Straightforward Synthesis of Molsidomine and Mesocarb Analogue via Mechanochemical Desymmetrization of CDI

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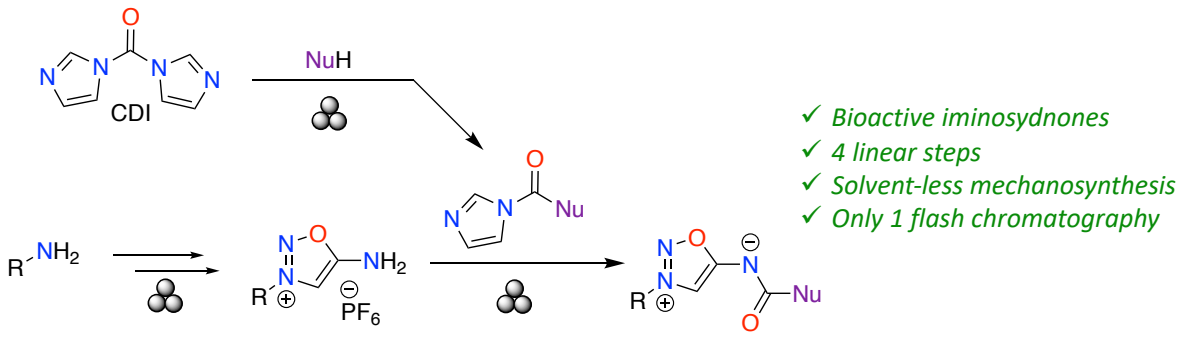
Abstract



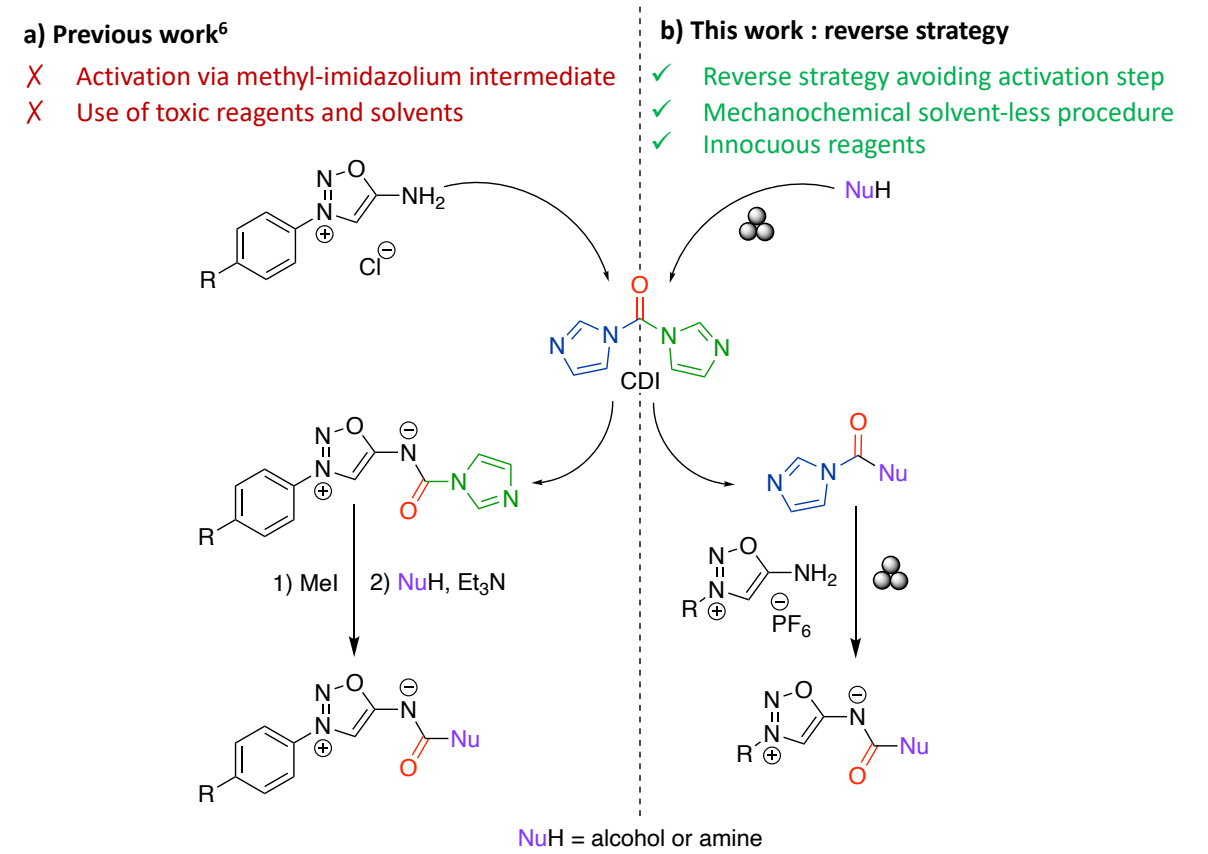
The mechanosynthesis of N6-functionalized iminosydnones was performed via a convergent strategy based on the desymmetrization of CDI. The whole process was carried out by ball-milling, offering an efficient and sustainable access to bioactive iminosydnones.

