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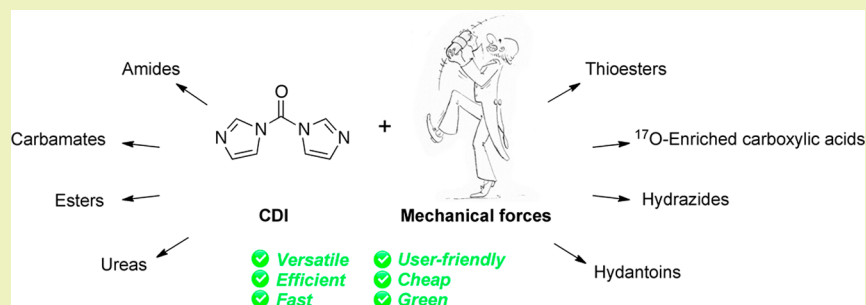
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# 1,1'-Carbonyldiimidazole and Mechanochemistry: A Shining Green Combination

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**ABSTRACT:** The application of mechanical forces to enable a chemical reaction, also known as mechanochemistry, is actually experiencing an impressive renewal of interest among the chemists community. One major advantage of this approach in organic synthesis lies in the possibility to run essentially solvent-free reactions. In recent years, some research groups have combined these types of solvent-free processes with the use of an eco-friendly reagent: 1,1'-carbonyldiimidazole (CDI). Thus, a wide range of molecules, including carboxylic acids, amines, and alcohols, could react efficiently with CDI under ball-milling conditions. By providing a vast array of products (amides, carboxylic acids, esters, ureas, hydantoin, etc.) in an efficient, fast, user-friendly, and green manner, this approach presents all the prerequisites to soon become a first choice methodology for all organic chemists. The reasons for the past and future successes of this combination are summarized, analyzed, and discussed herein.

**KEYWORDS:** CDI, 1,1'-Carbonyldiimidazole, Mechanochemistry, Ball-milling, Green chemistry, Sustainable chemistry, Solvent-free

## ■ INTRODUCTION

Although enabling the synthesis of an incredibly wide scope of molecules presenting exceptional complexity, organic synthesis generally suffers from the large amounts of toxic waste that are produced during syntheses.<sup>1</sup> Defining green metrics to evaluate the environmental impact of chemical processes has clearly revealed solvents as major contributors to the production of undesirable waste.<sup>2</sup> Yet, performing organic synthesis with less or no solvent in conventional batch reactors generally lead to material diffusion limitations. In order to solve these problems, some organic chemists have turned to the use of ball-mills. Thus, elevated mechanical forces could be applied to reaction mixtures thereby allowing for efficient mixing and reactivity of the reagents, isolation of products in high yields, reduction of the environmental impact and discovering unexpected selectivities.<sup>3,4</sup> Among the wide number of reactions that could benefit from this innovative approach, a reagent, 1,1'-carbonyldiimidazole (CDI), stood out by showing particular efficiency while generating noticeable interest from various research groups.

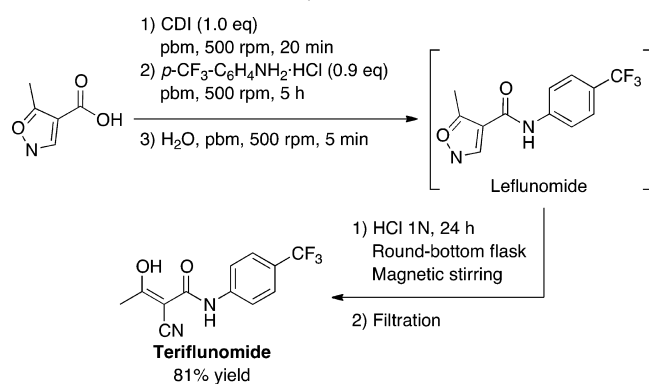
## ■ DISCUSSION

Since its very first synthesis in 1957,<sup>5,6</sup> 1,1'-carbonyldiimidazole (CDI) has been used for various applications in organic synthesis. Due to its electrophilic nature, it has mainly been

