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Solvent-Free Synthesis

Comprehensive Study of the Organic-Solvent-Free CDI-Mediated Acylation of Various Nucleophiles by Mechanochemistry**

Thomas-Xavier Métro,* Julien Bonnamour, Thomas Reidon, Anthony Duprez, Jordi Sarpoulet, Jean Martinez, and Frédéric Lamaty*[a]

In memory of Professor Bertrand Castro

Abstract: Acylation reactions are ubiquitous in the synthesis of natural products and biologically active compounds. Unfortunately, these reactions often require the use of large quantities of volatile and/or toxic solvents, either for the reaction, purification or isolation of the products. Herein we describe and discuss the possibility of completely eliminating the use of organic solvents for the synthesis, purification and isolation of products resulting from the acylation of amines and other nucleophiles. Thus, utilisation of *N,N'*-carbonyldiimidazole (CDI) allows efficient coupling between carboxylic acids and various nucleophiles under solvent-free

mechanical agitation, and water-assisted grinding enables both the purification and isolation of pure products. Critical parameters such as the physical state and water solubility of the products, milling material, type of agitation (vibratory or planetary) as well as contamination from wear are analysed and discussed. In addition, original organic-solvent-free conditions are proposed to overcome the limitations of this approach. The calculations of various green metrics are included, highlighting the particularly low environmental impact of this strategy.

Introduction

Acylation reactions are widely used in the synthesis of natural products and biologically active molecules,^[1] but they usually require large amounts of volatile and toxic solvents such as *N,N*-dimethylformamide or dichloromethane to be performed with efficiency. Indeed, a SciFinder survey of 680 000 amidation reactions has shown that 83 % of the reactions involve the use of either DMF (47 %) or CH₂Cl₂ (36 %).^[2] The removal of organic solvents from the reaction media to reduce environmental impact would be highly attractive as they account for the major part of the material used to manufacture active pharmaceutical ingredients.^[3] Unfortunately, solvent-free synthesis under classical batch stirring often implies either solid or highly viscous reaction mixtures along with mass-transfer limitations. In a wide number of examples, these difficulties could be efficiently overcome by using mechanically induced agitation provided by ball mills from the laboratory to the pilot

scale.^[4] Although enabling organic reactions to be performed in the absence of solvents, the recovery of the reaction mixture from the milling jar is often performed with the use of an organic solvent, raising questions concerning the “solvent-free” denomination of such processes. For our part, we have developed a strategy allowing the complete elimination of organic solvents in the synthesis, purification and isolation of products resulting from the acylation of amines and other nucleophiles. Other methods avoiding the use of organic solvent from reaction to product recovery have been previously published but they remain scarce. As an example, solvent-free recovery by the sublimation of nitrosobenzenes resulting from a reaction performed in a ball mill was described recently.^[5] Although carried out in the total absence of any organic solvent, this approach is limited to molecules presenting high vapour pressure properties. In some studies, the reaction mixture has been recovered from a ball mill reactor by using a cyclone under inert gas flow or by physical withdrawal directly from the milling jar followed by drying.^[6] When water-soluble inorganic salts were produced during the course of the reaction, they were removed by washing with water and/or trituration followed by filtration and drying, thereby avoiding the use of organic solvents.^[7] Unfortunately, these approaches were limited to addition or condensation reactions in which water or water-soluble inorganic salts were the only by-products. More recently, Štrukil et al. described the mechano-mediated synthesis of aromatic amides and dipeptides by using *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl) as coupling agent, nitromethane and NaCl as grinding assistants, 4-dimeth-

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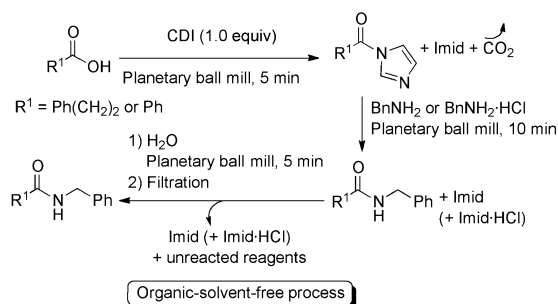
[**] CDI = *N,N'*-carbonyldiimidazole

ylaminopyridine (DMAP) as base and water to recover and purify the final products.^[8] Although water-based treatment and filtration are critical steps for the success of such organic-solvent-free processes,^[9] to the best of our knowledge, limitations concerning the water solubility and physical state (solid or liquid) of the products have never been considered or discussed previously. In addition, contamination from wear of the milling material is a phenomenon that has been widely described and analysed for other applications, but not for milling-mediated organic synthesis.^[10] Although critical for the purity of organic molecules synthesised by ball-milling in the complete absence of organic solvent from reaction to product isolation, product contamination from wear of milling material has never been analysed and discussed in depth.^[11] For our part, we have previously described the mechanosynthesis of amides from carboxylic acids and amine hydrochlorides by treatment with *N,N'*-carbonyldiimidazole (CDI) without using organic solvent from reaction to product recovery.^[12] Pursuing our efforts to provide the organic chemistry community with a set of solutions enabling to avoid the use of problematic solvents,^[13] we herein describe a comprehensive study of the organic-solvent-free CDI-mediated acylation of *N*-, *O*-, *S*- and *C*-nucleophiles by mechanochemistry, including analysis, discussion and solutions to limitations related to 1) the physical state and water solubility of the products and 2) contamination from wear.

Results and Discussion

Optimisation of the reaction based on stoichiometry and amine acidic/basic form

In most cases, coupling carboxylic acids with amine hydrochlorides in the presence of CDI has the advantage of producing easily separable compounds, namely solid hydrophobic amides, gaseous carbon dioxide and water-soluble by-products (carboxylic acids, imidazole and amines, the last two existing either as free bases or as hydrochloride salts). Thus, the treatment of hydrocinnamic acid with 1.0 equivalent of CDI in a 12 mL stainless-steel jar containing fifty 5 mm diameter balls in a planetary ball mill agitated at 500 rpm for 5 min furnished the corresponding acylimidazole (Scheme 1).



Scheme 1. Mechanochemistry of *N*-benzylamides from carboxylic acids and CDI.

