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Synthesis of Molsidomine and Mesocarb Analog via Mechanochemistry

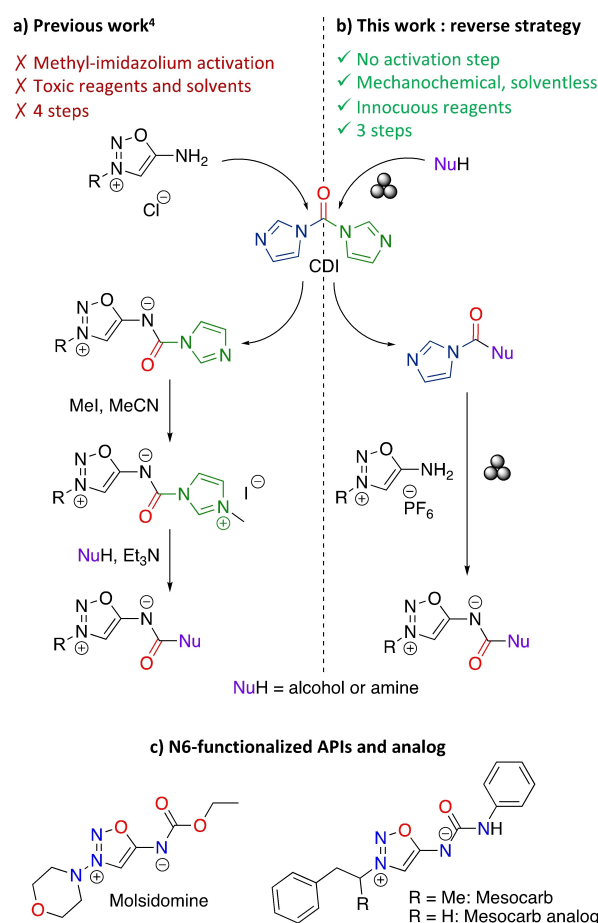
Nicolas Pétry,^[a] Xavier Bantreil,^[a, b] and Frédéric Lamaty*^[a]

Iminosydones (ImSyds) have renowned biological activities and attractive chemical properties for chemical biology. However, access to N6-functionalized iminosydones involves tricky and hazardous procedures. Thanks to an innovative mechanochemical strategy using 1,1'-carbonyldiimidazole (CDI) as an activating agent, a straightforward synthesis of molsidomine

and of a mesocarb analog, two bioactive iminosydones, was achieved. The whole process, involving 4 linear steps, was carried out in the solid state by ball-milling and with safe reagents, offering efficient and sustainable access to N-carbonylated iminosydones, in agreement with the principles of green chemistry.

Introduction

Sydones (Syds) and iminosydones (ImSyds), mesoionic compounds used for a long time in biomedical applications,^[1] proved recently to be substrates of choice for biorthogonal click reactions.^[2–5] Some iminosydnone-based Active Pharmaceutical Ingredients (APIs), like molsidomine and mesocarb have been developed at the industrial scale because of their potent NO-donor properties (Scheme 1c). Noteworthy, non-substituted ImSyds are always isolated as protonated salts as they rapidly decompose by ring opening in basic conditions. Hence, ImSyds are often prepared and used in a 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.^[1b,c,2,7] 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] 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.^[10] Mechanochemistry is now recognized as a sustainable technique in organic synthesis, providing solvent-less conditions, short reaction times and enhanced or unexpected



Scheme 1. CDI-mediated N6-functionalization of iminosydones.

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reactivity.^[11] Devices such as ball-mills allow rapid and efficient access to compounds of interest and help to shorten the development of APIs.^[12]

Relying on our expertise both in the mechanochemistry of mesoionics^[13] and in the applications of 1,1'-carbonyldiimidazole (CDI) for green synthetic procedures,^[14] we undertook the design of an innovative, efficient, and eco-friendly strategy for the N-exocyclic functionalization of free ImSyds. Two target

molecules were considered, and an original synthesis of molsidomine and of a mesocarb analog, entirely performed by mechanochemistry is described herein.