reacted with carboxylic acids, alcohols, and amines.<sup>7</sup> The safety of its side-products, namely, imidazole and carbone dioxide, are of particular interest in an era in which environmental impact is of increasing significance. Formation of 1 or 2 equiv of imidazole as a side-product also opens the possibility to avoid the use of an external base whenever required. To the best of our knowledge, the first use of CDI under solvent-free conditions was reported in 2012 and was applied to the production of acyl-imidazoles, carboxylic imidazole esters, amides, and carbamates.<sup>8</sup> Yet, the use of a spatula to mix the reagents prevented scale-up perspectives, and no control experiment was reported to exclude the possibility that formation of the intermediate and products could occur during the recovery with EtOAc.<sup>9</sup> The same year our group showed that carboxylic acids could be easily activated by CDI by using a planetary ball-mill (pbm),<sup>10</sup> thereby demonstrating this approach could be easily scaled up.<sup>11</sup> Of note, the proof that starting materials reacted during the milling treatment was obtained by sampling aliquots that were not solubilized before being analyzed by IR. After activation of carboxylic acids with CDI, the acyl-imidazole intermediates were reacted with various N-, O-, S-, and C-nucleophiles, furnishing the pure correspond-

ing products in high yields.<sup>12</sup> These latter could be recovered by filtration using only water, thereby avoiding the use of any organic solvent from reaction to product recovery. No further purification (by crystallization or column chromatography) was necessary. Besides, the acylation reactions were proved to be faster than when performed in solution, while presenting a sharply reduced environmental impact, both in terms of volume and toxicity of produced waste.<sup>12</sup> In addition, this protocol circumvented the use of dry organic solvent and nitrogen atmosphere frequently employed during synthesis in solution. As a representative and successful example of this approach, Teriflunomide, an API indicated in the treatment of multiple sclerosis,<sup>13</sup> was isolated in 81% overall yield (Scheme 1).

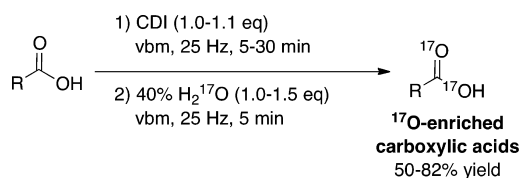
**Scheme 1. CDI-Mediated Synthesis of Teriflunomide<sup>a</sup>**



<sup>a</sup>Reproduced from ref 10 with permission from the Royal Society of Chemistry.

This approach was further applied by various research groups to the synthesis of a large array of benzoylhydrazides,<sup>14</sup> hydroxamic acids,<sup>15</sup> and glycoamides,<sup>16</sup> with strong emphasis on the efficiency, user-friendliness, and low environmental impact of the method. Of note, the capacity of this strategy to avoid traditional solubility and purification concerns was highlighted.<sup>15,16</sup> More recently, this approach was applied to the production of <sup>17</sup>O-enriched carboxylic acids in view of analysis by <sup>17</sup>O NMR spectroscopy.<sup>17</sup> Carboxylic acids were first activated by reaction with CDI in a vibrating ball-mill (vbm) to furnish the corresponding acyl-imidazoles. These intermediates were further hydrolyzed by ball-milling in the presence of small amounts of <sup>17</sup>O-enriched water (Scheme 2).