The latter was not isolated but its formation was followed by ex situ IR analysis of reaction samples.^[14] These samples were taken directly from the milling jar, immediately after the 5 min ball-milling had ended. They were analysed as such, without any solubilisation process. Thus, the disappearance of the hydrocinnamic acid IR band at 1692 cm^{-1} was observed along with the appearance of the acylimidazole IR band at 1730 cm^{-1} (Figure 1). The addition of 1.0 equivalent of benzyl-

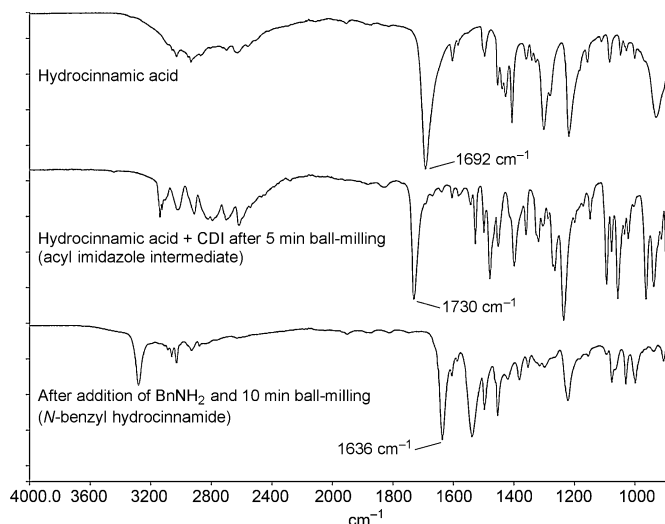


Figure 1. IR spectra for the mechanochemistry of *N*-benzylhydrocinnamide. IR spectrum of hydrocinnamic acid (top); IR spectrum after mixing hydrocinnamic acid with CDI for 5 min (middle); IR spectrum after addition of BnNH_2 and mixing for 10 min (bottom).

amine followed by mixing for 10 min led to the complete consumption of the acylimidazole, as indicated by the disappearance of its IR band at 1730 cm^{-1} and the formation of *N*-benzylhydrocinnamide (new IR band at 1636 cm^{-1}). The addition of deionised water to the jar followed by mixing for 5 min provided a suspension that could easily be transferred onto a glass frit, allowing separation of non-soluble *N*-benzylhydrocinnamide from the by-products (imidazole and possible traces of hydrocinnamic acid and benzylamine). Drying under vacuum over P_2O_5 furnished pure *N*-benzylhydrocinnamide in a yield of 76% (Table 1, entry 1). Interestingly, using benzyl-

Table 1. Optimisation of CDI-mediated mechanochemistry of *N*-benzylhydrocinnamide and *N*-benzylbenzamide.^[a]

Entry	Carboxylic acid	Amine	Amine [equiv]	Isolated yield [%]
1	hydrocinnamic acid	BnNH_2	1.0	76
2		$\text{BnNH}_2\cdot\text{HCl}$	1.0	82
3		BnNH_2	0.9	76
4		$\text{BnNH}_2\cdot\text{HCl}$	0.9	94
5	benzoic acid	$\text{BnNH}_2\cdot\text{HCl}$	0.9	88
6		BnNH_2	0.9	73
7		$\text{BnNH}_2\cdot\text{HCl}$	0.9	82 ^[b]

[a] Performed on a 1.35 mmol scale. [b] Performed on a 2.7 mmol scale.

amine hydrochloride salt (instead of benzylamine) provided *N*-benzylhydrocinnamide with an improved yield of 82% (Table 1, entry 2). Although the yield was not improved by using 0.9 equivalents of benzylamine (Table 1, entry 3), the treatment of hydrocinnamic acid with 1.0 equivalent of CDI followed by the addition of 0.9 equivalents of benzylamine hydrochloride furnished *N*-benzylhydrocinnamide in a yield of 94% (Table 1, entry 4). This 12% increase in reaction yield might be explained by a higher conversion of $\text{BnNH}_2\cdot\text{HCl}$ when hydrocinnamic acid and CDI were used in excess (Table 1, entry 4) compared with when hydrocinnamic acid, CDI and $\text{BnNH}_2\cdot\text{HCl}$ were utilised in equimolar amounts (Table 1, entry 2). It was hypothesised that the 10% excess of acylimidazole was hydrolysed to hydrocinnamic acid and imidazole during ball-milling with water and eliminated in the filtrate during the filtration step. This hypothesis was confirmed by HPLC analysis, which revealed the presence of both hydrocinnamic acid and imidazole in the filtrate. When hydrocinnamic acid was replaced with benzoic acid, *N*-benzylbenzamide was obtained in a yield of 88% (Table 1, entry 5). As for the hydrocinnamic acid, the use of benzylamine as a free base furnished *N*-benzylbenzamide in a lower yield of 73% (Table 1, entry 6).

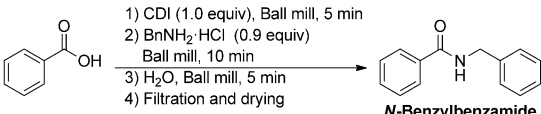
Finally, increasing the filling ratio by performing the same reaction on a larger scale (2.7 mmol instead of 1.35 mmol) in the same combination of jar and balls furnished the amide in a slightly lower yield of 82% (Table 1, entry 7). It appears that after optimisation of these latter parameters, optimal yields were obtained when carboxylic acid was treated with 1.0 equivalent of CDI in a 12 mL stainless-steel jar containing fifty 5 mm diameter balls followed by the addition of 0.9 equivalents of benzylamine hydrochloride on a 1.35 mmol scale (Table 1, entries 4 and 5).

Influence of milling material on reaction efficiency and contamination from wear

As these amides were isolated without being solubilised and filtered, one could wonder about the presence of contaminants arising from wear of the balls and container.^[10] To address this point, the content of metal contaminant in *N*-benzylbenzamide was measured either by inductively coupled plasma mass spectrometry (ICP-MS) or by gravimetric analysis. When the standard procedure was applied to the synthesis of *N*-benzylbenzamide, ICP-MS analysis indicated the presence of very low amounts of the two main components of the stainless-steel grinding jar (366 ppm Fe and 169 ppm Cr; Table 2, entry 1).^[15] As expected, solubilising the product in EtOAc followed by filtration either through cotton or through a 0.2 μm PTFE filter eliminated the contaminants to such an extent that neither iron nor chromium were detectable by ICP-MS analysis (Table 2, entries 2 and 3). In this case, using an organic solvent can be regarded as lowering the interest of the present methodology. Nevertheless, it has to be noted that in this peculiar situation, the only property expected from the organic solvent is to be able to solubilise the product, which leaves the chemist with a large number of possibilities in the choice of acceptable solvent.