Introduction

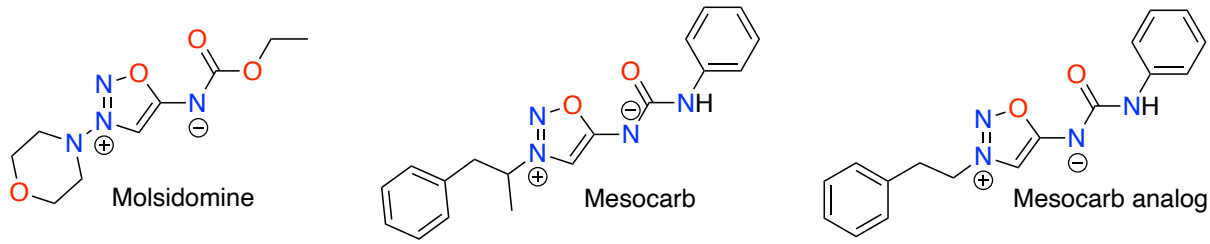
Sydnones (Syds) and iminosydnones (ImSyds), mesoionic compounds used for a long time in biomedical applications,[1] proved recently to be substrates of choice for biorthogonal click reactions.[2, 3, 4, 5] Among ImSyds, molsidomine and mesocarb are famous drugs developed at the industrial scale because of their potent NO-donor properties (Scheme 1c). Noteworthy, non-substituted ImSyds rapidly decompose by ring opening in basic conditions and are thus always isolated as protonated salts. That's why ImSyds have often been used under an N6-functionalized form. Since the seminal works of Daeniker and Masuda,[6] most methods for N6 derivatization reported in the literature remained based on the reaction of ImSyd salts with strong electrophiles like acid chlorides, chloroformates or isocyanates in the presence of a weak base.[7, 2] In the years 2000, ImSyd carbamates including molsidomine were prepared via a *p*-nitrophenyl carbamate then substituted by various alcohols.[8] However, the last step of the industrial preparation of mesocarb still called on the use of toxic phenylisocyanate.[9] More recently, the team of Taran developed a straightforward access to ImSyd-based prodrugs thanks to carbonylimidazolium activation (Scheme *1*a).[4] Indeed, 1,1'-carbonyldiimidazole (CDI) is well-known as an effective acylating agent, providing easily amides, ureas and carbamates, either directly from a carbonylimidazole intermediate,[10] or via an activated carbonylimidazolium salt.[11] This CDI-based strategy allowed to circumvent the major drawbacks of the previous methods, i.e. moderate yields, the use of toxic and/or highly reactive reagents and a narrow scope, but still required a methylation step to activate the

carbonylimidazole intermediate. Yet, developing more straightforward synthetic routes is crucial in a context of shortage of resources and complies with several of the 12 principles of green chemistry.[12] Mechanochemistry is now recognized as a sustainable technique in organic synthesis, providing solvent-less conditions, short reaction times and enhanced or unexpected reactivity.[13] Thanks to devices like ball-mills or extruders, it allows rapid and efficient access to compounds of interest and help to shorten the development of active pharmaceutical ingredients (APIs).[14]

Relying on our expertise both in the mechanosynthesis of mesoionics[15] and in the applications of *N,N'*-carbonyldiimidazole (CDI) for green synthetic procedures,[16] we undertook to design an innovative, efficient and eco-friendly strategy for the *N*-exocyclic functionalization of free ImSyds. Application to a totally mechanochemical synthesis of molsidomine and of a mesocarb analog will be described.



