Mechanochemical 1,1'-Carbonyldiimidazole-Mediated Synthesis of Carbamates

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ABSTRACT: 1,1'-Carbonyldiimidazole (CDI) was used as an eco-friendly acylation agent for the mechanochemical preparation of carbamates. The anticonvulsant *N*-methyl-*O*-benzyl carbamate was obtained in a vibrational ball-mill, while planetary ball-mill was suitable to develop a new sustainable method to access *N*-protected amino esters with no racemization. Compared to the synthesis in solution, mechanochemistry proved to be a powerful tool enhancing the reactivity of both alcohol and carbamoyl-imidazole intermediate, under mild conditions, without the need of activation as usually reported for solution synthesis. This new technology provides a sustainable method for the synthesis of carbamates using 1,1'-carbonyldiimidazole.

KEYWORDS: Mechanochemistry, Carbamates, 1,1'-Carbonyldiimidazole, Amino esters, Protecting groups, Anticonvulsant

INTRODUCTION

The needs to develop new green and sustainable methods and processes¹ for a chemistry “benign by design”^{2,3} has led scientists in both academia and industry to “think chemistry differently”, using safer reagents or solvents, diminishing the generation of toxic and nontoxic waste, and limiting solvent use.⁴ Mechanochemistry^{5–9} is a strong emerging field of research to perform organic reactions in the absence of solvent.^{10–12} We have applied the ball-milling technology to the preparation of active pharmaceutical ingredients (API)^{13–16} or food additives¹⁷ starting from α -amino acid derivatives and to disclose new eco-friendly alternatives to solvent-based chemistry, for the selective protection of *N*-^{21,22} or C-terminal¹⁹ amino acid derivatives (respectively carbamates or esters), essential building blocks for peptide synthesis.²⁰

1,1'-Carbonyldiimidazole (CDI) is safe and versatile acyl transfer agent easy to handle, compared to the commonly used toxic isocyanates, (tri)phosgene, or chloroformates. Available in kilogram quantities and cheap (3 €/gram), it was successfully applied for the preparation of carbonates, ureas, amides, urethanes, esters,^{21–23} or as a coupling agent for peptide synthesis^{24–28} in solution. It is also a convenient reagent adopted in the pharmaceutical industry for the large scale preparation of API^{29,30} in clean environmental conditions, since it generates relatively innocuous and easy to remove byproducts (imidazole and carbon dioxide). Pursuing our interest in the development of eco-friendly methodologies to access organic carbamates,^{21,22} known for their applications in agrochemistry,³¹ as pharmaceuticals³² or in synthetic chemistry as protecting group for amines,^{32–35} we decided to explore CDI as the acylating agent for carbamate synthesis under

mechanochemical activation. Surprisingly, only one study reported the preparation of carbamates using CDI in a solvent-free process, where the reactants were grinded with a spatula, not suitable for a scale-up perspective.³⁶

We report herein a systematic investigation for the CDI-mediated mechanochemical preparation of various carbamates using different primary or secondary alcohol/amine combinations. The revisited and new synthesis of the anticonvulsant drug *N*-methyl-*O*-benzyl carbamate^{37,38} was successful in a vibrational ball-mill, while *N*-protected benzyloxycarbonyl- (Z)-, allyloxycarbonyl- (Alloc), or methoxycarbonyl- (Moc) amino esters were prepared in a planetary ball-mill, with no racemisation. To the best of our knowledge, this represents the first report on the CDI-mediated *N*-carbamoylation of amino esters by mechanochemistry. In a green chemistry perspective, this pathway represents a further and significant advance in the chemistry beyond the use of halogens (chloroformates), to access protected amino esters as carbamates.

RESULTS AND DISCUSSION

Two general procedures allow to access carbamates using CDI (Scheme 1): by reacting the electrophilic carbamoyl imidazole with an alcohol (Method A)^{23,39} or by nucleophilic attack of an amine on the electrophilic alkoxycarbonyl imidazole (Method B).^{23,36,40,41} Carbamoyl imidazole is the nontoxic alternative to isocyanate, while imidazole carboxylic esters safely replace chloroformates.