We next evaluated the efficiency of this approach in a vibratory ball mill. Thus, utilising a 10 mL screw-top stainless-steel jar equipped with two 10 mm diameter stainless-steel balls agitated at 30 Hz within a vibratory ball mill furnished *N*-benzylbenzamide in a yield of 85% (Table 2, entry 4). Unfortunately, ICP-MS analysis of the product revealed higher amounts of iron and chromium than when using the planetary ball mill (1400 ppm Fe and 1000 ppm Cr; Table 2, entry 4). When using a smaller container and balls (5 mL jar and two 5 mm diameter balls), both the iron and chromium content in the product were lower (642 ppm Fe and 176 ppm Cr; Table 2, entry 5), which can be explained by a lower intensity of collisions between the balls and walls.^[10] The previous experiments were realised in jars that had been used several times, and we expected to reduce contamination by using jars that had never been used before. Unfortunately, higher metal contamination was observed when *N*-benzylbenzamide was synthesised in brand new jars (Table 2, entry 6 vs. entry 4 and entry 7 vs. entry 5). This phenomenon could be explained by the presence of fragilities on the metallic surface created during machining of the milling material. These fragilities would disappear after a few hours of milling. In these experiments, the lower yields of *N*-benzylbenzamide can be explained by material losses during jar manipulation due to a less hermetic closure system compared with the screw-top jars utilised previously (59 vs. 85% in 10 mL jars and 67 vs. 75% in 5 mL jars). It was next envisaged to reduce contamination from wear by performing reactions with milling material lighter than stainless steel ($\rho_{\text{stainless steel}} = 7.8 \text{ g cm}^{-3}$). Thus, changing the jar material to ZrO_2 ($\rho_{\text{zirconium oxide}} = 5.9 \text{ g cm}^{-3}$) furnished *N*-benzylbenzamide with a satisfying yield of 86%,^[16] albeit as a powder containing 12200 ppm zirconium (Table 2, entry 8). On the other hand, the lowest contamination resulting from wear was obtained when using a planetary ball mill with the jar and balls made of agate, a much lighter milling material than stainless steel ($\rho_{\text{agate}} = 2.65 \text{ g cm}^{-3}$). Indeed, less than 100 ppm silicon and 48 ppm iron were obtained in *N*-benzylbenzamide when the reaction was performed with the jar and balls made from agate (Table 2, entry 9).^[15] Although the yield was slightly lower in this case (67%), completion of the reaction indicated that heavy balls such as those made of stainless steel were not mandatory for the success of this CDI-mediated mechanosynthesis of *N*-benzylbenzamide. Indeed, performing the same reaction in a 25 mL PTFE jar containing one 10 mm diameter PTFE ball with a steel core ($\rho_{\text{PTFE ball}} = 3.3 \text{ g cm}^{-3}$) also produced *N*-benzylbenzamide in a yield of 69% (Table 2, entry 10). Because under these conditions wear produced PTFE particles, the contaminant content was quantified by gravimetric analysis. This indicated that 2400 ppm contaminant was present in *N*-benzylbenzamide when produced with PTFE milling material (Table 2, entry 10). To our delight, it was discovered that even lighter milling material such as rubber can induce the mechanosynthesis of *N*-benzylbenzamide ($\rho_{\text{rubber}} \approx 1.3 \text{ g cm}^{-3}$). Thus, utilising an 18 mm diameter rubber ball in a PTFE jar furnished *N*-benzylbenzamide in a yield of 80% (Table 2, entry 11). In this case, gravimetric analysis of the product indicated a contaminant content of less than 1000 ppm. As the reliability of gravi-

Table 2. Influence of the milling material on reaction efficiency and contamination from wear.



1) CDI (1.0 equiv), Ball mill, 5 min
2) BnNH₂·HCl (0.9 equiv)
Ball mill, 10 min
3) H₂O, Ball mill, 5 min
4) Filtration and drying

N-Benzylbenzamide

Yield and analysis of contaminant content

Entry	Material & size of jar	Material, number & diameter of balls	Type of ball mill	Jar status	Post-treatment	Reaction scale [mmol]	Yield [%]	Type of analysis	Contaminant content in ppm (metal)
1	stainless steel, 12 mL	stainless steel, 50×5 mm	planetary	used	suspension in H ₂ O and filtration	1.35	88	ICP-MS	366 (Fe); 169 (Cr)
2					solubilised in EtOAc and filtered through cotton			ICP-MS	< 30 (Fe); < 30 (Cr) ^[a]
3					solubilised in EtOAc and filtered through 0.2 μm PTFE filter			ICP-MS	< 30 (Fe); < 30 (Cr) ^[a]
4	stainless steel, 10 mL screw-top	stainless steel, 2×10 mm	vibratory	used	suspension in H ₂ O and filtration	1.13	85	ICP-MS	1400 (Fe); 1000 (Cr)
5	stainless steel, 5 mL screw-top	stainless steel, 2×5 mm		used		0.56	75	ICP-MS	642 (Fe); 176 (Cr)
6	stainless steel, 10 mL	stainless steel, 2×10 mm		new		1.13	59	ICP-MS	7400 (Fe); 1400 (Cr)
7	stainless steel, 5 mL	stainless steel, 2×5 mm		new		0.56	67	ICP-MS	1200 (Fe); 314 (Cr)
8	ZrO ₂ , 10 mL screw-top	ZrO ₂ , 2×12 mm		used		1.13	86 ^[b]	ICP-MS	151 (Fe); 12 200 (Zr); 740 (Y)
9	agate, 50 mL	agate, 4×12 mm	planetary			2.7	67	ICP-MS	< 100 (Si); ^[a] 48 (Fe)
10	PTFE, 25 mL screw-top	PTFE with steel core, 1×10 mm	vibratory			5.0	69 ^[c]	gravimetric	2400
11	PTFE, 25 mL screw-top	rubber, 1×18 mm				1.35	80	gravimetric	< 1000 ^[a]
12	stainless steel, 250 mL	stainless steel, 50×10 mm	planetary			22.5	92 ^[b]	gravimetric	42 000
13	stainless steel, 250 mL	rubber, 10×18 mm				22.5	91 ^[b]	gravimetric	3400

[a] Contaminant content below the detection limit of the analytical method. [b] Corrected yield based on the contaminant content. [c] Agitation performed at 20 Hz.