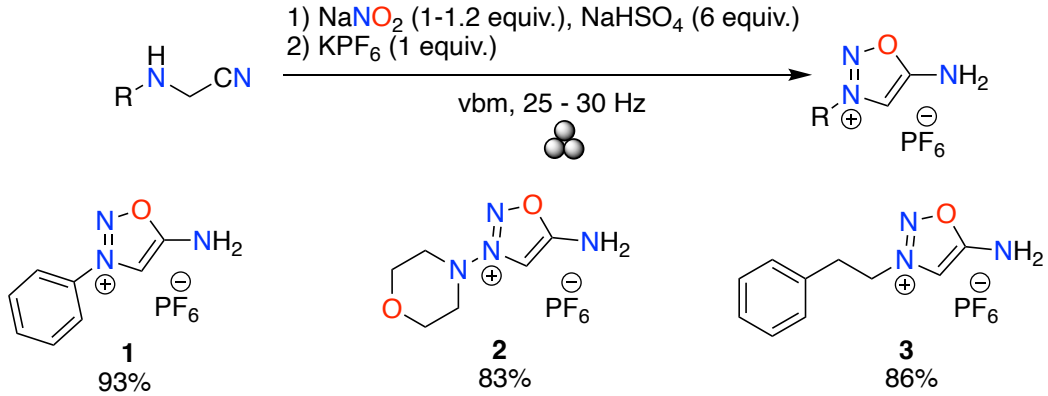
c) N6-functionalized APIs and analog



Scheme 1. CDI-mediated N6-functionalization of iminosydnones

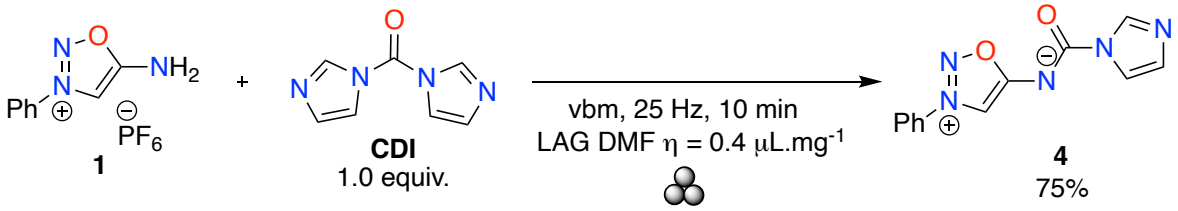
Results and discussion

ImSyds **1**-**3** were synthesized following the method we reported recently: this efficient and ecofriendly access to the iminosydnone core relies exclusively on the use of ball-milling.[17] After the mechanochemical preparation of the amino-nitrile precursors, a one-pot two-step sequence with only solid reagents, $NaHSO_4$ providing the protons both for the nitrosation and the cyclization step, allowed to obtain the ImSyds core. Thanks to an anion metathesis, the desired ImSyds were isolated as unprecedented hexafluorophosphate salts, the whole process being performed in a ball-mill (**Scheme 2**). In this way, model substrate **1**, the active metabolite of molsidomine **2** and the precursor of a mesocarb analog **3** were synthesized efficiently and in an eco-friendly manner.



Scheme 2. Mechanosynthesis of the iminosydnone core

In a first approach combining CDI and mechanochemistry to derivatize ImSyds, we attempted to transpose directly the method developed by Riomet et al.[4] in a solvent-less manner in a vibratory ball-mill (vbm). Despite its efficiency, the reported procedure lacked sustainability, requiring toxic solvents like DMF, acetonitrile or dichloromethane.[4] Classical optimization of the mechanochemical parameters (milling frequency, time, addition of a liquid additive) for this transformation with model substrate **1** led to the isolation of ImSyd-carbonylimidazole **4** with a satisfactory yield of 75% (**Scheme 3**, see SI for details).



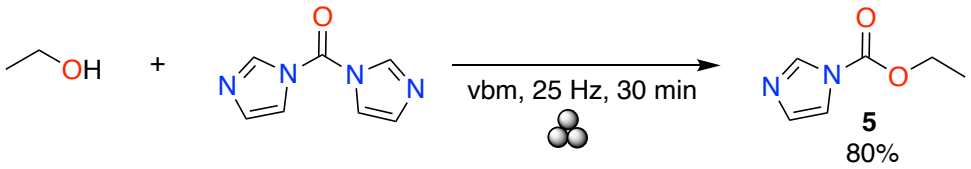
Scheme 3. Mechanosynthesis of ImSyd-carbonylimidazole intermediate

However, like other substituted carbamoylimidazoles,[11b,e] ImSyd-carbonylimidazole intermediates are poorly reactive towards nucleophilic substitution in solution,[4] and even under mechanochemical conditions, compound **4** did not react with nucleophiles in our hands. Thus, activation through formation of an imidazolium salt appeared necessary, but using an excess (4 equiv.) of iodomethane, a toxic, volatile and flammable reagent in the ball-mill was neither safe nor in accordance with our green chemistry approach.