Scheme 1. CDI-Mediated Preparation of Carbamates

Scheme 2. Solvent-free Preparation of *N,O*-Dibenzyl Carbamate **1** Using Vibrational Ball-Milling

These approaches gave high yields of carbamates using standard solution chemistry. However, from a green chemistry point of view, the main disadvantages relies on the use of excess of reagents and harmful bases (e.g., pyridine, NaH, KOH, etc.), inert atmosphere, long reaction times (up to 24 h), and the use of volatile organic solvents (VOC) such as acetonitrile, toluene, DMF, THF, for both reaction and workup. Very recently an example of synthesis of carbamates according to Method B (Scheme 1) was also described carrying out the second step in water.³⁶

In order to reduce the environmental impact of solvent-based procedures and for understanding the mechanochemical behavior and reactivity differences between amines and alcohols, carbamate preparation was investigated using both methods and the preparation of *N,O*-dibenzyl carbamate **1** was the benchmark using a vibrational ball-mill. Since the electronic properties and/or steric effects are the same on both sides of each heteroatom, the outcome of the reaction would depend on the specific reactivity displayed by each nucleophile (amine or alcohol) attacking CDI in the first (and/or in the second) step.

Method A was investigated first: equimolar amounts of benzylamine and CDI were reacted for 1 h at 30 Hz in a stainless steel jar using 2 balls (5 mm Ø). The reaction was monitored by HPLC, showing full conversion of the starting benzylamine. Then, benzyl alcohol was added directly into the jar, together with K_2CO_3 (3 equiv), and the milling was pursued for 1 h more. The carbamoyl imidazole intermediate was fully converted, but *N,O*-dibenzyl carbamate **1** was recovered only in 76% yield (determined by 1H NMR), together with some *N,N'*-dibenzylurea (20%). Similar results were observed when the CDI/benzylamine ratio was increased or when cycled milling was set up.^{15,19} Reducing the milling time during the first step led to incomplete conversion of benzylamine.

To verify if *N,N'*-dibenzyl urea formation came from the high reactivity of benzylamine in these conditions, less reactive nucleophilic amines such as potassium phthalimide or 4-nitro aniline were used in the first step. The corresponding carbamoyl imidazoles were not observed at all. When allylamine was used, benzyl *N*-allyl carbamate was not detected in the crude, but the corresponding *N,N'*-diallylurea—a potent inhibitor of tumor growth⁴²—was obtained in 94% yield after precipitation in 10% aqueous citric acid.

Aiming to drive the reactivity of the system to prevent the formation of urea byproduct, preparation of *N,O*-dibenzyl carbamate **1** was investigated by reducing the vibration frequency at 25 Hz for both steps. Although, the reaction

time was doubled for both steps, the yield dropped to 60% and urea formation increased (36%, determined by 1H NMR). Increasing the number of balls to four was detrimental, leading to *N,N'*-dibenzylurea with a 100% selectivity (and yield). We speculated that less violent shocks would reduce the kinetic of formation of urea versus carbamate: stainless steel jars were replaced by less hard and dense materials such as Teflon or polycarbonate. Unfortunately, the results were not improved and no trace of *N,O*-dibenzyl carbamate **1** was detected in the crude at 30 Hz.

In solution, carbamoyl imidazole intermediates (Method A, Scheme 1) are not reactive enough toward nucleophilic attack: activation either by alkylation of the distal nitrogen of the imidazole nucleus⁴³ and/or by deprotonation of the alcohols by strong inorganic bases (NaOH or NaH 60% in mineral oil³⁸) in the second step, along with prolonged reaction times (up to 1 day) and heating, were necessary to afford carbamates. In contrast, mechanochemistry allowed the preparation of carbamate **1** in a satisfying yield, in mild conditions, and shorter reaction times, using no harmful reactants, with no need to further activate the reactants.

Taking into account that (i) the strong mechanochemical activation was not suitable for synthesis of carbamates starting from more nucleophilic amines compared with analogous alcohol (Method A, Scheme 1) (ii) alcohols can react with CDI in the first step to afford imidazole carboxylic ester (Method B, Scheme 1), changing the order of the reaction sequence would be a simple alternative to overcome the limitations experimented during Method A.