metric analysis performed on a 100 mg sample is much lower than that of ICP-MS analysis, both the efficiency and wear resistance of the rubber milling material in the production of *N*-benzylbenzamide was tested on a larger scale. First, the reaction was performed on a 22.5 mmol scale in a 250 mL jar containing fifty 10 mm diameter stainless-steel balls, which produced *N*-benzylbenzamide in a yield of 92%,^[16] albeit containing 42 000 ppm metallic contaminants, as analysed by gravimetric analysis (Table 2, entry 12). Changing the stainless-steel balls to ten 18 mm diameter rubber balls furnished *N*-benzylbenzamide in a yield of 91% with a much lower contaminant content of 3400 ppm (Table 2, entry 13). The higher contaminant content obtained with rubber balls on a 22.5 mmol scale (Table 2, entry 13) compared with the contamination resulting from the experiment realised with one rubber ball on a 1.35 mmol scale (Table 2, entry 11) can be explained by the higher intensity of collisions between the balls and walls. However, these results clearly show that contamination from wear can be substantially reduced by a judicious choice of milling material. As solvent-free organic syntheses often imply “soft” reaction mixtures, selecting lighter grinding materials instead of classical heavy materials such as stainless steel could greatly help in reducing the contaminant content of products issuing

from procedures avoiding the use of organic solvent from reaction to product recovery.

Influence of milling time on contamination from wear

The influence of milling time on contamination content was also studied. The reaction mixture of the *N*-benzylhydrocinnamide synthesis was sampled every 5 min and analysed by atomic absorption spectroscopy (AAS) to determine the iron content. Hydrocinnamic acid and CDI were first agitated for 5 min in the ball mill. After the addition of benzylamine followed by mixing for 5 min, the iron content reached 190 ppm (Figure 2). When the reaction mixture was sampled after 10 and 15 min of agitation, the iron content had increased to 216 and 319 ppm, respectively. These results confirm that contamination from wear increased with time, highlighting the importance of the optimisation of reaction time in completely solvent-free ball-mill-mediated organic syntheses to reduce product contamination from wear. This analytical study of the metal traces issuing from the wear of balls and container shows that as long as the presence of metal traces is compatible with the intended use of the products, synthesis and purification can be realised in the complete absence of organic sol-

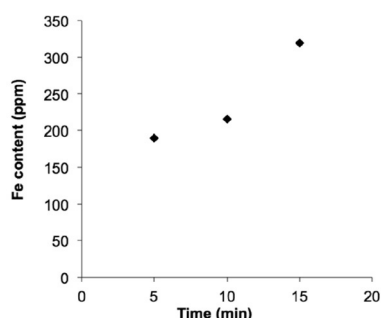
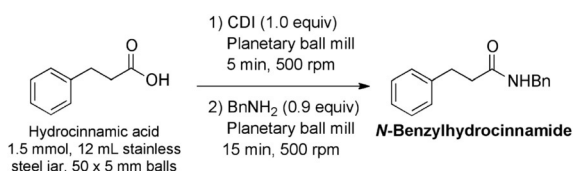


Figure 2. Iron content as a function of time during the synthesis of *N*-benzylhydrocinnamide.

vents. If the presence of metal traces is inconsistent with the required use of the products, these impurities can be largely removed by solubilisation of the amide in a low-toxic solvent such as EtOAc followed by simple filtration. In addition, contamination from wear can be greatly reduced by an appropriate choice of milling material and by optimisation of milling time.

Scope and limitations for acylation of *N*-nucleophiles

To give a global view of the substrate scope and limitations of this approach, preliminary results from a study that we published previously have been included in the following discussion.^[12] Application of this approach to other carboxylic acids and amines was realised on the 1.35 mmol scale in a 12 mL stainless-steel jar containing fifty 5 mm diameter balls under planetary ball-milling agitation. Linear carboxylic acids such as hexanoic acid, 4-phenylbutyric acid or phenylacetic acid reacted efficiently with CDI and benzylamine hydrochloride to furnish the corresponding amides in high yields (Table 3, compounds 1–3). It is worth noting here that neither a bromine atom nor

a polar nitro group on the aromatic ring of phenylacetic acid prevented the amides 4 and 5 from being isolated in good yields (69 and 91%, respectively; Table 3). Similarly, the treatment of α -methylphenylacetic acid with CDI and benzylamine hydrochloride led to isolation of *N*-benzyl-2-phenylpropanamide (6) in a yield of 70% (Table 3, compound 6). The higher yield of amide 3 (93%) compared with that of amide 6 could be explained by a greater steric hindrance in 2-phenylpropionic acid compared with in phenylacetic acid. However, HPLC analysis revealed the presence of amide 6 in the aqueous filtrate. Thus, EtOAc extraction of the filtrate obtained from the synthesis of 6 followed by purification on silica gel led to an increased yield of 6 of 86%. This result indicates that a lower yield of amide 6 (without extraction of the filtrate) could be explained by a higher water solubility of the product. Similarly, CDI activation of highly hindered acids such as 1-adamantanecarboxylic acid is not a limitation in this approach as the latter could be transformed into amide 7 in a good yield of 77% (Table 3). Primary amines other than benzylamine could also be acylated with high efficiency. Thus, phenethylamine and 2,4-dimethoxybenzylamine hydrochlorides furnished the corresponding amides in yields of 96 and 84%, respectively (Table 3,

Table 3. Scope and limitations of the CDI-mediated mechanochemical synthesis of amides.^[a]

1) CDI (1.0 equiv) 2) R ² R ³ NH·HCl (0.9 equiv) 3) H ₂ O Ball mill 4) Filtration and drying			
1 99%	2 85%	3 93%	4 69%
5 91%	6 70% (86%) ^[b]	7 77%	8 96%
9 84%	10 64%	11 83%	12 82% ^[c]
13 77% ^[d]	14 68% (99% ee) ^[e]	15 78% ^[f] (98% ee) ^[e]	16 19% ^[g] , 49% ^[h] (>95% de) ^[j]
17 81% ^[i] (>95% de) ^[j]	18 44% ^[k]	19 62% ^[l] (oil, 3.6g)	20 46% ^[m] (oil, 3.3g)
21 0% ^[n] (74%) ^[b]			

