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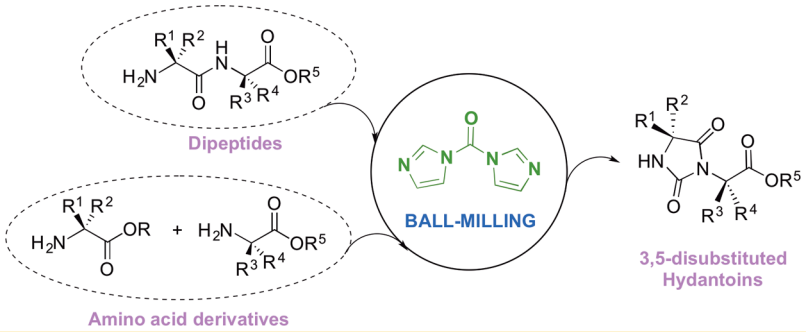
Mechanochemical Preparation of 3,5-Disubstituted Hydantoins from Dipeptides and Unsymmetrical Ureas of Amino Acid Derivatives

Laure Konnert,[†] Lori Gonnet,[†] Ivan Halasz,[‡] Jean-Simon Suppo,[§] Renata Marcia de Figueiredo,[§] Jean-Marc Campagne,[§] Fredéric Lamaty,[†] Jean Martinez,[†] and Evelina Colacino*,[†]

[†]Université de Montpellier, Institut des Biomolécules Max Mousseron UMR 5247 CNRS, ENSCM, Place E. Bataillon, Campus Triolet, cc 1703, 34095 Montpellier, France

[‡]Ruđer Bošković Institute, Bijenička cesta 54, Zagreb, Croatia

[§]Institut Charles Gerhardt Montpellier (ICGM), UMR 5253 CNRS-UM-ENSCM, Ecole Nationale Supérieure de Chimie, 8 Rue de l'Ecole Normale, 34296 Montpellier Cedex 5, France



ABSTRACT: 5-Substituted-3-(alkoxycarbonyl)alkyl-hydantoin derivatives were prepared by mechanochemistry from amino esters or dipeptides, via a 1,1′-carbonyldiimidazole-mediated one-pot/two-step cyclization reaction involving amino acid unsymmetrical urea **A** and carboxy-imidazolyl-dipeptide ester **B** intermediates. Comparative experiments in solution were also performed. The successful preparation of an antibacterial agent precursor was also investigated.

INTRODUCTION

Compounds containing the 2,4-imidazolidinedione scaffold are a well-known family of bioactive products (hydantoin family) with numerous therapeutic properties (also pesticides).[1] The hydantoin core offers numerous possibilities of substitutions, allowing building a large diversity of potential structures. In particular, 5-substituted-3-(alkoxycarbonyl)alkyl-hydantoin derivatives (Figure 1) present a particular substitution pattern, which make them interesting peptidomimetics[2] and bioactive compounds with antiepileptic, anticonvulsant, antiarrhythmic, or antibacterial properties.[1,3−5] They have been notably presented as inhibitors of dihydro-orotate dehydrogenase from *Clostridium* (*Zymobacterium*) *oroticum* for the potential treatment of parasitic diseases.[6,7]

From the synthetic point of view, these structures have been often reported as byproducts in peptide synthesis.[8−11] However, their structural and biological interests have given rise to the development of several methodologies for their preparation. The reaction of amino acid derivatives with isocyanates led to the formation of such hydantoins, after cyclization of the corresponding ureido derivatives in strong acidic conditions[5,12,5,13] (Figure 1a). *N*-alkylation with halogeno acetates and their derivatives,[14,7,15,16] and Michael addition[17] reactions, allowed the introduction of the carboxyalkyl group at the *N*-3 position of hydantoins, with a particular interest in phenytoin derivatives[3,18−20,4,17] (Figure 1b). Miscellaneous procedures reported the reaction between acetylenic diesters and isocyanides,[21] or phosphates,[22] in the presence of an hydantoin molecule (Figure 1b). The rearrangement of Boc-protected dipeptide compounds,[23] diketopiperazines,[24] seven-membered cyclopeptides,[25] and oxazolidinones[26] were also described (Figure 1c).

Due to our ongoing work on the use of mechanochemistry for the preparation of carbamates from amino acid derivatives,[27−29] and biologically relevant compounds by grinding in a ball-mill,[29,30,31] it seemed appealing to develop mechanochemical strategies to access 5-substituted-3-(alkoxycarbonyl)-alkyl-hydantoins. Specifically, our previously developed procedure on the 1,1′-carbonyldiimidazole (CDI)-mediated mechanochemical synthesis of 3,5-disubstituted hydantoins[31] might be applicable to the preparation of similar structures, via a one-pot/two-step cyclization reaction involving amino acid unsymmetrical urea **A** (Method A) or a carboxy-imidazolyl-dipeptide ester **B** (Method B) (Scheme 1).

To the best of our knowledge, Štrukil et al.[32−35] achieved the only described mechanochemical preparation of unsymmetrical (thio)-ureas from either iso(thio)cyanates or benzotriazolyl-activated

