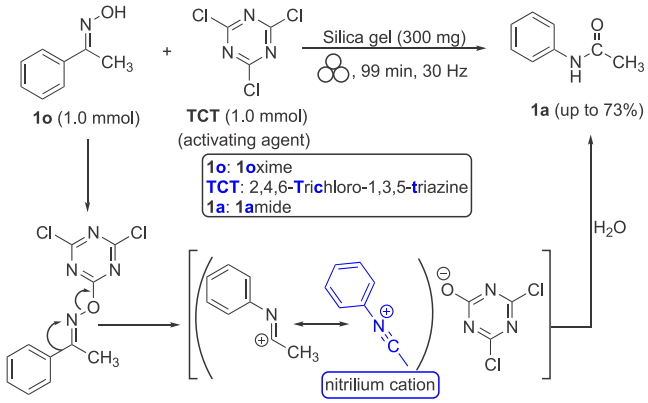
mechanochemical processes have highlighted that only a small fraction of reagents is involved in individual impacts.[97−100] Overall, the process works similarly to a highly diluted reaction (dispersion), while maintaining all the advantages of neat processes in solution. Since most oximes are solid and many of them also have high melting points,[101] 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.[102−104] Nowadays, the reaction between HCl NH_2OH 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_2OH for reaction with ketones.[105] Unfortunately, HCl NH_2OH 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.[83] 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)[106−119] 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 $ZnCl_2$ (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 equimolecular 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,[120,121] 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,[122,123] and recently used for a less environmentally wasteful preparation of isocyanides.[124] *p*-TsCl is an inexpensive solid reagent that is much easier to handle and less toxic than other established activating agents for BKRs. 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**.[125] 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[126,127] 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

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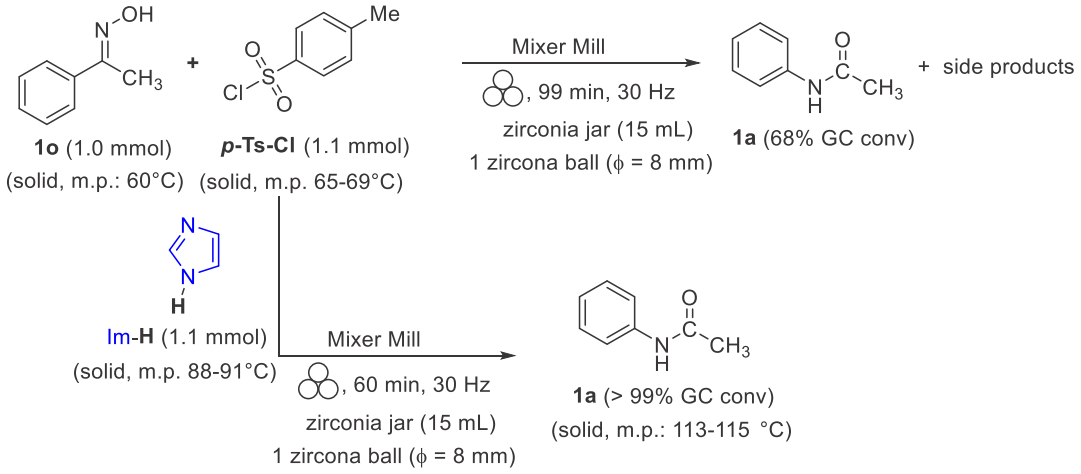
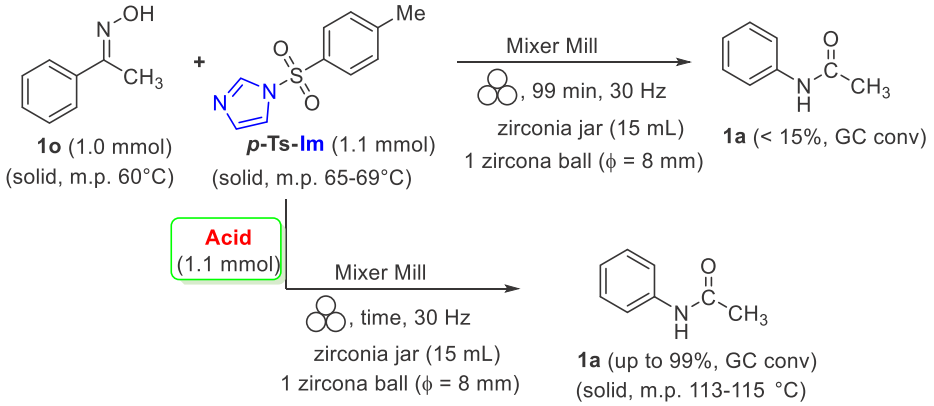
Scheme 4. Screening of the Reaction Parameters for the Maximization of the Degree of Conversion of Ketoxime 1o to Amide 1a