[a] Realised on a 1.35 mmol scale unless otherwise noted. [b] After extraction of the aqueous phase with EtOAc. [c] Completed within 20 min. [d] Completed within 1.5 h. [e] Determined by chiral HPLC, see the Supporting Information for details. [f] Completed within 30 min. [g] After agitation for 50 min with (*S*)-methylbenzylamine hydrochloride on a 1.35 mmol scale. [h] Completed within 30 min with (*S*)-methylbenzylamine on a 0.45 mmol scale. [i] Determined by ¹H and ¹³C NMR spectroscopy. No signal corresponding to the diastereoisomer was observed. [j] Realised with 0.5 mmol of (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid, 1.0 equiv of CDI and 1.9 equiv of (*S*)-methylbenzylamine. [k] Completed within 6 h. [l] Completed within 3 h. [m] Completed within 4 h. [n] Completed within 3 h 10 min.

compounds **8** and **9**). Non-hindered nitrogen nucleophiles such as *O*-benzyl hydroxylamine and phenylhydrazine were also efficiently benzoylated, furnishing amide **10** and hydrazide **11** in yields of 64 and 83 %, respectively. α -Substituted primary amines reacted more slowly than non-substituted primary amines. Indeed, agitation of 20 min and 1.5 h, respectively, were necessary to obtain the full conversion of benzoylimidazole intermediates when benzhydramine and cyclohexylamine hydrochlorides were used. Yet, the corresponding amides **12** and **13** were both isolated in good yields (82 and 77 %, Table 3). When enantiopure α -substituted primary amines such as (*S*)- α -methylbenzylamine and phenylalanine *tert*-butyl ester hydrochlorides were used as nucleophiles, the corresponding amides **14** and **15** were obtained as enantiopure compounds in yields of 68 and 78 %, respectively.

We next evaluated the stereoselectivity of the process with enantiopure carboxylic acids as starting materials. When 1.5 mmol of Boc-protected *L*-phenylalanine was treated with 1.0 equivalent of CDI and then with 0.9 equivalents of (*S*)- α -methylbenzylamine during 50 min, the amide **16** was isolated in a very low yield (19%), which can be explained by a sticky reaction media preventing efficient agitation of the reaction mixture (Table 3). This limitation could be solved by both performing the reaction on a 0.45 mmol scale and by using (*S*)- α -methylbenzylamine as a free base. Under these conditions, amide **16** was isolated in a yield of 49% without any loss of chirality as no signal corresponding to the diastereoisomer was observed by ^1H NMR spectroscopy. Similarly, the reaction of 1.5 mmol of both enantiopure Naproxen and CDI followed by agitation with 1.35 mmol of (*S*)- α -methylbenzylamine hydrochloride furnished only traces of the amide **17**. As previously, performing the CDI-mediated activation of Naproxen on a smaller scale (0.5 mmol in this case) followed by agitation with 1.9 equivalents of (*S*)- α -methylbenzylamine as a free base furnished the amide **17** in high yield (81 %) and diastereomeric excess (Table 3).

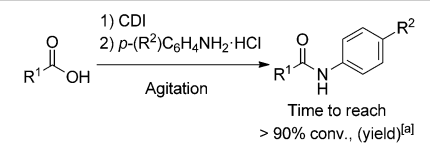
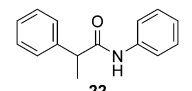
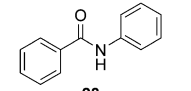
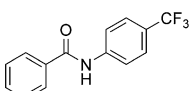
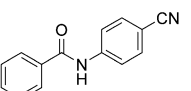
Coupling with secondary amines was next envisioned. The treatment of hydrocinnamic acid with CDI followed by the addition of dibenzylamine hydrochloride required agitation for 6 h to furnish amide **18** in a yield of 44 % (Table 3). LC-MS analysis of the aqueous filtrate revealed no trace of amide **18** but the presence of both hydrocinnamic acid and dibenzylamine. Thus, the relatively low yield of **18** can be explained either by incomplete conversion of the starting materials or by partial hydrolysis of the hydrocinnamic acyl-imidazole during the process. The recovery of the product after agitation with water is efficient as long as the product is a solid. As *N,N*-di-*n*-propyl-3-phenylpropanamide (**19**) is an oil that solubilises imidazole at ambient temperature, we envisaged carrying out the reaction on a larger scale to realise an organic-solvent-free treatment of the liquid reaction mixture. Indeed, performing the reaction with 25 mmol of hydrocinnamic acid, 1.1 equivalents of CDI and 1.1 equivalents of di-*n*-propylamine allowed an easy transfer of the liquid reaction mixture directly into a Kugelrohr apparatus. Subsequent distillation followed by aqueous washings and drying produced 3.6 g of *N,N*-di-*n*-propyl-3-phenylpropanamide (**19**) in a yield of 62 % (Table 3). The same approach

starting from 2-methyl-3-nitrophenylacetic acid furnished 3.3 g of amide **20** in a moderate yield of 46 %, slightly better than that previously reported in the literature using a different strategy.^[17] It is worth noting that in these cases distillation of the reaction mixture would also efficiently eliminate any contaminant issuing from wear. Another requirement for the success of this approach is the hydrophobicity of the products. When coupling benzoic acid with morpholine, the reaction mixture was completely solubilised after the addition of water to the jar, excluding filtration as a way to recover the product. Yet, EtOAc extractions of this aqueous homogeneous phase furnished *N*-benzoylmorpholine (**21**) in a yield of 74 % (Table 3). This result shows that the solubility of amide **21** in water prevented its organic-solvent-free recovery and purification, but not its formation from benzoic acid, CDI and morpholine in the absence of solvent under mechanically-mediated agitation.