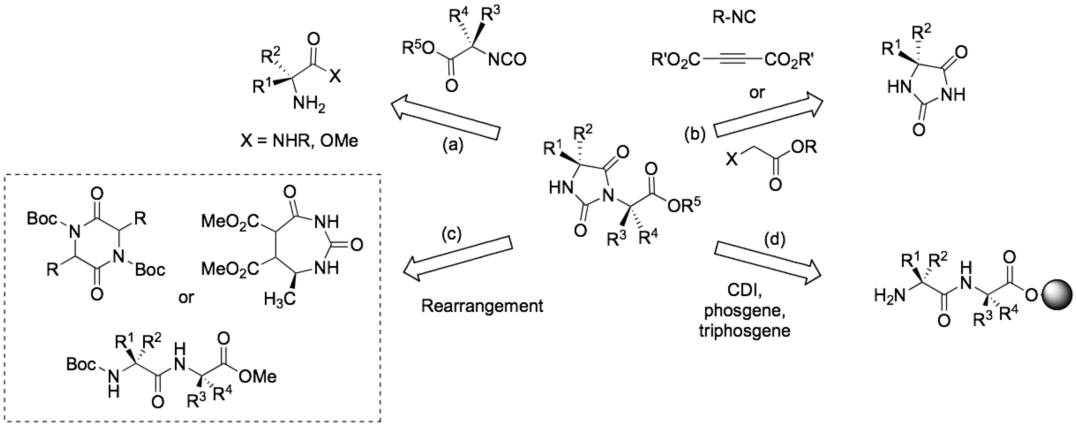
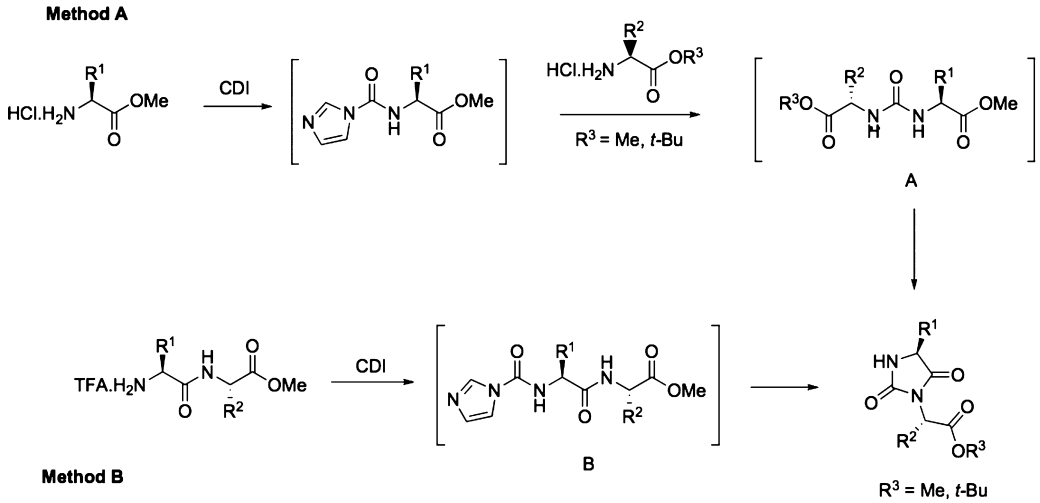


Figure 1. 5-substituted-3-(alkoxycarbonyl)alkyl-hydantoin structures.

Scheme 1. Synthesis of 5-Substituted-3-(alkoxycarbonyl)alkyl-hydantoins by Mechanochemistry



thiocarbonyls.[32] In solution, thiohydantoins were prepared from dissymmetrical thioureas derived from amino acids.[36,37] We have described the synthesis of unsymmetrical ureas containing one amino ester, from either potassium cyanate[30,29] or isocyanates,[31] but no mechanochemical desymmetrization from amino acid urea derivatives and using CDI as an activating agent has been reported so far. In solution, CDI has been used for the preparation of symmetrical[6] and unsymmetrical[38,39] ureas from amino acid derivatives. However, these synthetic methods often require the use of toxic solvents such as DMF, the use of a base such as triethylamine, and extra reagents such as methyl trifluoromethanesulfonate[40,39] to enhance the reactivity of the carboxamido intermediate.

Amino acid ureas have been reported to cyclize into hydantoins in the presence of concentrated HCl.[6,41] In only one case the symmetrical urea was formed when using CDI.[6] So far, no study has reported on the preparation of hydantoins from dissymmetrical ureas obtained from amino acid derivatives and the safe, cheap, and easy-to handle CDI (Scheme 1, method A), neither in solution nor by mechanochemistry. Furthermore, mechanochemical reaction conditions avoid the use of solvents and provide a strong activation in reactions involving CDI,[29] thus avoiding the addition of extra base or activating agents to the reaction mixture.

Another possible strategy to prepare 5-substituted-3-(alkoxycarbonyl)-alkyl-hydantoins under ball-milling conditions was to explore the reactivity of CDI toward dipeptides, instead of single amino esters, (Scheme 1, method B). Liu et al. reported the rearrangement of *N*-Boc-dipeptides into the corresponding hydantoins in solution, in the presence of triflic anhydride.[23] On solid support, the preparation of hydantoins proceeded through the formation of an isocyanate function on resin-bound peptides. This isocyanate could be generated after removal of the Fmoc-protecting group from the *N*-terminal moiety of the peptide,[42] but more generally by nucleophilic attack of this amino moiety on the triphosgene[43,44] or CDI-activated[45,9] carbonyl of the carboxylic function.

The mechanochemical pathway is an interesting alternative to solid-phase synthesis, for which the scale-up would be quite difficult (Figure 1d). We report herein two unprecedented mechanochemical synthetic routes to access 5-substituted-3-(alkoxycarbonyl)alkyl-hydantoins. The first one consists of the synthesis of unsymmetrical ureas (A) from amino esters and CDI and their one-pot cyclization into the targeted hydantoins (Scheme 1, method A). The second one describes the CDI activation of *N*-terminal moieties of dipeptides followed by cyclization (Scheme 1, method B). The disclosed methodology is a valid eco-friendly alternative (replacing the use of triphosgene)[46] to prepare 5-benzyl-3-(methyloxycarbonyl)benzyl hydantoin **2e** (Table 2, entry 5), which the corresponding carboxylic acid is an antiparasite agent, inhibitor of dihydro-orodotase dehydrogenase from *Clostridium* (*Zymobacterium*) *oroticum*.[6,7]