Henceforth, a different strategy was considered to avoid the activation of ImSyd-carbonylimidazole with iodomethane. Two routes are available to desymmetrize CDI to functionalize ImSyds, depending on which nucleophile reacts first with CDI.[18] Inspired by the

previous results obtained in our group on the synthesis of carbamates and hydantoins thanks to CDI-activation, [15b,d,e] a more straightforward synthetic route was designed: reacting first the required nucleophile, an alcohol or an amine, with CDI should lead to a carbonylimidazole intermediate which may then, in appropriate conditions, be attacked directly by the exocyclic nitrogen of the ImSyd salt to furnish the desired ImSyd-carbamate or ImSyd-urea, respectively **(Scheme 1b**).

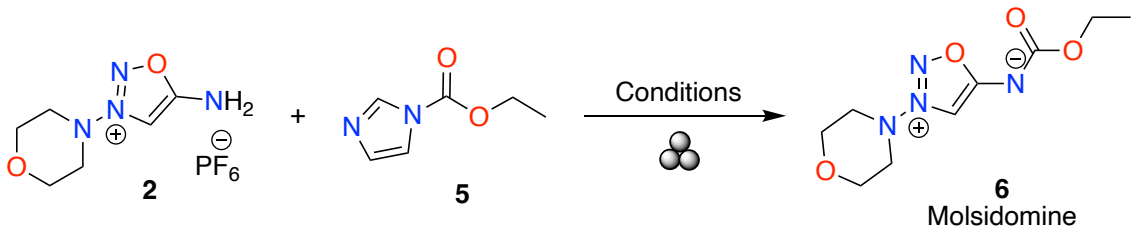
In the case of molsidomine, an ethyl-iminosydnone carbamate, this method could be easily applied.[16b] Indeed, reacting first an alcohol with CDI and then an amine gave better results than the reverse sequence, avoiding the formation of a symmetrical urea. Hence, reaction between ethanol and CDI proceeded smoothly in a vbm at 25 Hz for 30 min, and simply diluting the crude reaction mixture with EtOAc and removing imidazole by an aqueous acid washing allowed to isolate pure imidazole carboxylic ester **5** with 80 % yield (**Scheme 4**).



Scheme 4. Straightforward mechanochemical access to 5

Then, first attempt to react the ImSyd salt precursor **2** with an excess of **5** in a ball-mill failed, a complex mixture being obtained (Table 1, entry 1). Applying liquid assisted grinding (LAG) with EtOAc to this transformation improved the reaction.[19] Mixing **2** with 1.1 equiv. of **5** for 2 hours in a vbm gave an incomplete conversion to molsidomine **6** with a moderate isolated yield of 27% (**Table 1**, entry 2). Increasing milling time, liquid additive and carbonylimidazole amounts allowed to reach a 42% yield but still with incomplete conversion. Portionwise addition of **5**, together with increased reaction time and use of MeCN as liquid additive, gave similar results (**Table 1**, entry 4). Observing that several cycles of milling were necessary to achieve high conversions, we decided to switch from a vibratory to a planetary ball-mill. This latter is particularly adapted to long reaction time, and the method of milling can have a dramatic effect on the issue of a chemical transformation.[20] Gratifyingly, full conversion was obtained when reacting **2** and **5** for 12 cycles of 40 min in a pbm **(Table 1,** entry 5). Pure molsidomine **6** was finally isolated with a satisfactory yield of 65% (**Table 1**, entry 6). Of note, this mechanosynthesis of molsidomine is more straightforward and safer than previous preparations of this API, avoiding an activation step with *p*-nitrophenyl chloroformate and allowing for the first time the base-free N6-functionalization of an ImSyd.