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 equimolecular amount of *p*-toluensulfonic 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**, α, 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.[98−100] 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):

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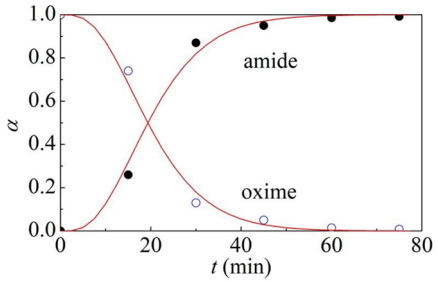


Figure 1. Relative amounts of initial oxime and final amide, α, as a function of the milling time, t. Best-fitted curves are shown.

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

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

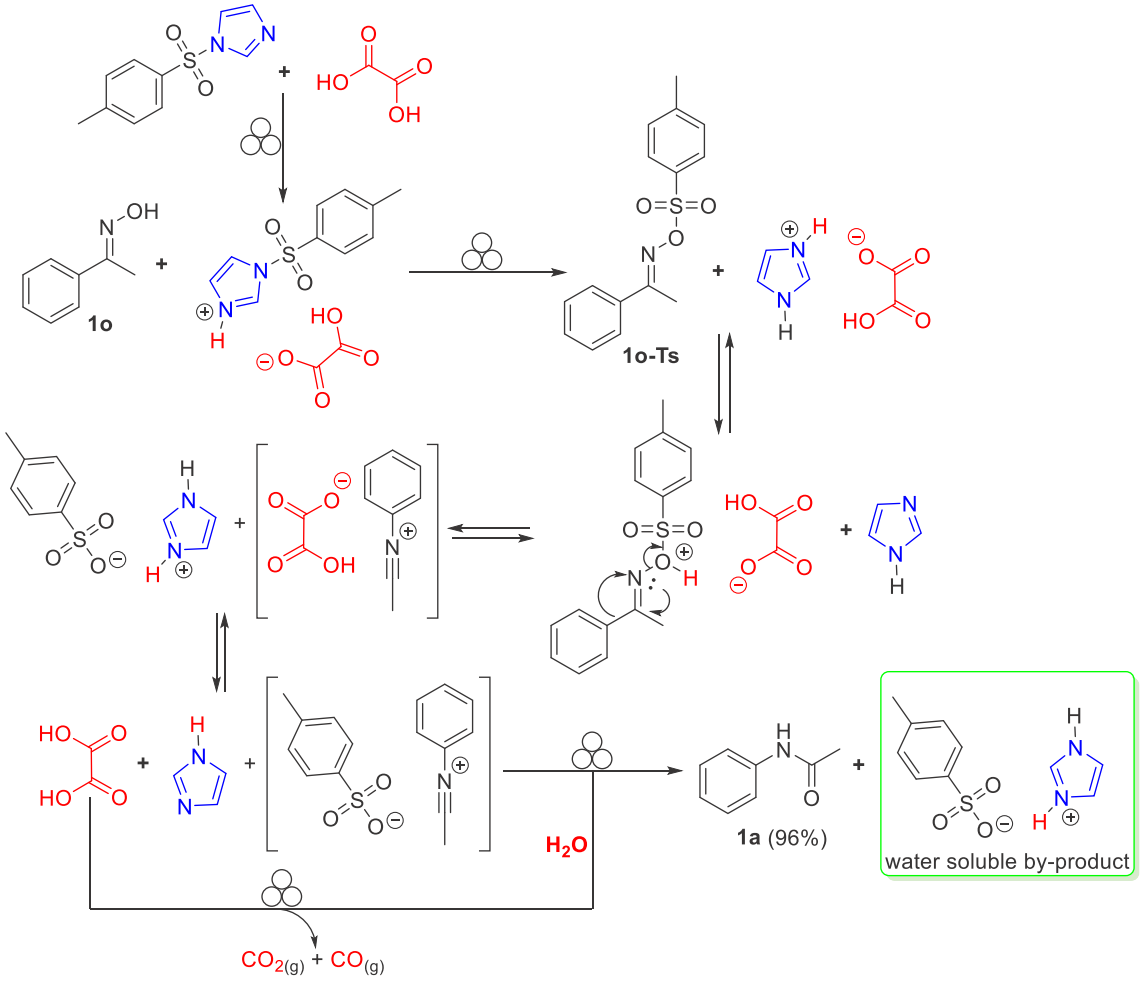
where α is the mass fraction of initial oxime or final amide, k is the apparent rate constant of the mechanochemical transformation, and t is the milling time. Despite the rough assumptions, eq 1a satisfactorily best fits the experimental data. Therefore, we can infer that it captures the fundamental features of the transformation kinetics. The best-fitting equation yields a k value approximately equal to 0.18 min^{-1}. On the basis of previous work,[98−100] 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 μg of oxime is effectively processed during each individual impact.