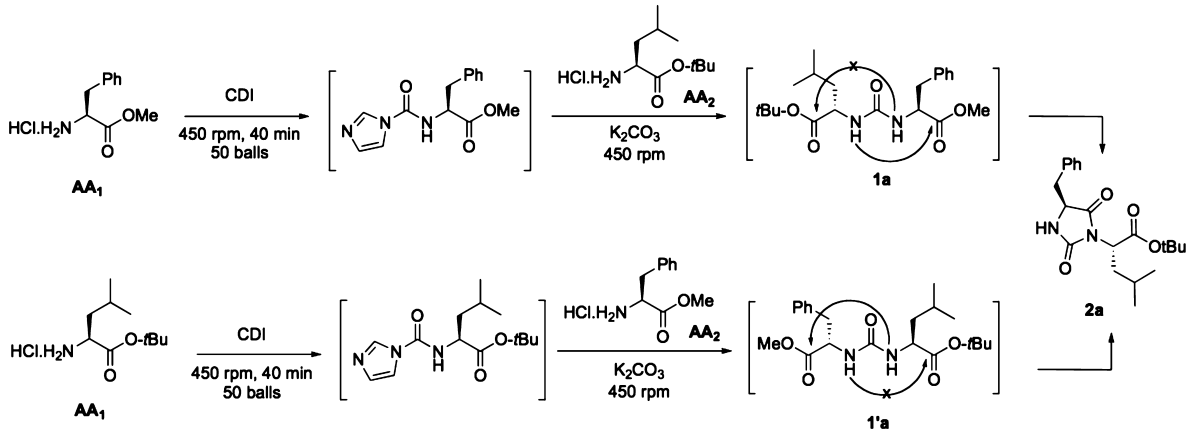
RESULTS AND DISCUSSION

Synthesis of 3-Substituted Alkoxycarbonyl Hydantoins from Unsymmetrical Ureas of Amino Esters (Method A). We have recently reported the CDI-mediated mechanochemical preparation of *N*-protected carbamates of amino esters[29] and 3,5-dialkyl substituted hydantoins,[31] in a planetary ball-mill (PBM). Relying on our precedent one-pot/two-step procedure, an amino ester hydrochloride $\mathbf{AA_1}$ was reacted with CDI, leading to the corresponding 1*H*-imidazole-carboxamido intermediate (first step) (Table 1). Milling the mixture in the presence of *α*- or *β*-amino *tert*-butyl esters $\mathbf{AA_2}$, added in the second step, led to dissymmetrical carbonyl diamino esters **1**, that were smoothly converted into hydantoins by a chemoselective base-mediated intramolecular cyclization (Tables 1 and 2). Therefore, formation of regioisomeric hydantoins could be avoided when cyclizing either by one-pot generated symmetrical carbonyl diamino esters or by means of a one-pot stepwise addition to the grinding jar containing methyl/*tert*-butyl esters (Table 1).

Strictly applying the previously described experimental conditions to the synthesis of 5-benzyl-3-(*tert*-butoxycarbonyl)-isobutyl-hydantoin **2a** led to only moderate yields; the cyclization of the unsymmetrical urea **1a** was incomplete (entry 1). Switching the addition order of the amino esters did not significantly improve the reaction yield (entry 2), however, it was increased to 63% when the second step of the reaction was carried out for 4 h at 450 rpm (entry 3). From this preliminary optimization, several combinations of amino methyl and *tert*-butyl esters were tested to scope the variety of substrates. Most of the corresponding hydantoins were obtained in satisfying to good yields (Table 2), with the exception of **2b** and **2e** (entries 2 and 5). The grinding parameters were found to be essential. Indeed, whereas good yields were obtained with **2a**, **2c**, and **2d** in a PBM, while no or low conversion was observed in the case of **2b** and **2e**. Regardless of the milling parameters set for PBM, the cyclization reaction into hydantoin **2b** could not be improved, and the yield remained moderate. Indeed, the cyclization reaction led to a mixture of the symmetrical carbonyl diamino methyl ester of valine (urea formed in the first step) and the corresponding dissymmetrical urea **1b** (formed in the second step), both structures attributed to the base of LC/MS analyses of the crude mixture. The best results were obtained using the PBM for 2 h (entry 2). It is noteworthy that the procedure was applicable to quaternary amino esters (entry 3) as well as to *β*-amino acid derivatives (entry 4) from which the hydantoin **2d** was recovered in 88% yield. The preparation of **2e**, issued from the symmetrical urea of phenylalanine methyl ester, could also be achieved in a satisfying yield of 58% using VBM (entry 5). The yield was not improved by extending the reaction time up to 6 h (52%, entry 5) or by changing the base. When Na_2CO_3, $NaHCO_3$, and triethylamine were used instead of K_2CO_3, conversion of the starting amino ester was not complete, and the cyclization reaction failed. Disappointingly, it was not possible to prepare hydantoin **2e** by performing the reaction in a PBM for 4 h. Cyclization did not occur, and only the corresponding symmetrical urea **1** was obtained, confirming that PBM was not suitable to prepare **2e** hydantoin, probably due to the sticky texture of the milling mixture. Results were not improved when variable quantities of inert grinding additives, such as NaCl,[47−49] were added to modify the mechanical properties of the mixture. As previously experimented for other organic transformations,[29,28] the differences in grinding phenomena and parameters occurring in the PBM with respect to VBM could be the explanation. Noteworthy, the carboxylic acid of compound **2e** is a dihydro-orotate dehydrogenase inhibitor[6] and thus may be easily obtained from **2e**. The workup of the reaction was very simple, as the products were recovered by precipitation/filtration by addition of water to the crude mixture in the milling jar (**2a**, **2d**, and **2e**) or by extraction in ethyl acetate (**2b** and **2c**).