Table 1. Optimization of the mechanosynthesis of Molsidomine



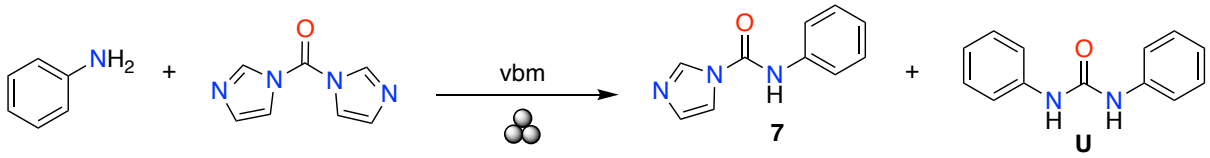
Entry	Equiv. of 5	Additive[a] (μL.mg^{-1})	Milling conditions	t (min)	HPLC Conv. (%)	Yield (%)
1	2.0	–	vbm, 30 Hz	90	n.d.[b]	n.d.[b]
2	1.1	EtOAc (0.2)	vbm, 30 Hz	2x60	n.d.[b]	27
3	1.4	EtOAc (0.5)	vbm, 30 Hz	5x60	80	42
4	3.3[c]	MeCN (0.5)	vbm, 30 Hz	7x60	<100	43
5	1.2	EtOAc (0.6)	pbm, 600 rpm	12x40	100	86 (45)[d]
6	1.2	EtOAc (0.5)	pbm, 600 rpm	12x40	100	65

[a] Amount of additive given against solid reagent. [b] n.d.: not determined. [c] Added in 3 portions of 1.5, 1.0 and 0.8 equiv. [d] Contamination by residual Im.HPF_6 after flash chromatography, final yield of pure **3** after precipitation of side product in $CHCl_3$ is given in brackets.

Then the mechanochemical preparation of the mesocarb analog **8** was undertaken. Because of the problematic availability of amphetamine, the starting material necessary for the ImSyd core, we chose to target the demethylated analog **8**. This compound being formally a phenyl-iminosydnone urea, according to our strategy, it was necessary to prepare the intermediate phenylcarbamoyl imidazole **7** from CDI and aniline (**Table 2**). In solution, arylamines were reported to be less prone to form symmetrical ureas than alkylamines when reacting with CDI, and aryl-carbamoylimidazole were obtained with good yields, although formation of urea cannot be totally ruled out.[10c,d] Exploring the reactivity of aniline with CDI in mechanochemical conditions, a mixture of the expected carbamoyl product and of *N,N'*-diphenylurea in a 88:12 molar ratio was obtained when milling an equimolar mixture of both reagents in a vbm at 25 Hz (**Table 2**, entry 1). It is known that CDI is prone to hydrolysis by atmospheric moisture and batches of CDI often contain a variable proportion of imidazole measurable by ^{1}H NMR.[21] Thus, working with 1 equivalent of CDI might mean working with an excess of aniline that could favor the formation of urea. However, increasing the amount of CDI to 1.2 equiv. did not bring a significant improvement (**Table 2**, entry 2). Similar results were obtained when increasing the milling frequency from 25 to 30 Hz (**Table 2**, entries 3 and 4). The group of Batey reported that, for primary aliphatic amines, using the hydrochloride form instead of the free amine allowed to suppress the formation of symmetrical urea.[10g] However, in our case, the use of aniline hydrochloride in solvent-free conditions resulted in a larger proportion of urea (**Table 2**, entries 5 and 6). To dilute the solid mixture and reduce the formation of urea, a large excess of CDI and/or of a solid additive were used. Disappointingly, introducing 2.0 equiv. of CDI in the jar had a detrimental effect (**Table 2**, entry 7). Nevertheless, adding 5 equiv. of NaCl as inert/unreactive additive allowed to reduce the molar percentage of urea to 5%, regardless of the amount of CDI (**Table 2**, entries 8, 9 and 10). A double amount of NaCl gave slightly better

results, especially with an excess of CDI (**Table 2**, entry 13), but finally using 10 equiv. of NaCl with 1.2 equiv. of CDI proved to be the best combination (**Table 2**, entry 11).