This value is not far from those typically observed in mechanochemical transformations.[98−100] 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



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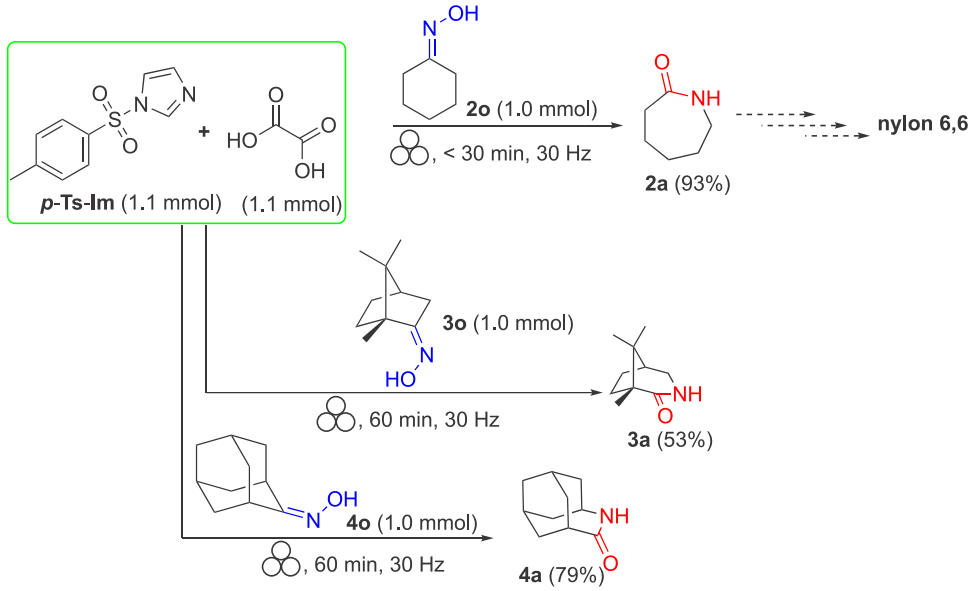
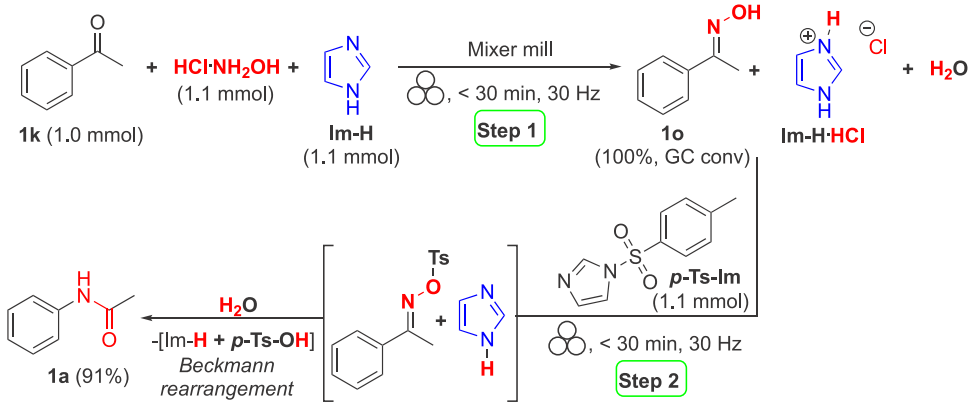
Scheme 7. Assessment of Robustness of the Mechanochemical BKR