Again, benzyl alcohol and benzyl amine were selected as the two nucleophilic unit for the one pot/two step reaction leading to *N,O*-dibenzylcarbamate **1** (Scheme 2).

Benzyloxycarbonylimidazole intermediate **1a** was formed straightforwardly in only 15 min at 30 Hz with full conversion of the benzyl alcohol (the reaction was monitored by HPLC). Benzylamine was added directly into the jar after the first step, without isolation or purification of the imidazolyl intermediate and the mixture was ball milled further.

In the presence of a stoichiometric amount of CDI, compound **1** was formed in good yield (80% determined by 1H NMR), but a byproduct was detected in the crude after the first step. Identified as dibenzylether, the impurity could be formed according to a decarboxylation mechanism previously observed in some mechanochemical reactions.¹⁹ However, the amount of CDI seemed to be important: increasing the quantity to 2 equiv, in the same reaction conditions at 30 Hz, the formation of dibenzylether was suppressed and *N,O*-

Table 1. Reaction Scope for the One-Pot/Two-Step Preparation of *N,O*-Disubstituted Carbamates in a Vibrational Ball-Mill^{a,b}

$R^1-OH \xrightarrow[30\text{ Hz, 15 min}]{CDI\ (2.0\ equiv)} R^1-O-C(=O)-N \begin{array}{c} \diagup \\ \diagdown \end{array} N \xrightarrow[30\text{ Hz, 90 min}]{R^2NH_2\ (1.0\ equiv),\ K_2CO_3\ (1.0\ equiv)} R^1-O-C(=O)-NH-R^2$ <p> $1a\ R^1 = PhCH_2$ $10a\ R^1 = C_6H_{11}$ </p> <div style="border: 1px dashed black; padding: 5px; display: inline-block;"> $2\ N \begin{array}{c} \diagup \\ \diagdown \end{array} NH + H_2O \rightarrow CO_2$ Potassium citrate Waste after work-up </div>				
Entry	R^1-OH	R^2-NH_2	Product	Yield (%) ^{c,d}
1	PhCH ₂ -	PhCH ₂ -		1 79 (83) ⁴⁸
2		CH ₂ =CH-CH ₂ -		2 Quant. (74) ⁴⁹
3		CH ₃ CH ₂ - ^e		3 Quant. (93) ⁵⁰
4		<i>c</i> -C ₆ H ₁₁ -		4 72 (93) ⁵¹
5		CH ₃ - ^e		5 100 (87) ³⁸
6	CH ₂ =CH-CH ₂ -	PhCH ₂ -		6 92 (70) ⁵²
7		CH ₂ =CH-CH ₂ -		7 73 (n.r.) ^f
8		<i>c</i> -C ₆ H ₁₁ -		8 72 (37) ⁵³
9	CH ₃ -	PhCH ₂ -		9 99 (84) ⁵⁴
10		<i>c</i> -C ₆ H ₁₁ -		10 41 (80) ³⁹
11	<i>c</i> -C ₆ H ₁₁ -	PhCH ₂ -		11 90 (81) ⁴⁸
12		CH ₂ =CH-CH ₂ -		12 90 (n.r.) ^f
13		CH ₃ CH ₂ - ^e		13 92. (n.r.) ^f

^aTypical procedure using 5 mL stainless steel jar, 2 stainless steel balls (5 mm diameter) in a vibrational ball-mill at 30 Hz: (step 1) alcohol (0.58 mmol) and 1,1'-carbonyldiimidazole (1.17 mmol) for 15 min; (step 2) amine (0.58 mmol) and K₂CO₃ (0.58 mmol) for 90 min. ^bMilling load (ML) was kept constant at 81.3 mg/mL. ^cIsolated yields after workup. ^dYields in solution with miscellaneous methods. ^eThe RNH₂·HCl (0.58 mmol) and K₂CO₃ (1.17 mmol) were used. ^fn.r. = not reported.

dibenzyl carbamate **1** was recovered in 79% yield after a simple workup based on precipitation by addition of aqueous citric acid, also effective for elimination of the excess of CDI and of two equivalents of imidazole as salts (entry 1, Table 1).