Synthesis of 3-Substituted Alkoxycarbonyl Hydantoins from Dipeptides (Method B). Several TFA salts of dipeptide methyl esters **3** were synthesized following usual procedures in solution.[50] Then, they were reacted with CDI in a PBM in neat conditions without base. As described above, the reaction consisted of the nucleophilic attack of the free

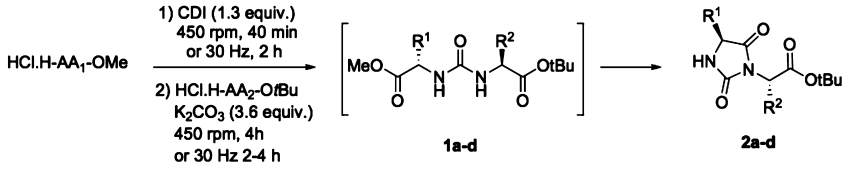
Table 1. Optimization of the Reaction Conditions for the Preparation of 5-Substituted-3-(alkoxycarbonyl)alkyl-hydantoins[a]

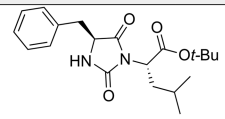
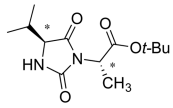
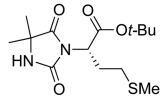
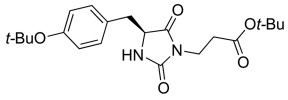
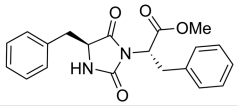


entry	AA[b] derivative **1**	AA[b] derivative **2**	reaction time (step 2) (h)	yield (%)[c] **2a**
1	HCl·H-Phe-OMe	HCl·H-Leu-O*t*Bu	2	40
2	HCl·H-Leu-O*t*Bu	HCl·H-Phe-OMe	3	47
3	HCl·H-Phe-OMe	HCl·H-Leu-O*t*Bu	4	63

[a]Conditions: (Step 1) L-*α*-amino ester $\mathbf{AA_1}$ (1 equiv) and CDI (1.3 equiv) at 450 rpm, 50 balls (5 mm, stainless steel, 5 mm Ø) for 40 min; (step 2) L-*α*-amino ester $\mathbf{AA_2}$ (1.6 equiv) and K_2CO_3 (3.6 equiv) at 450 rpm. [b]AA = Amino acid. [c]Yield of isolated compounds.

Table 2. Synthesis of 5-Substituted-3-(alkoxycarbonyl)alkyl-hydantoins from Ureas of Amino Esters



Entry	HCl.H-AA$_1$-OMe[a]	HCl.H-AA$_2$-O*t*Bu[a]	Product		Yield (%)[b] PBM	Yield (%)[b] VBM
1	HCl.H-Phe-OMe	HCl.H-Leu-O*t*Bu		**2a**	63	n.p.[c]
2	HCl.H-Val-OMe	HCl.H-Ala-O*t*Bu		**2b**[d]	43[e]	n.s.[c]
3	HCl.H-Aib-OMe	HCl.H-Met-O*t*Bu		**2c**	60	n.p.[c]
4	HCl.H-Tyr(*t*Bu)-OMe	HCl.H-β-Ala-O*t*Bu		**2d**	88	n.p.[c]
5	HCl.H-Phe-OMe	HCl.H-Phe-OMe		**2e**	n.s.[c]	58[f] (52)[g]

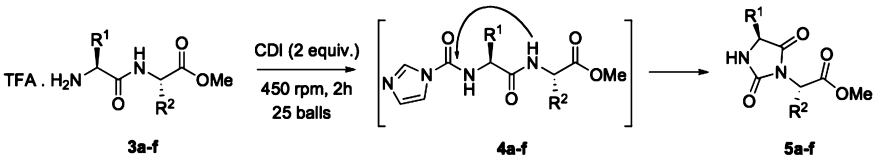
[a]The amino esters were of L-configuration. [b]Isolated yields. [c]n.p. = not performed, n.s. = not successful. [d]Mixture of diastereoisomers (dr 57:43) determined by ^{1}H NMR. [e]The second step was performed for 2 h only. [f]Conditions: HCl·H-Phe-OMe (2 equiv), CDI (1 equiv) and K_2CO_3 (3 equiv) were milled in a VBM at 30 Hz for 2 h. [g]Yield is given for 6 h reaction in the VBM.

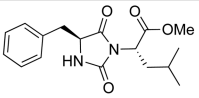
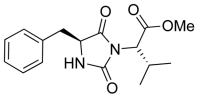
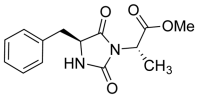
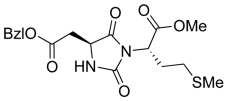
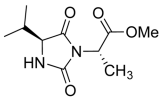
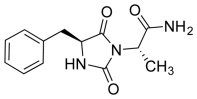
N-terminal moiety of the peptides, on the CDI activated carboxylic acid group, to afford activated 1*H*-imidazole-carboxamido species **4** that cyclized directly into the hydantoins. At this stage, we wondered if the intermediate of the reaction was either the 1*H*-imidazolyl carboxamido derivative **4** (Table 3) or the corresponding isocyanate, generated in similar procedures in solution.[51] Indeed, mechanochemistry is known to induce, in some cases, different reactivities than in the corresponding reactions in solution. By *in situ* Raman spectroscopy, it was recently demonstrated that the mechanochemical reaction between anilines and bis(benzotriazolyl)methanethione afforded the aryl *N*-thiocarbamoylbenzotriazoles that could be isolated, species that decompose instantly into isocyanates in solution synthesis.[32] By analogy to the benzotriazole intermediates, we assumed that the reaction went through the formation of intermediate **4**. Once the 1*H*-imidazole-carboxamido intermediate **4** was formed, the intramolecular nucleophilic attack of the amide peptide bond on the *C*-activated imidazolyl carboxamide led to an intramolecular cyclization reaction to produce hydantoins **5**, never described so far (Table 3).