We next explored the reactions with aniline derivatives, which are known to react sluggishly with acyl-imidazole intermediates.^[18] When 2-phenylpropionylimidazole, prepared from 2-phenylpropionic acid and CDI, was treated with aniline hydrochloride in the absence of solvent in a ball mill, the corresponding amide **22** was isolated in a yield of 91 % after only 10 min of reaction (Table 4). It is worth noting that when performed in boiling [0.39 M] EtOAc, the same reaction required 3 h to reach 86 % conversion.^[19]

Similarly, *N*-phenylbenzamide (**23**) was obtained in a yield of 93 % after 10 min when the reaction was performed without solvent in a ball mill, whereas 1 h was necessary to reach 90 % conversion when the reaction was realised in *N*-methyl-2-pyrrolidone (NMP) at 50 °C (Table 4).^[18] As in solution, the presence of an electron-withdrawing group such as a trifluoromethyl or cyano group on the aromatic ring slowed the reaction. Indeed,

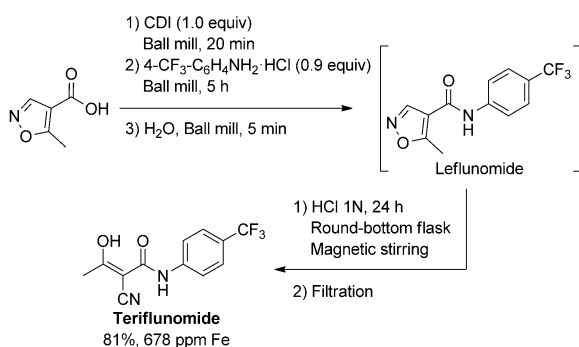
Table 4. Comparison of the rate of acylation of aniline hydrochloride derivatives under solvent and solvent-free conditions.

	
 22 [0.39 M] EtOAc, reflux: 3 h ^[b] Solvent-free: 10 min (91%)	 23 [0.41 M] NMP, 50 °C: 1 h ^[c] Solvent-free: 10 min (93%)
 24 [0.41 M] NMP, 50 °C: 29 h ^[c] Solvent-free: 30 min (82%)	 25 [0.41 M] NMP, 50 °C: > 143 h ^[c] Solvent-free: 3.5 h (77%) ^[d] 0.9% w/w Fe ^[e]

[a] Reaction time to reach 86% conversion for **22** and > 90% conversion for compounds **23**–**25**. [b] See ref. [19]. [c] See ref. [18]. [d] From 4-amino-benzonitrile, yield corrected based on contaminant content. [e] Determined by AAS.

30 min and 3.5 h were required to produce amides **24** and **25** from *p*-trifluoromethylaniline hydrochloride and *p*-aminobenzonitrile, respectively (Table 4). Yet, these acylation reactions were still more rapid than in [0.41 M] NMP at 50 °C; under these conditions, 29 h and more than 143 h were necessary to reach 90% conversion. It is worth noting that the contamination from wear in the case of the reaction of benzoylimidazole with *p*-aminobenzonitrile was relatively low (0.9% w/w) when considering that the ball-mill-mediated agitation was performed for 3.5 h.

This approach was next applied to the production of the active metabolite of Leflunomide,^[20] which was approved for commercialisation under the name Teriflunomide (trade name Aubagio) by the FDA in 2012 for the treatment of multiple sclerosis.^[21] Indeed, the treatment of 5-methyl-4-isoxazolecarboxylic acid with CDI followed by mixing with 4-(trifluoromethyl)aniline hydrochloride during 5 h and then with water during 5 min produced Leflunomide as a fine suspension in water (Scheme 2). This amide was not isolated but submitted to hydrolysis under acidic conditions with magnetic stirring to furnish Teriflunomide in a yield of 81% after filtration and drying. AAS analysis of the final product revealed only low traces of iron (678 ppm). As one could expect higher wear contamination resulting from a relatively long grinding time, this low iron content could be explained by the partial oxidation of metallic particles during the acidic aqueous treatment, water solubilisation of the corresponding cations and elimination during the filtration step.

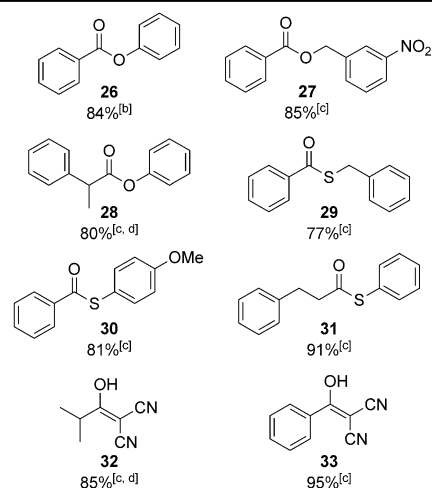
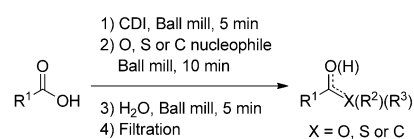


Scheme 2. Mechanosynthesis of Teriflunomide.

Application to O-, S- and C-nucleophiles

This organic-solvent-free CDI-mediated acylation strategy was also applied to other nucleophiles. Indeed, when benzoylimidazole resulting from CDI activation of benzoic acid was ball-milled with phenol, phenyl benzoate (**26**) was isolated in a yield of 84% (Table 5). Similarly, the treatment of benzoic acid with CDI in a vibratory ball mill agitated at 25 Hz followed by the addition of 3-nitrophenylmethanol furnished 3-nitrobenzyl benzoate (**27**) in a yield of 85% (Table 5). Phenyl 2-phenylpropanoate (**28**) was isolated in a yield of 80% by using the same approach, yet it had to be recovered from the milling jar with EtOAc due to its low melting point. Thiols could also be

Table 5. Examples of the organic-solvent-free CDI-mediated acylation of O-, S- and C-nucleophiles.^[a]



[a] Realised on a 1.35 mmol scale. [b] Performed in a planetary mill rotated at 500 rpm. [c] Performed in a vibratory mill at 25 Hz. [d] Recovered with EtOAc.

used as nucleophiles as phenylmethanethiol and 4-methoxybenzenethiol furnished the corresponding benzothioates **29** and **30** in yields of 77 and 81%, respectively (Table 5). When 3-phenylpropanoylimidazole was ball-milled with thiophenol, the corresponding *S*-phenyl 3-phenylpropanethioate (**31**) was isolated in a yield of 91%.

We next envisioned applying this approach to C-nucleophiles. The first attempt using the 1,3-dione dimedone (5,5-dimethyl-1,3-cyclohexanedione) as the nucleophile did not furnish any acylated product (neither C- nor O-acylated). The addition of *N,N*-diisopropylethylamine (DIEA) as base to the reaction mixture did not lead to a successful reaction. In contrast, the treatment of isobutyrylimidazole resulting from the CDI activation of isobutyric acid with malononitrile furnished enol **32** in a yield of 85% (Table 5). Yet, the solubility of the product in both neutral and acidic water forced us to recover it from the aqueous phase by extraction with EtOAc. Finally, benzoic acid could be transformed into enol **33** in a yield of 95% after reaction with CDI followed by the addition of malononitrile (Table 5). Despite being completely solubilised after ball-milling with water, enol **33** could be recovered without using organic solvent by acidification of the aqueous reaction mixture and filtration of the resulting precipitate. These results show that, as long as the final products are solids and not soluble in water, O-, S- and C-nucleophiles can be acylated with high efficiency without using organic solvents from reaction to product recovery.