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.[128] It can be directly prepared from *p*-toluensulfonic acid by reaction with 1,1′-carbonyldiimidazole (CDI).[128−135] 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).[136] 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_2CO_3 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.[137]

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).[138]

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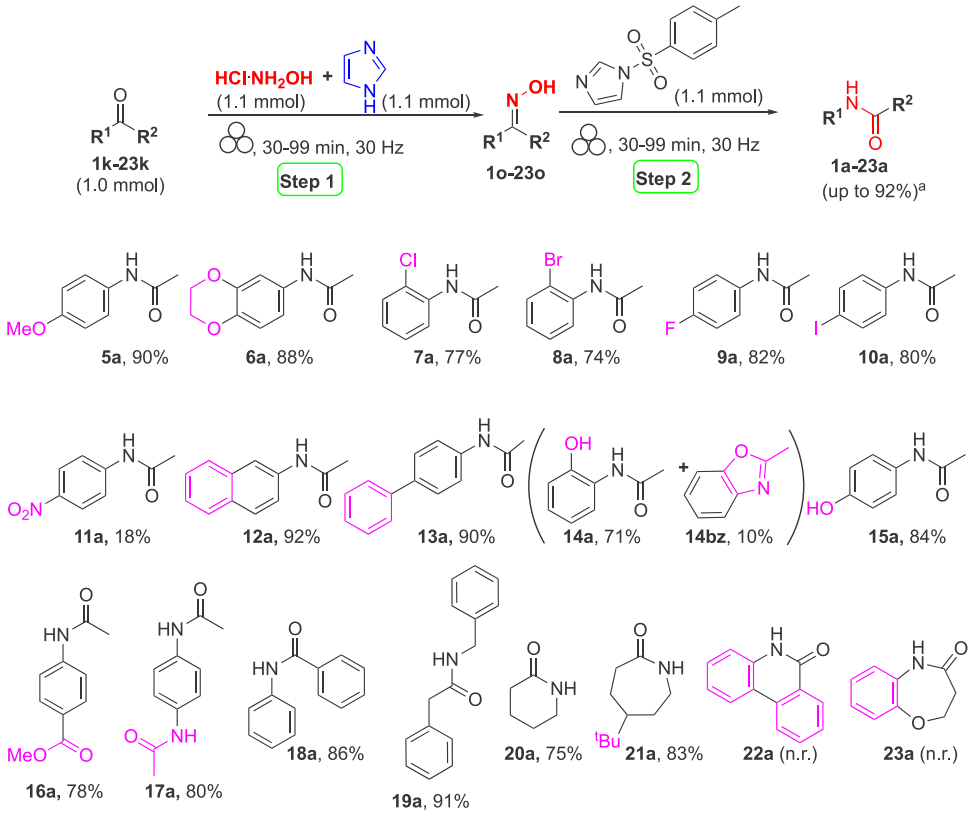
Scheme 9. Reaction Scope of Mechanochemical BKR



[a]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).[137]

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).[139] Under optimal ball-milling conditions, 4-phenylacetophenone and 2-acetonaphthone were also compatible 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).[140]

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**).[141] 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.[142] In this regard, the preparation of active pharmaceutical ingredients (APIs) by mechanochemistry is a recent area of investigation referred to as "medicinal mechanochemistry",[143−147] which paves the way for a sustainable pharmaceutical development. Since the pioneering mechanochemical preparation of Pepto-Bismol metallo-drug,[148] other APIs were prepared at both laboratory and large scale.[149−153]