The strong activation provided by mechanochemistry allowed to access *N,O*-dibenzyl carbamate **1** starting from a relatively poor nucleophile like an alcohol, in very mild conditions compared to solvent-based protocols, avoiding the use of strong bases (to generate a more nucleophilic

Scheme 3. Plausible Mechanism Leading to *N*-Methyl-*O*-benzyl Carbamate 5

alcoholate), large excess of amine or the need to activate the imidazolidine carboxylic ester (by alkylating the distal nitrogen of the imidazole nucleus^{44,45} or by displacement of the imidazole by toxic pyridinium salts⁴⁶).

It is known that benzyl imidazole carboxylic ester **1a** is thermally unstable and decomposes in solution into *N*-benzyl imidazole with evolution of carbon dioxide, which is the driving force of the side-reaction.²³ This side-reaction was not observed under mechanochemical conditions, as shown by the LC/MS analyses of the crude mixture for both steps of the synthesis.

Since no more optimization was necessary, in order to investigate whether this approach was of general applicability, other imidazole carboxylic esters were prepared in situ using methanol, allyl alcohol, or cyclohexanol in the first step and milled together with various primary and secondary amines in the same mechanochemical conditions (Table 1).

The method proved to be general for the solvent-free preparation of carbamates: various combinations of primary or secondary alcohols with amines (aliphatic, aromatic, primary, or secondary) reacted straightforward, leading to the corresponding carbamates in very good yields. Reactions were monitored by HPLC, following the full conversion of the corresponding imidazole carboxylic ester intermediates during the second step, while the final products were generally recovered pure after a simple work-up based on precipitation by addition of aqueous citric acid^{15,18,19} (for solid carbamates) or by liquid–liquid extraction (for liquid carbamates), using ecofriendly solvents such as dimethylcarbonate (DMC) or AcOEt. This procedure allowed to reduce the costs of synthesis compared to methods in solution (one-pot/two-step reaction), with higher yields, producing nontoxic waste products (water-soluble imidazole, gaseous CO₂ and potassium citrate, which is a food additive and a medication) while purification by column chromatography was in general, not necessary.

Benzoyloxy- and cyclohexyloxy imidazole esters (**1a**, 86% yield and **10a**, 94% yield respectively) esters could also be isolated by precipitation in acidic water after the first step, in high and comparable yields to solution synthesis (Table 1). This gives clear evidence of their stability: they could be stored at room temperature without decomposition and they could be also used in the next step directly, even without elimination of imidazole (one equivalent) issued from the first step.

Although the steric hindrance around the imidazolyl moiety was not problematic to access the imidazolidine carboxylic esters from primary (entries 1–10) or secondary alcohols (entries 11–13), sterically hindered tertiary alcohols such as *t*-BuOH or 1-adamantol were not reactive at all in the first step, even in the presence of strong base (KOH) or using the corresponding alkoxide (e.g.: *t*-BuOK). This behavior is in contrast with solution synthesis,^{41,47} leading to *t*-butyl imidazole carboxylic ester in these conditions, or by water-assisted grinding.³⁶

The steric hindrance might drive the reactivity of the entering amine in the second step (entries 4, 8, and 10).

Indeed, carbamates formed by reacting a secondary amine (cyclohexylamine) led to average lower yields (entries 4, 8, and 10) compared to those obtained by using primary amine as nucleophiles, on the same imidazole carboxylic ester derivative. This was further confirmed by comparing the yield obtained for pair of carbamates with inverted alkyl substituents on the heteroatoms: *N*-cyclohexyl-*O*-benzyl carbamate **4** (72%, entry 4) and *N*-benzyl-*O*-cyclohexyl carbamate **11** (90%, entry 11) or *N*-cyclohexyl-*O*-allyl carbamate **8** (72%, entry 8) and *N*-allyl-*O*-cyclohexyl carbamate **12** (90%, entry 12). Higher yields were obtained when the cyclohexyl group was introduced as the alcohol moiety, ruling out any dependence on electronic effects on the side of the amine.⁴⁸ In fact, in the absence of steric hindrance, the twin carbamates **2** and **6** were obtained in comparable yields (entries 2 and 6) for inverted alkyl substituents.