Table 2. Mechanochemical conditions of reaction of CDI with aniline



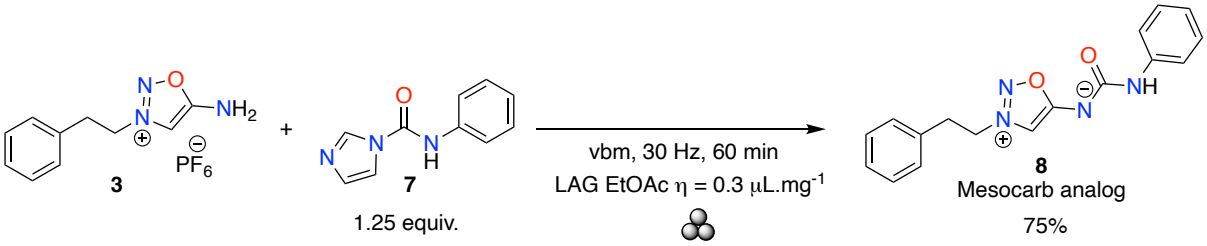
Entry	CDI equiv.	Additive (equiv.)	Frequency (Hz)	Conv. (%)[a]	Ratio 7/U (%)[a]	Purity (mass % of 7)[a]	Corr. Yield (%)[b]
1	1.0	–	25	100	88:12	n.d.[c]	n.d.[c]
2	1.2	–	25	100	89:11	n.d.[c]	n.d.[c]
3	1.0	–	30	100	90:10	n.d.[c]	n.d.[c]
4	1.2	–	30	100	89:11	82	66
5[d]	1.0	–	30	100	77:23	n.d.[c]	n.d.[c]
6[d]	1.2	–	30	100	77:23	n.d.[c]	n.d.[c]
7	2.0	–	30	100	84:16	n.d.[c]	n.d.[c]
8	1.2	NaCl (5)	30	100	95:5	88	72
9	1.5	NaCl (5)	30	100	95:5	88	77
10	2.0	NaCl (5)	30	100	96:4	87	75
11	1.2	NaCl (10)	30	100	97:3	92	95
12	1.5	NaCl (10)	30	100	97:3	90	78
13	2.0	NaCl (10)	30	100	98:2	84	77

[a] Conversion and ratio **7**/urea were determined by ^{1}H NMR after a milling time of 30 min. [b] Calculated from the purity and the obtained mass of solid. [c] n.d.: not determined. [d] $PhNH_2$.HCl was used instead of aniline.

Two work-up protocols were examined to isolate the carbamoylimidazole, either suspending the crude mixture in cold water followed by filtration and drying, as reported previously,[16a] or extracting the product in EtOAc followed by aqueous washings. Although the second method allowed to avoid partial hydrolysis of **7**, the first method was found to be more efficient to remove remaining imidazole and more environmentally friendly.

Hence, thanks to the fine tuning of the milling conditions, compound **7** was obtained with a satisfying purity of 92% after treatment and an excellent corrected yield of 95%. Although attempts of recrystallization failed, our mechanosynthesis of **7** represents a significant improvement in terms of sustainability and of efficiency in comparison with results reported in the literature for this compound,[22] and we decided to use **7** in the final step without further purification despite the presence of traces of urea.

With compounds **7** and **3** in hands, the synthesis of mesocarb analog **8** was attempted. Fortunately, ImSyd **3** turned out to be more reactive than ImSyd **2**, and functionalization of its exocyclic nitrogen proceeded smoothly in a vbm for 1 h, without base but using just a slight excess of carbamoyl derivative **8** and LAG with EtOAc. After purification by flash chromatography to remove residual urea, the desired analog **4** was obtained with a very good yield of 75% (Scheme 5). This solvent-less method was found to be direct, easy to set up and safer than procedures previously reported using phenylisocyanate in pyridine.[9]



Scheme 5. Mechanochemical Mesocarb analog synthesis

Conclusion

In summary, we have developed a straightforward, efficient and eco-friendly mechanosynthesis of the API molsidomine and of an analog of mesocarb. Thanks to a strategy based on a reverse mechanochemical desymmetrization of CDI, a versatile and safe reagent, N6-functionalization of iminosydnones could be performed successfully via reaction with carbonylimidazole intermediates, avoiding the use of hazardous reagents like isocyanates or chloroformates. Furthermore, the mechanochemical activation could enhance the reactivity of iminosydnone hexafluorophosphate salts, which could react with the carbonylimidazole intermediates in the absence of a base. Thanks to fine tuning of the mechanochemical parameters, the two targeted molecules were obtained, via a convergent synthetic strategy, with overall yields of 54 and 65% respectively. Hence, this solvent-less procedure demonstrates the potential of mechanochemistry to access original heterocyclic structures useful in medicinal chemistry.

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