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-

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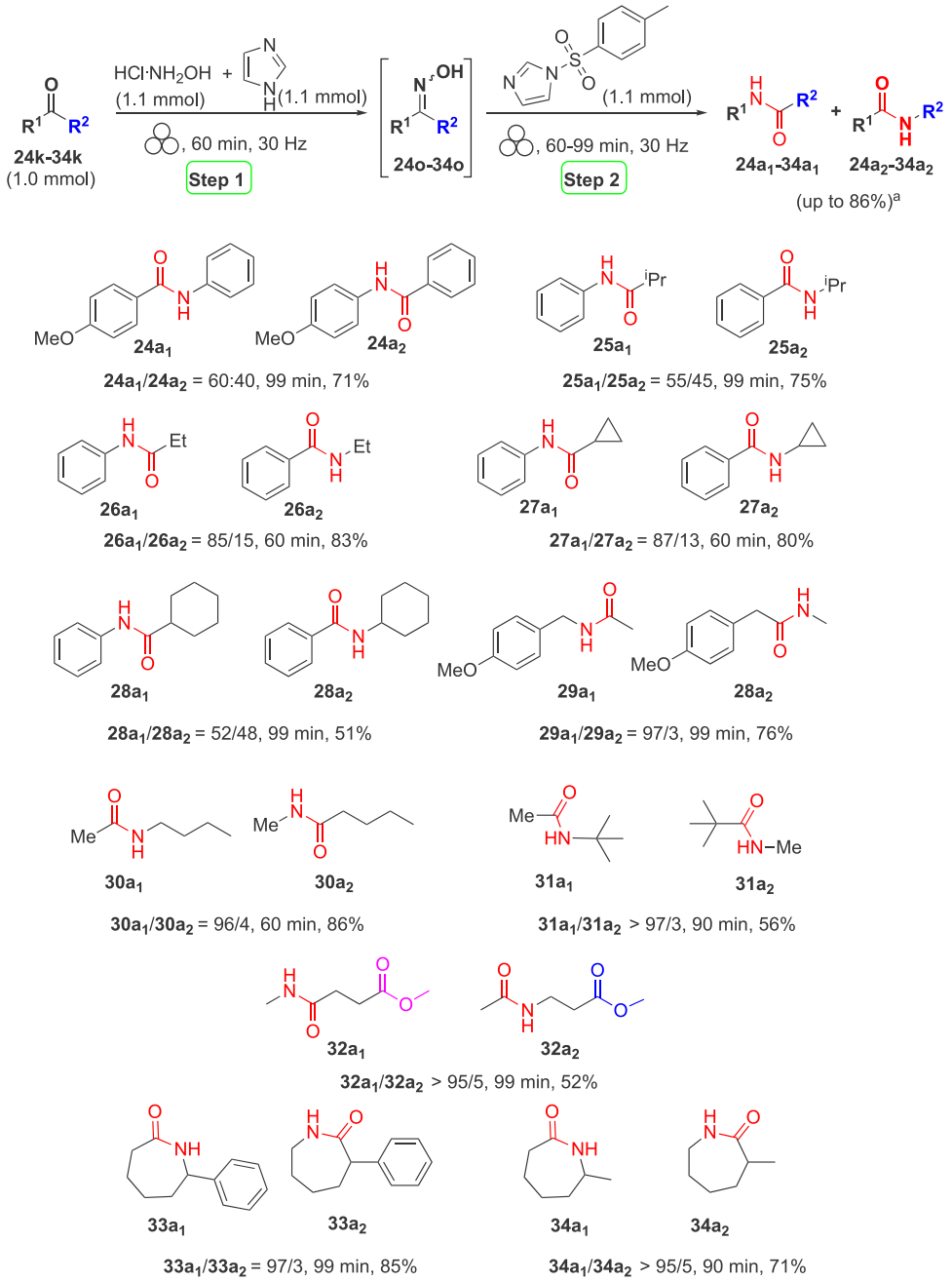
Scheme 10. Reaction Scope of Mechanochemical BKR by Using Unsymmetrical Ketones



[a]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,[154] ketoxime synthesis is always a challenging process requiring the use of a special heated jar.[101,155] 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.[103] 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.[155]