We were pleased to find that Method B applied straightforward, also for the mechanochemical preparation of *N*-methyl-*O*-benzyl carbamate **5** (entry 5), biologically relevant for its anticonvulsant properties,³⁷ in higher yield (99%) and milder reaction conditions compared to solution synthesis (87%) according to Method A,³⁸ requiring long reaction times (18 h) and activation of the alcohol by hydrides. The nucleophilic MeNH₂ is a gas at room temperature or above, thus not suitable as reactant, escaping the shocks⁵⁵ during the milling. The benzyloxycarbonylimidazole intermediate **1a** (formed during the first step) could react with the solid (but non-nucleophilic!) methyl amine hydrochloride salt in the presence of solid base K₂CO₃, according to a general base catalysis mechanism, as plausibly suggested in Scheme 3.

It can be assumed that the benzyloxycarbonylimidazole ester **1a** and methyl amine hydrochloride were in close vicinity one to each other due to hydrogen bonding, enhancing the electrophilicity of the carbonyl group (A). Helping the removal of the hydrochloride salt, the first equivalent of base will provide a small concentration of MeNH₂ by deprotonation^{38,56} (B) while the second equivalent will be involved in proton transfer for the benzyloxycarbonyl imidazole ester **1a** activation by protonation of imidazole (C).⁵⁶ The plausibility of a general base catalysis mechanism was assumed considering that no reaction was observed by the direct reaction of the ammonium salt in the absence of base.

In most of the cases, the mechanochemical preparation of carbamates **1–13** by the general Method B, led to higher yields compared to the syntheses in solution by using miscellaneous methodologies, with the additional advantage that purification by column chromatography was in general not necessary.

Unfortunately, hydroxylamine hydrochlorides or substituted hydrazides were not reactive with benzyloxy imidazole carboxylic ester **1a** in the second step, except for *t*-butyl carbazate, which afforded *N*¹-carboxylbenzyl-*N*²-*tert*-butoxycarbonyl hydrazine in moderate (nonoptimized) yield (44%), opening new perspectives for the solvent-free preparation of

Table 2. CDI-Mediated Preparation of *N*-Protected Amino Ester in a Planetary Ball-Milling^{a,b}

entry	R ¹ -OH	<i>L</i> -amino ester ^c	ML (mg/mL)	carbamate derivative	yield (%) ^d	
1	PhCH ₂	H-Phe-O ^t Bu	92.3	Z-Phe-O ^t Bu	14	94
2		H-Leu-O ^t Bu	91.6	Z-Leu-O ^t Bu	15	94
3		H-Cys(Bn)-OMe	92.4	Z-Cys(Bn)-OMe	16	94
4		H-Thr(O ^t Bu)-OMe	91.3	Z-Thr(O ^t Bu)-OMe	17	72
5	CH ₂ =CHCH ₂	H-Phe-O ^t Bu	92.6	Alloc-Phe-O ^t Bu	18	96
6		H-Leu-O ^t Bu	91.8	Alloc-Leu-O ^t Bu	19	93
7		H-Cys(Bn)-OMe	98.9	Alloc-Cys(Bn)-OMe	20	94
8	CH ₃ ^e	H-Phe-O ^t Bu	93.2	Me-Phe-O ^t Bu	21	97
9		H-Leu-O ^t Bu	92.0	Me-Leu-O ^t Bu	22	87
10		H-Cys(Bn)-OMe	93.3	Me-Cys(Bn)-OMe	23	94

^aTypical procedure using 12 mL stainless steel jar, 25 stainless steel balls (5 mm diameter) in a planetary ball-mill at 450 rpm: (step 1) alcohol (0.58 mmol) and 1,1'-carbonyldiimidazole (1.17 mmol) for 15 min; (step 2) *L*-amino ester hydrochloride salt (0.58 mmol) and DIPEA (1.17 mmol, 204 μ L) for 2 h. ^bML = milling load. ^cStarting *L*-amino esters were hydrochloride salts. ^dIsolated yields after workup.

^e(Step 2) methanol (0.58 mmol) and 1,1'-carbonyldiimidazole (1.17 mmol) were ground twice by 15 min cycles, with a pause of 2 min between the two cycles.

hydrazines with orthogonal protecting groups on each nitrogen atom.