The corresponding hydantoins were readily obtained in good yields under nonoptimized conditions (Scheme 1). The only byproducts of the reaction identified were the symmetrical urea of the dipeptides. Indeed, in the first trial, consisting of the milling of TFA·H-Phe-Leu-OMe with 2 equiv of CDI at 450 rpm for 2 h, the hydantoin **5a** was obtained in 82% yield (entry 1). NMR of the crude showed the presence of the dipeptide urea in 8% yield compared to the desired compound. A shorter time of 1 h milling decreased the yield of **5a** to 76% (entry 1), while no improvement was observed when extending the milling time to 6 h (entry 2) for compound **5b**. The reactions were performed for 2 h using dipeptide methyl esters **3b**−**e** or the amide **3f** (entries 2−6). It could be noticed that cyclization of the postulated intermediates **4** occurred without the need of a base, in contrast with solid-phase synthesis.[45] Indeed, when prepared in solution, the intermediate **4c** proved to be very unstable and difficult to isolate, undergoing fast cyclization into hydantoin **5c**. Based on our previous findings,[29] we excluded an autocatalyzed/base regenerating system, promoting the cyclization, despite the presence of 1 equiv of imidazole, generated in the mixture after the first step. Indeed, the strong activation provided by mechanochemistry allowed the direct reaction of a non-nucleophilic dipeptide (HX salt) **3** with CDI (without the need of a base to generate *in situ* a free amine). It is proposed that two sequential acid−base reactions were the driving force of the reaction, leading to intermediates **A** and postulated **B**, each having the distal nitrogen of the imidazole nucleus activated by protonation (Scheme 2).

Mechanochemistry allowed the preparation of hydantoins **5** in slightly shorter reaction times (2 h) compared to solution-based protocols (4 h under stirring), and with no need to further activate the reactants. Generally, the yields were higher under mechanochemistry, and the purification of the crude was easier. Moreover, the reaction was versatile, as dipeptides with various side chains and *C*-terminal functions (Table 3, **3f**, entry 6) were transformed into hydantoins. Product **5f** was obtained in a 29% NMR yield, but we did not succeed in its purification from the imidazole (entry 6). IR experiments confirmed that hydantoins **5** had been obtained, instead of dipeptide isocyanates, which can be prepared from phosgene or triphosgene in solution.[51] The typical absorbance band at 2270 cm^{-1} was not detectable in the crude, confirming the formation of the desired hydantoins, which

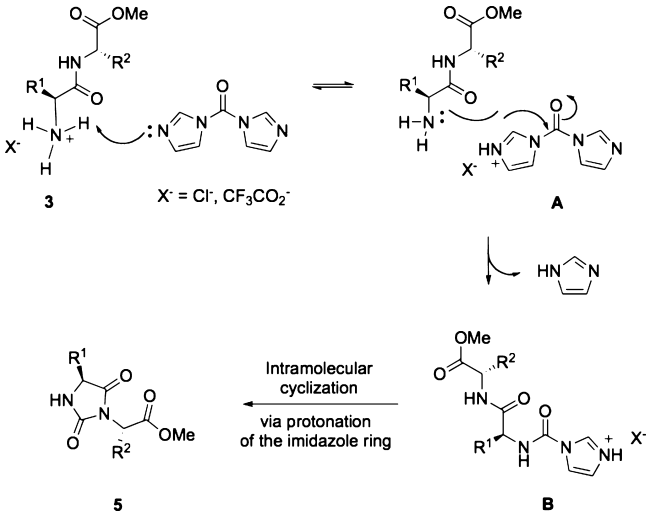
Table 3. Preparation of 5-Substituted-3-(alkoxycarbonyl)alkyl-hydantoins from Dipeptides



Entry	Dipeptide methyl ester		Product		Yield (%)[a]
1	TFA. H-Phe-Leu-OMe	**3a**		**5a**	82 (76)[b]
2	TFA. H-Phe-Val-OMe	**3b**		**5b**	70 (75)[c]
3	HCl. H-Phe-Ala-OMe	**3c**		**5c**	57 (96)[d]
4	HCl. H-Asp(OBzl)-Met-OMe	**3d**		**5d**	76
5	TFA. H-Val-Ala-OMe	**3e**		**5e**	78 (62)[d]
6	TFA. H-Phe-Ala-NH_2	**3f**		**5f**	29[e,f]

[a]Isolated yields. [b]Yield after 1 h milling. [c]Yield is given for 6 h reaction in the PBM. [d]Yield is given for synthesis in solution. [e]^{1}H NMR yield. [f]Full conversion by LC/MS analyses for synthesis in solution.

Scheme 2. Proposed Mechanism to Hydantoins 5



is in contrast with previous reports reporting formation of stable isocyanates in solution.

Method B was also applied to the preparation of compound **2e** from TFA·H-Phe-Phe-OMe, for sake of comparison with the solution procedure usually carried out in harsh conditions (triphosgene and pyridine under reflux for 12 h).[46] By mechanochemistry, the cyclization according to Method B was not possible, with or without a base, and by modifying the milling parameters (e.g., extending the reaction time or increasing the number of milling balls). It is acknowledged that new compounds or novel reactivities can be accessed using mechanochemistry, because different energetic (and mechanistic) pathways are involved compared to the synthesis in solution. In this particular case, mechanochemistry failed where solution chemistry was successful. As a consequence, the preparation of hydantoin **2e** according to our initial approach (Method A) remained the only new and alternative route to this compound by mechanochemistry.

Overall, our procedure presented a number of advantages also over the described solid-phase synthesis: (1) ball-milling allowed a solvent-free reaction that avoids the use of toxic DMF; (2) no extra base was required as the hydantoins were readily obtained by the simple mechanochemical reaction between dipeptides and CDI; (3) the postulated intermediates **4** did not require any activation by extra reagents; (4) only 2 equiv of CDI were required, which is much less than in solution reaction;[44,45] and finally (5) ball-milling provides a cheaper alternative and possible scale-up of the reaction compared to solid-phase synthesis, which was the only reported pathway for the preparation of the desired hydantoins from dipeptides. These five points support the use of mechanochemistry to prepare hydantoins with less waste production, for a more sustainable and environmental green chemistry.