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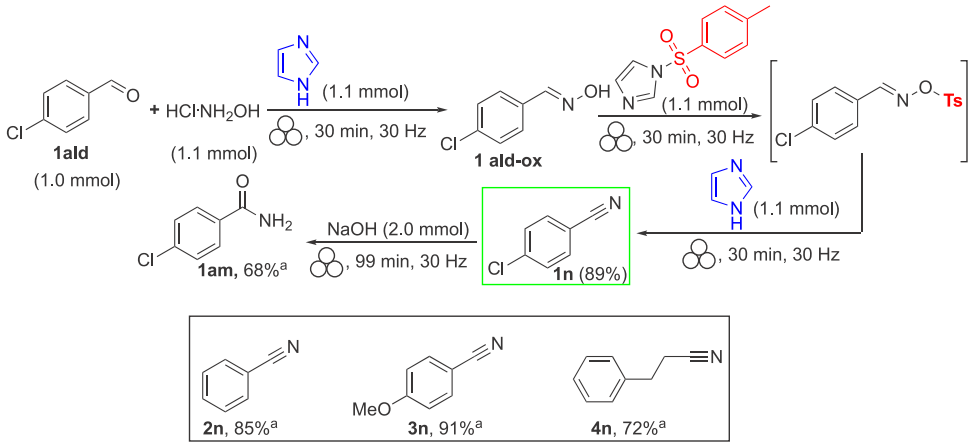
Scheme 11. Preparation of an Array of Nitriles



[a]Isolated yields.

As expected, and in accordance with many other studies in solution reported in the literature,[156,157] 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 substitutes 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,[33,34] 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, $\mathbf{24a_1}$ and $\mathbf{24a_2}$).[158] BKR of phenylisopropyl ketone **25k** provided a mixture (around 1:1) of the two corresponding amides, $\mathbf{25a_1}$ and $\mathbf{25a_2}$, while the rearrangement of propiophenone gave amide $\mathbf{26a_1}$ as the main compound. Similar results were also obtained with the cyclopropyl phenyl ketone, which afforded amide $\mathbf{27a_1}$ 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.[102]

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 $\mathbf{30a_1}$ and $\mathbf{30a_2}$). The presence of a bulky alkyl group on the ketone significantly promotes the reaction chemoselectivity in preparing oxime $\mathbf{31k_1}$, with the isomer bearing the −OH group, in the anti-position to the branched/longer chain, as the major product (>95%). Amide $\mathbf{31a_1}$ 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·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.[159] 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).

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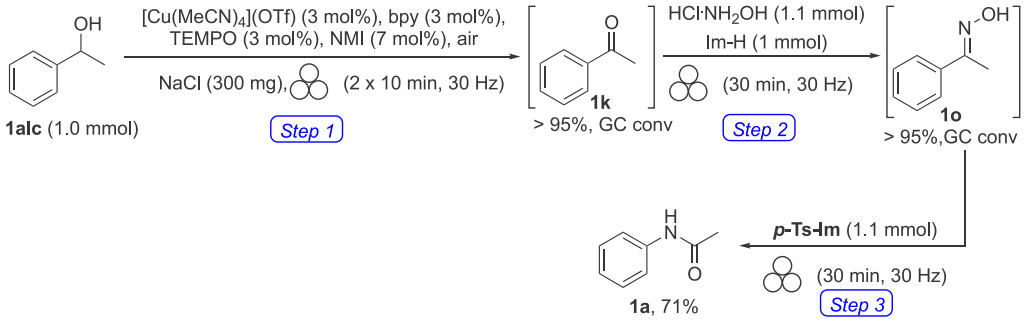
ACS Sustainable Chem. Eng. 2021, 9, 2100−2114

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 $[Cu(MeCN)_4]OTf$ (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).[160]

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)[161] 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).[162] 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 NH_2OH 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).[163]

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[120] ($E \gg 243$ and 12,[164] 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).

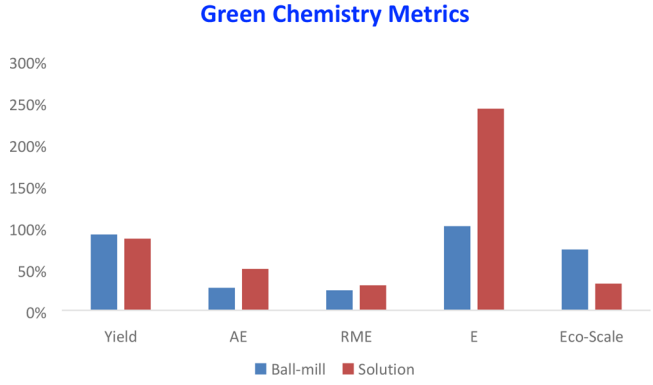


Figure 2. Comparative graphical plot of green chemistry metrics calculated for the preparation of acetanilide **1a** from acetophenone **1k**.

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.[152,165,166]

ASSOCIATED CONTENT

Supporting Information

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

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

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Notes

The authors declare no competing financial interest.

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