The methodology illustrated so far was flexible enough to prepare *N*-protected benzyloxycarbonyl- (*Z*)-, allyloxycarbonyl- (Alloc), or methoxycarbonyl- (Moc) amino esters in a one-pot/two steps fashion, just reacting the suitable alcohol with CDI in the first step, followed by the addition of the amino ester derivative in the second step.

Although CDI has been employed to prepare carbamoyl derivatives of α -amino acid esters^{57–59} or nucleosides⁶⁰ in solution (Method B, 50 °C for 5 h or longer), no example of mechanochemical reaction has been described so far.

First attempts to prepare Z-Phe-O^tBu **14** (Table 2, entry 1) in a vibrating ball-mill by reacting benzyl alcohol and CDI in the first step, followed by addition of *L*-phenylalanine *t*-butyl ester hydrochloride and K₂CO₃, according to the procedure illustrated so far for the preparation of carbamates in Table 1, were unsuccessful.

Despite many trials, vibrating ball-mill proved to be unsuitable to promote the full conversion of benzyloxycarbonyl imidazolidine **1a** intermediate. Several technical and process parameters were investigated to drive the reaction to completion including the frequency (up to 30 Hz), the milling time (up to 4 h), the grinding materials for balls and jars (stainless steel, zirconium oxide, or tungsten carbide), size and number of milling balls (up to four with variable diameters), or mode of operation (continuous or cycled). In all cases, unreacted intermediate **1a** remained in the crude and the *Z*-protected amino ester **14** was always recovered in moderate yield (44%) together with the urea byproduct. Improvements were not possible even when the liquid base diisopropylethylamine (DIPEA) was used instead of solid K₂CO₃.

Based on our previous findings,^{15,18,19} the synthesis of Z-Phe-O^tBu **14** was tested in a planetary ball-mill, speculating that differences in pressure and stress phenomena during milling could drive the reaction to completion. The best reaction conditions are illustrated in Table 2.

Preparation of imidazole carboxylic esters in the planetary ball-mill did not require any adjustment in terms of milling time

for both steps, compared to the conditions already optimized using the vibrating ball-mill. The alcohol and CDI were milled at 450 rpm for 15 min, affording the corresponding imidazolyl intermediate. In the case of volatile alcohols such as methanol, that could vaporize during the milling, thus escaping the shocks,⁵⁵ the milling was set in two cycles of 15 min each (with a pause of 2 min in between) to reduce the probability that methanol would vaporize due to the high pressure (at the contact point of the shocks) and heat that might be generated during milling. In the second step, the amino ester hydrochloride was added, together with K₂CO₃ as a base (2 equiv). In comparison with the previous data in Table 1, where only one equivalent of base was used, herein, the second equivalent was necessary to deprotonate the starting amino ester to switch the reactivity of the amine salt to a nucleophilic species, able to react with the imidazole carboxylic ester intermediate. Z-Phe-O^tBu **14** was obtained in 78% yield. However, the use of K₂CO₃ was associated with some problems related to the physical state of the mixture, which became too sticky, hampering the milling, leading to incomplete conversion of the benzyloxycarbonyl imidazole intermediate **1a**, thus affecting the yield.

Considering that one equivalent of imidazole was generated in the mixture after the first step, possibly able to deprotonate the amine presents in the form of the hydrochloride salt, and that a second equivalent was liberated in situ during the second step, the reaction was also tested in the absence of added base, speculating that an autocatalyzed/base regenerating system⁶¹ might occur. However, no reaction was observed between the imidazole carboxylic ester **1a** and HCl·H-Phe-O^tBu, showing that imidazole (p*K*_a = 6.95) was not basic enough to abstract the proton from the amino ester hydrochloride (p*K*_a = 7.11 for HCl·H-Phe-O^tBu), as the relative p*K*_a values in solution indicated. Being aware that the reaction could proceed in the presence of K₂CO₃ (p*K*_a = 10.25), a liquid base having similar value of p*K*_a was used. In the presence of DIPEA (p*K*_a = 10.5), formation of protected amino ester was straightforward and the reaction went to completion, leading to Z-Phe-O^tBu **14** in good yield (94%, Table 2, entry 1).