Evaluation of the environmental impact

We then evaluated the environmental impact of this approach based on the mechanosynthesis of *N*-benzylbenzamide and compared it with previously reported reaction conditions using various reagents: *N,N*-diisopropylbenzylamine-2-boronic acid (IBA),^[22] *N,N'*-dicyclohexylcarbodiimide (DCC),^[23] thionyl chloride (SOCl₂),^[24] *N,N'*-carbonyldiimidazole (CDI)^[25] and sulfated tungstate.^[26] First of all, it has to be highlighted that CDI in THF under classical stirring or without solvent in a ball mill was the most efficient reagent as *N*-benzylbenzamide was isolated in the highest yield (92%, Table 6, entries 4 and 6). Yet, the use

Entry	Reagent	Yield [%]	Atom economy [%]	sEF ^[a]	cEF ^[b]	GHS pictograms ^[c]	Eco-scale ^[d]
1	IBA ^[22]	50	92.1	2.38	396.2	8	44
2	DCC ^{[23][e]}	82	48.5	2.75	66.1	8	62
3	SOCl ₂ ^{[24][e]}	72	60.6	2.32	24.6	8	54
4	CDI in THF ^{[25][e]}	92	54.0	2.01	41.9	9	67
5	sulfated tungstate ^[26]	81	92.1	1.55	23.5	9	49.5
6	solvent-free CDI	92	49.3	2.36	20.8	6	79

[a] Simple E-factor [b] Complete E-factor. [c] Cumulative number of GHS pictograms. [d] See ref. [28]. [e] See ref. [26] for raw data.

of CDI is detrimental to the atom economy of the reaction like other reagents that have to be used in stoichiometric quantities. Indeed, the atom economy is 54.0 and 49.3% when CDI is used in THF and without solvent, respectively (Table 6, entries 4 and 6). In contrast, the atom economy reaches 92.1% when catalysts such as IBA or sulfated tungstate are employed (Table 6, entries 1 and 5). The yield and atom economy are both simple and powerful parameters for evaluating the environmental impact of a reaction, but they omit critical issues such as the amounts of organic solvents and water required to perform the reaction and isolate the final product. Indeed, solvents and water account for 56 and 32%, respectively, of the total mass of material used in the pharmaceutical industry.^[3] Although green metrics such as the environmental factor (E-factor)^[27] and process mass intensity (PMI)^[3] have been developed to take into account the quantity of waste produced during a reaction or the total mass of materials required to obtain the final product, respectively,^[3] the lack of homogeneity in the consideration of water and organic solvents in the calculations by the chemistry community has led to confusion and difficulties in the interpretation of these parameters.

This observation led Roschangar et al. to propose definitions of the “simple E-factor” and the “complete E-factor” as well as their mode of utilisation.^[29] The simple E-factor (noted sEF) omits water and solvents in the calculations, whereas the complete E-factor (noted cEF) takes into account every material entering into the process without taking into consideration any

water or organic-solvent recycling steps. With a simple E-factor value of 2.36, the organic-solvent-free CDI-mediated mechanosynthesis of *N*-benzylbenzamide presents no clear advantage over the other strategies (Table 6). On the other hand, the CDI-mediated mechanosynthesis of *N*-benzylbenzamide appears to be the most interesting approach when considering every material utilised (including water and organic solvent) with the lowest complete E-factor score of 20.8 (Table 6). Another very simple way to evaluate the environmental impact of an experimental procedure, especially for the chemist who is going to perform the reaction at the bench, is to look at the cumulative number of GHS pictograms of the materials he is going to manipulate. Considering all the strategies reported for the synthesis of *N*-benzylbenzamide, our approach has a cumulative number of GHS pictograms of 6, whereas for all the other strategies this number is equal to or greater than 8 (Table 6).

Finally, when considering the Eco-scale score,^[28] a green metric ranging from 0 (completely failed reaction) to 100 (ideal reaction) taking into account yield, cost, safety, technical setup, temperature and reaction time, workup and purification, the CDI-mediated mechanosynthesis of *N*-benzylbenzamide has the highest score (79), which corresponds to an excellent synthesis. These excellent green metric scores can partially be explained by the use of non-toxic water in the process. One could argue that the utilisation of water, a precious resource on earth, results in the contamination of water with organic material, implying costly aqueous-phase post-treatments and an overall negative influence on the environmental impact of the process. Yet, to the best of our knowledge, none of the previously described acylation strategies have avoided water contamination with organic material, due to the systematic use of water washings to obtain pure acylated products. Consequently, environmental impact superiority of the present approach over classical strategies does not rely only on the use of water as an innocuous entity, but, inter alia, on its original and specific use (water-assisted ball-milling) enabling the complete elimination of organic solvents during the purification and recovery steps.

Conclusion

The acylation of amines and other nucleophiles can be efficiently performed in the absence of any organic solvent from reaction to product recovery when combining CDI activation of carboxylic acids and ball-milling agitation. This strategy is applicable to a wide range of carboxylic acids and nucleophiles provided that the corresponding final products are immiscible in water and that their contaminant contents are compatible with their intended use. However, we have shown that the amount of contaminant issuing from wear can be severely reduced by optimisation of the reaction time and appropriate choice of milling material. In particular, a “soft” reaction mixture, such as those frequently encountered in solvent-free or solventless organic syntheses, does not require dense milling materials. Indeed, utilising lighter milling material such as agate, PTFE, or even rubber enables a sharp reduction of contamination from wear without limiting the reaction efficiency.

In the limited number of cases in which the products are soluble in water, organic-solvent-based extraction appears to be a convenient solution to the recovery of the final products from the aqueous phase, although preventing the whole process from being organic-solvent-free from reaction to product recovery. Yet, the absence of organic solvent during the reaction is still a decisive advantage as a tremendous reduction of the reaction time has been observed when performing the acylation of aniline derivatives under mechanical agitation. Finally, calculation and analysis of the various green metrics have shown that this approach can be an efficient way to mitigate the environmental impact of nucleophile acylation reactions.