■ CONCLUSIONS

We presented here two methodologies for the preparation of new structures of 5-substituted-3-(*tert*-butoxycarbonyl)alkyl-hydantoins, belonging to a class of biologically active molecules,

by mechanochemistry. In the first part, we described a novel procedure in which unsymmetrical ureas prepared from amino esters were cyclized into the corresponding hydantoins (Method A). In the second part, we presented an improved and a more environmental-friendly procedure for the synthesis of hydantoins by intramolecular cyclization of dipeptides (Method B). The key reagent of these synthetic methods was 1,1′-carbonyldiimidazole (CDI), which enabled the activation of the amino functionality of dipeptides and amino acid derivatives. The syntheses required no or few optimization, allowed the use of various substrates, afforded the new compounds in good yields, and were carried out following a more sustainable synthetic route brought about by the ball-milling technology. Moreover, compared to the previously reported methods in solution, both methodologies displayed higher atom and solvent economy, also overcoming the *N*-1/*N*-3 regioselectivity problems usually encountered in alkylation reactions of hydantoins.[16] From a more general perspective, this work contributes to advance an area recently termed as medicinal mechanochemistry,[52] with the emergence and the development of mechanochemical techniques for the preparation of API,[48,53,35] opening new trends and perspectives for the pharmaceutical industry, in "thinking chemistry differently".

■ EXPERIMENTAL SECTION

General Remarks. All reagents were commercially available and used without any further purification. L-α-amino esters were used. TFA salts of dipeptide methyl esters were synthesized following usual procedures in solution.[50] NMR spectra were recorded at room temperature with the appropriate deuterated solvent ($CDCl_3$ or d_6-DMSO). Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.27 ppm for ^{1}H and $CDCl_3$: δ = 77.04 ppm for ^{13}C NMR). *J* values are given in Hz. ^{1}H and ^{13}C NMR spectra were registered at 300 MHz and 400 MHz. HRMS measurements were performed on a TOF mass analyzer. Melting points were measured on a Büchi Melting Point 510 apparatus (or M-560 for compound **5c**) and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer equipped with high-pressure diamond cell. Optical rotation for compounds **2a−e** and **5a−e** was measured in $CHCl_3$ at λ = 589 nm (Na lamp). Analytical high-performance liquid chromatography (HPLC) was performed with a variable-wavelength diode detector using a CHROMOLITH RP18 column (50 × 4.6 mm), flow 5 mL/min, linear gradient CH_3CN in water 0−100% (+0.1% TFA) in 4.5 min. LC-MS analyses were performed with HPLC, column Onyx C_{18}, (25 × 4.6 mm), flow 3 mL/min linear gradient CH_3CN in water 0−100% (+0.1% HCO_2H) in 2.5 min. The ball-milling experiments were performed in a vibrational ball using 5 mL mill steel jar (2 stainless steel balls, 5 mm Ø) and in a planetary mill, 12 mL steel jar (25 or 50 stainless steel balls, 5 mm Ø).

General Procedure for the Synthesis of 5-Substituted-3-(tert-butoxycarbonyl)alkyl-hydantoins (Method A). Conditions in a PBM (Compounds **2a−d**): The amino acid methyl ester (1 equiv) and CDI (1.3 equiv) were added to a 12 mL stainless steel milling jar with 50 stainless steel milling balls (5 mm diameter). The reactants were milled for 40 min at 450 rpm. The amino acid *tert*-butyl ester (1.6 equiv) and K_2CO_3 (3.6 equiv) were added to the jar, and the reaction mixture was milled for 4 h at 450 rpm. Conditions in a VBM (Compound **2e**): A 5 mL stainless steel milling jar with 2 stainless steel milling balls (5 mm diameter) were used at 30 Hz for the specified time (Table 1). Distilled water was added to the jar, and the desired compounds precipitated. They were recovered either by filtration (**2a**,**d**) or by extraction of the aqueous layer with ethyl acetate (**2b**,**c**). The organic layer was washed three times with 10% aq. citric acid and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude compounds **2a−c** were further purified by column chromatography (linear gradient of EtOAc in cyclohexane from 0 to 20%).

*(S)-tert-Butyl 2-((S)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)-4-methylpentanoate **2a** (Table 2, Entry 1).* The reaction scale was 0.83 mmol (188.3 mg, 63% yield). White solid, mp 160−162 °C, $[\alpha]_D^{28}$ −8.77 (*c* = 5.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34−7.19 (m, 5H), 5.90 (s, 1H), 4.56 (dd, *J* = 11.5 Hz, *J* = 4.4 Hz, 1H), 4.28 (dd, *J* = 8.0 Hz, *J* = 3.3 Hz, 1H), 3.28 (dd, *J* = 13.9 Hz, *J* = 3.6 Hz, 1H), 2.90−2.83 (m, 1H), 2.16−2.04 (m, 1H), 1.77−1.68 (m, 1H), 1.44 (s, 9H), 0.84 (d, *J* = 6.6 Hz, 6H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 172.7, 168.6, 156.3, 135.5, 129.4, 129.1, 127.6, 82.5, 58.3, 52.0, 38.3, 36.8, 28.1, 25.0, 23.3, 21.2; MS ESI-(+): *m/z* 361 $[M + H]^+$, 337, 305, 259; HRMS ESI-(+): calcd for $C_{20}H_{28}N_2O_4$ $[M + H]^+$ 361.2127, found 361.2127.

*(S)-tert-Butyl 2-((S)-4-Isopropyl-2,5-dioxoimidazolidin-1-yl)-propanoate **2b** (Table 2, Entry 2).* The reaction scale was 1.49 mmol; (175.2 mg, 43% yield). Mixture of diastereoisomers (maj.:min. 57:43). Colorless oil, $[\alpha]_D^{28}$ + 0.40 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.57−6.55 (m, 1H), 4.66−4.60 (m, 1H, maj. and min.), 3.93−3.91 (m, 1H, maj. and min.), 2.25−2.21 (m, 1H, maj. and min.), 1.54 (d, *J* = 7.3 Hz, 3H, maj.), 1.52 (d, *J* = 7.3 Hz, 3H, min.), 1.43 (s, 1H, maj.), 1.42 (s, 1H, min.), 1.05 (d, *J* = 7.0 Hz, 3H, maj.), 1.04 (d, *J* = 7.0 Hz, 3H, min.), 0.95−0.92 (m, 3H, maj. and min.); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): *maj.*: 173.1, 168.7, 157.8, 82.6, 62.6, 48.9, 30.6, 28.2, 19.2, 16.4, 15.1; *min.*: 173.1, 168.7, 157.7, 82.6, 62.7, 48.9, 30.6, 28.2, 19.1, 16.3, 15.1; MS ESI-(+): *m/z* 271 $[M + H]^+$, 247, 215, 197, 169; HRMS ESI-(+): calcd for $C_{13}H_{22}N_2O_4$ $[M + Na]^+$ 293.1477, found 293.1474.