**Scheme 2. Carboxylic Acid <sup>17</sup>O-Labeling by Activation with CDI**

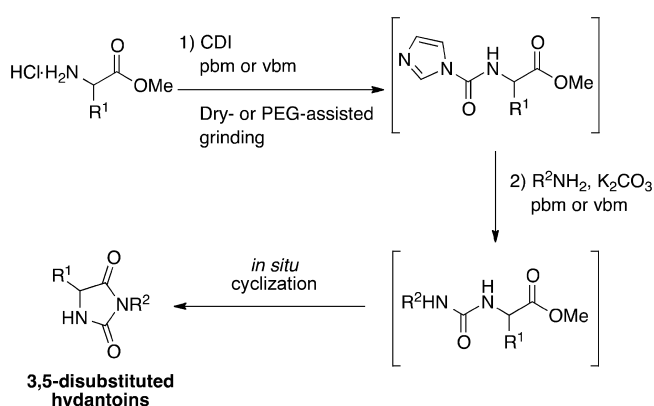


The corresponding isotopically enriched carboxylic acids were isolated in 50–82% yields after classical workup. Compared to more conventional solvent-based labeling schemes, this protocol enabled the production of <sup>17</sup>O-enriched carboxylic acids in a very efficient, user-friendly, and low-cost manner. By drastically lowering the required amounts of the costly <sup>17</sup>O-enriched water, this mechanochemical approach

opens an avenue for further research based on <sup>17</sup>O NMR spectroscopy.

Besides, CDI leads to the production of carbamates when reacted with an alcohol and an amine. Thus, ball-milling alcohols with CDI furnished carboxylic imidazole esters that reacted efficiently with amines to furnish the corresponding carbamates in high yields. This strategy could be applied to the synthesis of various *N*-Z-, *N*-Alloc- and *N*-Moc-protected amino esters, while avoiding the use of problematic and more frequently used isocyanates and/or chloroformates.<sup>18</sup> Besides, ball-milling amines with CDI furnished carbamoyl imidazole intermediates that were transformed to unsymmetrical ureas after successive addition of a second amine. These unsymmetrical ureas cyclized *in situ* to furnish hydantoin in high yields (Scheme 3).<sup>19–21</sup>

**Scheme 3. Hydantoin's Mechanochemistry by Using CDI**



An alternative route to these hydantoin could be achieved by reacting dipeptides of general formula TFA·H-AA<sub>1</sub>-AA<sub>2</sub>-OR with CDI.<sup>20</sup> Of note, PEG derivatives were identified as safe and eco-friendly liquid grinding assistants for the production of these hydantoin.<sup>21</sup> When compared to conventional syntheses of hydantoin, combining the use of CDI and ball-milling generally furnished hydantoin in a more efficient and faster manner, while avoiding conventional harsh conditions.

Overall, many reasons can explain the success of combining the use of CDI and mechanochemistry. First, CDI is a white crystalline solid available in kilogram quantities, and its stability under atmospheric conditions is sufficient to avoid tedious and time-consuming precautions.<sup>22</sup> It is cheap, and both CDI and its byproducts imidazole and carbon dioxide are safe. While CO<sub>2</sub> is efficiently evacuated from the reaction mixture due to its gaseous nature, it is worth noting that imidazole can easily be removed by simple aqueous washings. These properties were advantageously utilized, in combination with ball-milling, for the production and isolation of products otherwise difficult to isolate.<sup>15,16</sup> These properties also enabled to produce fine organic molecules without any organic solvent from reaction to product recovery.<sup>10,12</sup> Besides, it can be hypothesized that the relatively low melting point of imidazole (mp 88–91 °C) favors the formation of eutectics. This may avoid reagents diffusion limitations that sometimes happen during solvent-free ball-milling.<sup>23</sup> The formation of such eutectics is most probably the main reason why the majority of the studies mentioned herein do not report the use of external liquid grinding assistants. Similarly, production of gaseous CO<sub>2</sub> may certainly help in mixing the reagents with efficiency. In cases where production

of CO<sub>2</sub> is a driving force for the reaction, the absence of an organic solvent may also favor the release of CO<sub>2</sub> and therefore accelerate the reaction speed.<sup>24</sup> While the lower reactivity of CDI compared to similar reagents (coupling agents, isocyanates, chloroformates) has often been mentioned as a disadvantage in solution,<sup>25</sup> its utilization under solvent-free conditions is certainly filling this gap.

## ■ CONCLUSION

The versatile reactivity of CDI leads to the production of an exceptionally wide array of organic chemicals of high added value. Besides, the intrinsic properties of CDI makes it very adapted for applications in ball-milling. For these reasons, one can easily foresee that associating CDI and ball-milling will undoubtedly gain further popularity among the chemists community aiming at improving both efficiency and environmental impact of their chemical enterprise. As for CDI, the development of reagents taking into account their solvent-free, sustainable, and practical use in ball-milling will certainly contribute to the development and dissemination of green organic mechanosynthesis.