Experimental Section

All reagents were purchased from Aldrich Chemical Co., Fluka and Rhône-Poulenc and used without further purification. The milling treatments were carried out either in a Retsch PM100 Planetary Mill or in a vibrating Retsch Mixer Mill 200. FTIR spectra were recorded on a Perkin–Elmer Spectrum 100 FT-IR spectrophotometer. ^1H NMR spectra were recorded on a Bruker Avance DPX 200 MHz spectrometer and are reported in ppm using the solvent as the internal standard (CDCl_3 at 7.24 ppm). The NMR data are reported as follows: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad; coupling constant in Hz; integration. ^{13}C NMR spectra were recorded on a Bruker Avance AM 75 MHz spectrometer and are reported in ppm using the solvent as the internal standard (CDCl_3 at 77.2 ppm). Analytical samples for NMR analysis were filtered through Rotilabo[®] syringe filters (PTFE, unsterile, 0.20 μm pore size). Mass spectra were obtained by LC-MS by means of ESI using a Water Alliance 2695 LC instrument coupled to a Waters ZQ spectrometer with an electrospray source, a simple quadrupole analyser and a UV Waters 2489 detector. HRMS analyses were performed with a Q-ToF (Waters, ESI, 2001) spectrometer. Enantiomeric excesses were measured by using a Beckman Coulter System Gold 126 Solvent Module HPLC machine and System Gold 168 Detector with a 4.6 \times 250 mm Daicel Chiralpak OD columns using *n*-hexane and 2-propanol as solvents. ICP-MS analyses were realised by the Service Central d'Analyse of the CNRS. Atomic absorption analyses were realised on a Philips Pye Unicam SP9 spectrometer. Samples were placed under an air/acetylene atmosphere.

General procedure for the acylation of N-, O-, S- and C-nucleophiles

The carboxylic acid (1.5 mmol) and CDI (243 mg, 1.5 mmol) were introduced into a 12 mL stainless-steel grinding bowl with 50 stainless-steel balls (5 mm diameter). The bowl was closed and subjected to grinding for 5 min in the planetary ball mill operated at 500 rpm. Then the nucleophile (1.35 mmol) was added. The bowl was closed and subjected to grinding for 10 min in the planetary ball mill operated at 500 rpm. Deionised water (4 mL) was added and the bowl was closed and subjected to grinding for 5 min in the planetary ball mill operated at 500 rpm. After this treatment, the resulting fine suspension was filtered, washed with deionised water and then dried under vacuum over P_2O_5 to obtain the final product.

Synthesis of *N*-benzylhydrocinnamide

Following the general procedure, 3-phenylpropionic acid (0.225 g, 1.5 mmol) was used as the acid and benzylamine hydrochloride (0.194 g, 1.35 mmol) as the nucleophile. *N*-Benzylhydrocinnamide was recovered as a white solid (0.302 g, 94%). M.p. 79–80 °C (lit.^[30] 80 °C); ^1H NMR (200 MHz, CDCl_3): δ = 7.38–7.12 (m, 10H), 5.60 (brs, 1H), 4.42 (d, J = 5.7 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 2.54 ppm (t, J = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 172.1, 140.9, 138.3, 128.7, 128.6, 128.5, 127.8, 127.5, 126.3, 43.6, 38.5, 31.8 ppm; MS (ESI): m/z : 240.1 $[M+H]^+$.

Synthesis of *N*-benzylbenzamide on a 22.5 mmol scale with rubber balls

Benzoic acid (3.053 g, 25 mmol) and CDI (4.062 g, 25 mmol) were introduced into a 250 mL stainless-steel grinding bowl with 10 rubber balls (18 mm diameter). The bowl was closed and subjected to grinding for 5 min in the planetary ball mill operated at 500 rpm. Then benzylamine hydrochloride (3.231 g, 22.5 mmol) was added. The bowl was closed and subjected to grinding for 10 min in the planetary ball mill operated at 500 rpm. Deionised water (40 mL) was added and the bowl was closed and subjected to grinding for 5 min in the planetary ball mill operated at 500 rpm. After this treatment, the fine suspension was transferred onto a glass frit, washed with deionised water and dried under vacuum over P_2O_5 to obtain *N*-benzylbenzamide as a white solid (4.33 g, 91%, corrected yield based on the content of contaminant). M.p. 104–105 °C (lit.^[31] 104 °C); ^1H NMR (200 MHz, CDCl_3): δ = 7.82–7.73 (m, 2H), 7.53–7.22 (m, 8H), 6.38 (brs, 1H), 4.64 ppm (d, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 167.8, 138.4, 134.6, 131.8, 129.0, 128.8, 128.1, 127.8, 127.2, 44.3 ppm; MS (ESI): m/z : 212.2 $[M+H]^+$.

Synthesis of Teriflunomide^[32]

5-Methylisoxazole-4-carboxylic acid (191 mg, 1.5 mmol) and CDI (243 mg, 1.5 mmol) were introduced into stainless-steel grinding bowl with 50 stainless-steel balls (5 mm diameter). The bowl was closed and subjected to grinding for 20 min in the planetary ball mill operated at 500 rpm. Then 4-trifluoromethylaniline hydrochloride (267 mg, 1.35 mmol) was added. The bowl was closed and subjected to grinding for 5 h in the planetary ball mill operated at 500 rpm, with 1 min break every 10 min and inversion of the rotation direction after each break. Deionised water (4 mL) was added and the bowl was closed and subjected to grinding for 5 min in the planetary ball mill operated at 500 rpm. After this treatment, the fine suspension was transferred to a round-bottomed flask, the pH was adjusted to 1 with concentrated hydrochloric acid and the suspension was stirred with a magnetic stirrer for 24 h. The suspension was then filtered and dried under vacuum over P_2O_5 to obtain a white solid. 2-Cyano-3-hydroxy-*N*-(4-trifluoromethylphenyl)-2-butenamide (Teriflunomide) as the major tautomer was recovered as a white solid (0.297 g, 81%). M.p. 230–232 °C; ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): δ = 10.97 (m, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 2.23 ppm (s, 3H); ^{13}C NMR (150 MHz, $[\text{D}_6]\text{DMSO}$): δ = 187.3, 166.5, 142.1, 126.3, 126.0, 123.7, 123.3, 122.7, 120.7, 120.2, 119.4, 80.5, 23.9 ppm; MS (ESI): m/z : 271 $[M+H]^+$.

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Keywords: acylation • amides • green chemistry • mechanochemistry • solvent-free synthesis

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