*(S)-tert-Butyl 2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-4-(methylthio)butanoate **2c** (Table 2, Entry 3).* The reaction scale was 0.86 mmol (161.9 mg, 60% yield). Waxy white solid, mp 83−85 °C, $[\alpha]_D^{28}$ −8.82 (*c* = 4.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.21 (s, 1H), 4.69 (t, *J* = 7.3 Hz, 1H), 2.54−2.36 (m, 4H), 2.08 (s, 3H), 1.45, 1.44, and 1.43 (s × 3, 15H, 2 × CH_3 and *t*-Bu); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 177.0, 167.8, 156.0, 82.7, 58.8, 52.2, 31.1, 28.1, 28.0, 25.1, 15.5; MS ESI-(+): *m/z* 317 $[M + H]^+$, 261, 243, 215, 167; HRMS ESI-(+): calcd for $C_{14}H_{24}N_2O_4S$ $[M + H]^+$ 317.1535, found 317.1533.

*(S)-tert-Butyl 3-(4-(4-tert-Butoxybenzyl)-2,5-dioxoimidazolidin-1-yl)propanoate **2d** (Table 2, Entry 4).* The reaction scale was 0.83 mmol (286 mg, 88% yield). White solid, mp 129−131 °C, $[\alpha]_D^{28}$ −8.26 (*c* = 5.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.08 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 5.45 (s, 1H), 4.21−4.18 (m, 1H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.21 (dd, 13.9 Hz, *J* = 2.7 Hz, 1H), 2.83−2.76 (m, 1H), 2.46 (t, *J* = 7.8 Hz, 2H), 1.43 (s, 9H), 1.33 (s, 9H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 173.1, 170.1, 156.9, 155.2, 130.1, 124.8, 81.4, 79.0, 58.7, 37.7, 34.8, 33.8, 29.2, 28.4; MS ESI-(+): *m/z* 391 $[M + H]^+$, 335, 279, 261; HRMS ESI-(+): calcd for $C_{21}H_{30}N_2O_5$ $[M + H]^+$ 391.2233, found 391.2231.

*(S)-Methyl 2-((S)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)-3-phenyl-propanoate **2e** (Table 2, Entry 5).* HCl·H-Phe-OMe (0.46 mmol, 2 equiv), CDI (1 equiv) and K_2CO_3 (3 equiv) were added to a 5 mL stainless steel milling jar with two stainless steel milling balls. The reactants were milled in a vibratory ball-mill at 30 Hz for 2 h. Water was then added to the reaction mixture, and the desired compound **2e** precipitated. The precipitate was recovered by filtration (47.1 mg, 58% yield). CAS [1634670-17-9].[46] White solid, mp 142−144 °C, $[\alpha]_D^{28}$ −9.41 (*c* = 5.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.31−7.09 (m, 10H), 5.19 (s, 1H), 4.06 (dd, *J* = 10.7 Hz, *J* = 3.4 Hz, 1H), 3.79 (s, 3H), 3.50−3.46 (m, 1H), 3.06 (dd, J = 13.9 Hz, J = 3.11 Hz, 3H), 2.14 (dd, *J* = 13.8 Hz, *J* = 10.7 Hz, 1H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 172.4, 169.1, 155.7, 136.6, 135.8, 129.3, 129.2, 129.1, 128.8, 127.6, 127.2, 58.3, 53.3, 53.1, 38.4, 34.3; MS ESI-(+): *m/z* 416 $[M+Na+ACN]^+$, 375 $[M + Na]^+$, 353 $[M + H]^+$, 322, 293.

*General Procedure for the Synthesis of 5-Substituted-3-(methoxycarbonyl)alkyl-hydantoins (Method B) (Compounds **5a−e**).* Dipeptide **3** (1 equiv) and CDI (2 equiv) were added to a 12 mL stainless steel milling jar with 25 stainless steel milling balls (5 mm diameter). The reactants were milled for 2 h at 450 rpm. Dichloromethane (2 mL) was added to the reaction mixture, and the organic layer was washed three times with 10% aq. citric acid and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*.

*General Procedure for the Synthesis of 5-Substituted-3-(methoxycarbonyl)alkyl-hydantoins (Method in Solution) (Compounds **5c**, **5e**, and **5f**).* A solution of dipeptide TFA salts **3c**, **3e**, and **3f**

(100 mg, 1 equiv) in CH_2Cl_2 (3 mL) with DIPEA (1 equiv) was added dropwise into a solution of CDI (1.2 equiv) in CH_2Cl_2 (3 mL) at 0 °C. After the addition was complete (30 min), the reaction was stirred for 3 h at room temperature. Reaction workup was performed as previously described for milling conditions.

(S)-Methyl 2-((S)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)-4-methylpentanoate ***5a*** *(Table 3, Entry 1).* The reaction scale was 0.62 mmol (162.5 mg, 82% yield). The crude was purified by column chromatography (linear gradient of EtOAc in cyclohexane from 0 to 20%). Sticky coloress oil, $[\alpha]_D^{28}$ −1.45 (c = 5.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36−7.20 (m, 5H), 5.32 (s, 1H), 4.69 (dd, J = 11.6 Hz, J = 4.3 Hz, 1H), 4.32 (ddd, J = 8.6 Hz, J = 3.8 Hz, J = 1.3 Hz, 1H), 3.73 (s, 3H), 3.29 (dd, J = 14.0 Hz, J = 3.8 Hz, 1H), 2.88 (dd, J = 14.0 Hz, J = 8.7 Hz, 1H), 2.22−2.13 (m, 1H), 1.84−1.75 (m, 1H), 1.17−1.10 (m, 1H), 0.86 (d, J = 6.5 Hz, 6H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 171.9, 169.3, 155.4, 134.4, 128.7, 128.3, 126.8, 57.5, 52.1, 50.4, 37.2, 35.9, 24.1, 22.5, 20.4; MS ESI-(+): m/z 319 $[M + H]^+$, 287, 259; HRMS ESI-(+): calcd for $C_{17}H_{22}N_2O_4$ $[M + H]^+$ 319.1658, found 319.1661.