It is worth to underline that irrespective of the pK_a values, useful to compare the relative basicity of two bases in solution, in the absence of solvent, the better reactivity (and yield) using DIPEA was probably due to other specific effects similar to those evoked during liquid-assisted grinding (LAG), relying on the physical state of the base (a liquid). This was also confirmed by the results obtained when the reaction was tested in the presence of solid K_2CO_3 ; carbamate was formed (78%) but the conversion of the alkoxycarbonyl imidazole intermediate was lower, even after extended reaction times (6 h).

For all these reasons, solid K_2CO_3 was replaced by liquid DIPEA, a base commonly used in peptide synthesis. This resulted in a successful choice allowing the preparation of diverse Z-, Alloc-, and Moc-carbamates amino esters, in very good yield after usual work up (Table 2). The final products 14–23 displayed full orthogonality of the protecting groups. The reaction was general and independent of the alcohol/amino ester combination. Surprisingly, when allyl alcohol was reacted with L-H-Leu-OMe, only urea was formed, instead of the desired protected amino ester (by comparison with entry 6).

It is well-known that in solution CDI reacts with *t*-BuOH leading to *t*-butyl imidazole carboxylic ester, a useful reagent for the preparation of the corresponding Boc-protected amino acids.⁶² Again, although vibrating ball-mill was not suitable to *t*-butyl imidazole carboxylic ester, planetary milling proved to be more effective. An excess of *t*-butanol or potassium *t*-butoxide (*t*-BuOK) was reacted with CDI in the first step. Because of the hindrance of the alcohol, milling time was extended to 1h (instead of 15 min). HPLC monitoring during the first step, followed by LC/MS analyses, showed formation of the corresponding *t*-butyl imidazole carboxylic ester intermediate. Then, in two parallel experiments, either L-H-Phe-OMe or L-H-Cys(Bn)-OMe was added into the jars and milled at 450 rpm for 2 h. The corresponding Boc-protected amino esters were obtained in low yield (30%), due to an incomplete conversion of the imidazole intermediate, possibly due to a high steric hindrance around the carbonyl undergoing the nucleophilic attack, hampering the reaction to proceed. This aspect will be further investigated in a separate study.

Possible racemization was also investigated by chiral HPLC analyses in the case of Z-Phe-O^tBu 14 (entry 1): the reaction was found to be stereoconservative in nature with retention of the optical purity (>99% ee),⁶³ with promising applications of the methodology herein illustrated for the preparation of API.⁵⁹

CONCLUSIONS

In summary, we have reported in this study a general and versatile green methodology based on the CDI-mediated mechanochemical one-pot/two step synthesis of carbamates. It was also successfully applied to the preparation of bioactive molecules (anticonvulsant benzyl methyl carbamate 5) in a vibrating ball-mill. *N*-protected amino ester derivatives (Z-, Alloc-, and Moc-carbamates) were also obtained straightforward under solvent-free conditions in a planetary ball-mill, with excellent yields, in mild conditions and with retention of optical purity. The mechanochemical reactions were higher yielding and faster compared to those in solution. The use of stable to air and easy to handle CDI as acyl transfer agent remains a valid and green alternative to chloroformates, preventing the production of halogenated waste, harmful to the environment. The method took also advantage of the increased reactivity of alcohols during mechanochemical activation (preventing the

use of strong bases or alkoxides like in solution synthesis), also avoiding: (i) the use of hazardous reactants for the activation of the imidazole carboxylic ester intermediate and (ii) the side-reactions experimented in solution. In most cases, the final products were obtained after a simple and eco-friendly workup based on precipitation of the carbamates by aqueous treatment with 10% citric acid, leading to a nontoxic waste, i.e., potassium citrate, both a food additive and a drug. We are convinced that the new and green methodology herein described for the preparation of *N*-protected amino esters as carbamates is a valid and general alternative to solvent-based procedures. Undoubtedly, ball milling opens up new perspectives and new reactivities for future directions in organic synthesis and for the preparation of biomolecules.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This article is dedicated to Dr. Rajender Varma on the occasion of his 65th birthday.

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