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### Notes

The authors declare no competing financial interest.

### Biographies



After having spent one year at Atofina Chemicals, USA, working on organic peroxides safety process research, Thomas-Xavier Métro graduated with a Master's degree in general chemistry from the Ecole Supérieure de Chimie Organique et Minérale and a Master's degree in medicinal chemistry from the Université de Pharmacie de Montpellier both in 2004. He achieved his Ph.D. in organic chemistry in 2008 from the Université Pierre et Marie Curie (Paris) under the supervision of Dr. Domingo Gomez Pardo and Prof. Janine Cossy, working on the rearrangement of amino alcohols and its application to the synthesis of (S,S)-reboxetine and SSR241586. After a first postdoc in process R&D at Sanofi Chimie in Sisteron and a second postdoc in medicinal chemistry at Sanofi-Aventis R&D in Montpellier, he joined the CNRS in 2011 as a Chargé de Recherche in the Green Chemistry and Enabling Technologies Team at the Max Mousseron Institute for Biomolecules (IBMM; Montpellier). Since then, his research activity is mainly based on the development of solvent-free/solvent-less

methodologies, aiming to provide the organic chemist with a set of solutions to reduce the environmental impact of his chemical enterprise.



Jean Martinez received his Ph.D. degree in organic chemistry from the University of Montpellier at the Ecole Nationale Supérieure de Chimie de Montpellier under the direction of Prof. F. Winternitz. He completed his chemical education as a postdoctoral fellow with Dr. E. Bricas, Orsay, University of Paris Sud, and then with Prof. M. Bodanszky, Case Western Reserve University, Cleveland, OH. Back in France, he was recruited as a CNRS research associate and then as a research director in Montpellier. Pursuing his investigation at the interface of chemistry and biology, he joined the University of Montpellier and was appointed a Full Professor in both organic chemistry and medicinal chemistry. He became successively the head of various research laboratories in Montpellier including the Laboratory of Chemistry and Pharmacology of Biologically Interesting Molecules, the Laboratory of Amino Acids, Peptides and Proteins. He founded the Institute of Biomolecules Max Mousseron in 2007 and acted as the director until December 2014. In 2015, in the same institute he stayed as the head of the Department of Amino Acids, Peptides and Proteins. His current research interests focus on peptide chemistry, stereoselective syntheses of biomolecules, design and production of original biomaterials, green chemistry, and biology and pharmacology of neuropeptides of the gastrointestinal tract.



Frédéric Lamaty graduated as a chemical engineer in 1988 from the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL now ESCPE, France). In 1992, he received his Ph.D. from Purdue University (West Lafayette, IN, USA) under the supervision of Professor Ei-chi Negishi in the field of Pd-catalyzed cyclizations. He then joined, as a Rhône-Poulenc postdoctoral fellow, the group of Professor Marc Julia at the Ecole Normale Supérieure in Paris to work on the synthesis of vitamin A. In 1994, he obtained a permanent position at the Centre National de la Recherche Scientifique (CNRS) in Montpellier and is currently

working as Directeur de Recherche at the Max Mousseron Institute for Biomolecules (IBMM). Since 2011, he is heading the Green Chemistry and Enabling Technologies team ([www.greenchem.um2.fr](http://www.greenchem.um2.fr)) at IBMM. His research topics in the area of catalysis, organic, and green chemistry are devoted to the synthesis of amino acids, peptides, and heterocycles, the use of alternative solvents (PEG, PEG-IL, glycerol, water), and enabling technologies (microwaves, ultrasounds, ball-milling, continuous flow) with an emphasis on mechanochemistry. He was awarded in 2011 the Prix des Techniques Innovantes pour l'Environnement ADEME-Pollutec for his activity in peptide mechanosynthesis in solvent-free conditions.

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## ■ ABBREVIATIONS

CDI, 1,1'-carbonyldiimidazole; pbm, planetary ball-mill; vbm, vibrating ball-mill

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