(R)-Methyl 2-((S)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)-3-methylbutanoate ***5b*** *(Table 3, Entry 2).* The reaction scale was 0.25 mmol (53.3 mg, 70% yield). The product was recovered by precipitation from 10% aq. citric acid. Colorless oil, $[\alpha]_D^{28}$ +1.05 (c = 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34−7.20 (m, 5H), 5.68 (s, 1H), 4.33 (d, J = 3.0 Hz, 1H), 4.30 (d, J = 6.0 Hz, 1H), 3.70 (s, 3H), 3.29 (dd, J = 14.0 Hz, J = 3.8 Hz, 1H), 2.86 (dd, J = 14.0 Hz, J = 8.6 Hz, 1H), 2.65−2.57 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 172.9, 169.3, 156.7, 135.4, 129.7, 129.3, 127.8, 58.6, 58.4, 52.8, 38.3, 28.4, 21.1, 19.5; MS ESI-(+): m/z 305 $[M + H]^+$, 273, 245; HRMS ESI-(+): calcd for $C_{16}H_{20}N_2O_4$ $[M + H]^+$ 305.1501, found 305.1502.

(S)-Methyl 2-((S)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)propanoate ***5c*** *(Table 3, Entry 3).* Dipeptide **3c** was used as a hydrochloric salt. The reaction scale was 0.87 mmol (137.0 mg, 57% yield). White solid, mp 96−97.7 °C, $[\alpha]_D^{24}$ −149 (c = 1.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.31−7.18 (m, 5H), 6.07 (s, 1H), 4.68 (q, J = 7.2 Hz, 1H), 4.30−4.27 (m, 1H), 3.72 (s, 1H), 3.26 (dd, J = 13.9 Hz, J = 3.7 Hz, 1H), 2.92−2.87 (m, 1H), 1.46 (d, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 172.5, 169.9, 156.5, 135.0, 129.5, 128.8, 127.4, 58.3, 52.8, 47.8, 37.8, 14.5; MS ESI-(+): m/z 277 $[M + H]^+$, 245, 217; HRMS ESI-(+): calcd for $C_{14}H_{17}N_2O_4$ $[M + H]^+$ 277.1188, found 277.1189.

(S)-Methyl 2-((S)-4-(2-(Benzyloxy)-2-oxoethyl)-2,5-dioxoimidazolidin-1-yl)-4-(methylthio)butanoate ***5d*** *(Table 3, Entry 4).* Dipeptide **3d** was as a hydrochloric salt. The reaction scale was 0.25 mmol (74.5 mg, 76% yield). Sticky colorless oil, $[\alpha]_D^{28}$ −3.60 (c = 5.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.45−7.17 (m, 5H), 6.50 (s, 1H), 5.15 (s, 2H), 4.89−4.85 (m, 1H), 4.40−4.37 (m, 1H), 3.72 (s,1H), 3.08−3.02 (m, 1H), 2.75−2.44 (m, 5H), 2.06 (s, 3H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 172.5, 170.4, 169.5, 156.5, 135.4, 129.0, 128.9, 128.7, 67.6, 53.7, 53.2, 51.9, 36.7, 31.1, 27.6, 15.6; MS ESI-(+): m/z 395 $[M + H]^+$, 363, 257. HRMS ESI-(+): calcd for $C_{16}H_{20}N_2O_4$ $[M + H]^+$ 305.1501, found 305.1502.

(S)-Methyl 2-((S)-4-Isopropyl-2,5-dioxoimidazolidin-1-yl)-propanoate ***5e*** *(Table 3, Entry 5).* The reaction scale was 0.32 mmol (56.9 mg, 78% yield). The crude was recovered either by column filtration on silica gel (EtOAc 100%) or precipitated by Me-THF. White solid, mp 160−162 °C, $[\alpha]_D^{28}$ +2.40 (c = 5.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.82 (s, 1H), 4.75 (q, J = 7.3 Hz, 1H), 3.97 (dd, J = 1.2 Hz, J = 3.6 Hz, 1H), 3.74 (s, 1H), 2.30−2.22 (m, 1H), 1.61 (d, J = 7.3 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C{1H} NMR (300 MHz, $CDCl_3$) δ (ppm): 172.9, 170.2, 157.1, 62.5, 53.0, 48.2, 30.6, 19.2, 16.1, 15.1; MS ESI-(+): m/z 229 $[M + H]^+$, 197, 169; IR (cm^{-1}) 3299, 2964, 1684, 1432, 1225, 1085; HRMS ESI-(+): calcd for $C_{10}H_{16}N_2O_4$ $[M + H]^+$ 229.1188, found 229.1188.

(S)-2-((S)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)propanamide ***5f*** *(Table 3, Entry 6).* Only the peaks corresponding to hydantoin are described. The reaction scale was 0.29 mmol (22.1 mg, 29% ^{1}H NMR yield). White solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.32 (s, 1H), 7.26−7.07 (m, 5H), 4.30 (t, J = 4.4 Hz, 1H), 4.13 (q, J = 7.4 Hz, 1H), 2.95 (d, J = 4.7 Hz, 2H), 1.08 (d, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (300 MHz, DMSO-d_6) δ (ppm): 173.0, 170.6, 156.1, 129.9, 128.1, 126.8, 56.7, 48.2, 36.4, 14.0; MS ESI-(+): m/z 262 $[M + H]^+$, 245, 217; HRMS ESI-(+): calcd for $C_{13}H_{15}N_3O_3$ $[M + H]^+$ 262.1192, found 262.1194.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: evelina.colacino@umontpellier.fr. Tel.: +33 (0)4 67 14 42 85. Fax: +33 (0)467 14 48 66.

Notes

The authors declare no competing financial interest.

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