Results and Discussion

Recently, we reported the efficient and eco-friendly mechano-synthesis of the iminosydnone core relying on the exclusive use of a ball-mill. The model substrate **1**, the active metabolite of molsidomine **2** and the precursor of a mesocarb analog **3** were prepared with excellent yields in two steps starting from the corresponding amines.^[13a] (Figure 1) Noteworthy, a mechanochemical anion metathesis using KPF_6 allowed to isolate the pure ImSyds as unprecedented hexafluorophosphate salts by a simple extraction with EtOAc. This solid-state approach using NaHSO_4 as a proton source and no solvent constitutes a significant improvement in terms of safety and environmental footprint by avoiding the use of toxic or dangerous solvents (THF, dioxane, methanol) and strong acid (HCl).^[7b,15] With these molecules in hand, we tackled the N6 functionalization of ImSyds via a mechanochemical route.

1,1'-Carbonyldiimidazole (CDI) is an effective acylating agent, providing amides, ureas and carbamates, either directly from a carbonylimidazole intermediate,^[16] or via an activated carbonylimidazolium salt.^[17] For the synthesis of N6-functionalized ImSyds, depending on which nucleophile reacts first with CDI, there are two possible strategies by desymmetrization of CDI.^[18] Few years ago, an access to ImSyd-based prodrugs was developed thanks to carbonylimidazolium activation (Scheme 1a).^[4] This CDI-based strategy gave access to a large number of N-carbonyl derivatives of ImSyds but required the activation of the imidazole moiety through a methylation extra-step, lacking of sustainability with the use of toxic and hazardous reagent (MeI) and solvents (DMF, acetonitrile or dichloromethane).^[4]

In a first approach, we developed a solvent-less version of the reaction between CDI and an ImSyd in a vibratory ball-mill (vbm) (Scheme 2). Optimization of the mechanochemical parameters (milling frequency, time, addition of a liquid additive) allowed the isolation of a model ImSyd-carbonylimida-

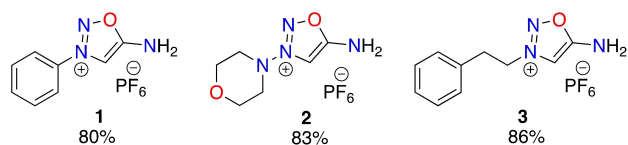
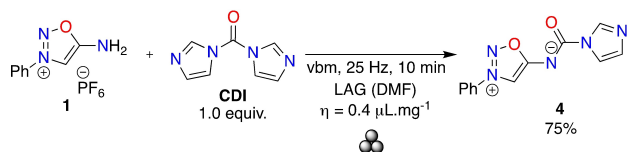


Figure 1. Mechanochemically prepared iminosydnone.^[13a]



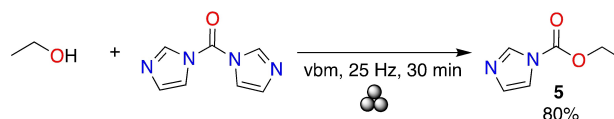
Scheme 2. Mechanosynthesis of iminosydnone carbonylimidazole.

zole with a similar yield than in solution (see Supporting Information for details). However, like other substituted carbamoylimidazoles,^[17b,d] iminosydnone carbonylimidazole intermediates were found to be poorly reactive towards nucleophilic substitution, also under mechanochemical conditions. To circumvent this issue and avoid the activation of the iminosydnone carbonylimidazole by methylation, the second approach of desymmetrization was considered.

Inspired by previous work performed in our group^[14c,d,f] a more straightforward synthetic route was designed (Scheme 1b). It consists of first reacting the required nucleophile, an alcohol or an amine, with CDI leading to a carbonylimidazole intermediate. In appropriate conditions, this latter could be attacked directly by the exocyclic nitrogen of the ImSyd salt to furnish the desired ImSyd-carbamate or ImSyd-urea, respectively (Scheme 1b).

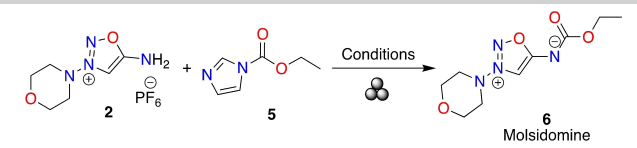
In the case of molsidomine, an ethyl-iminosydnone carbamate, this method could be easily applied,^[14f] reacting first an alcohol with CDI and then an amine to give better results than the reverse sequence, avoiding the formation of a symmetrical urea. Hence, the reaction between ethanol and CDI proceeded smoothly in a vbm at 25 Hz for 30 min, with no formation of diethyl carbonate. Simply diluting the crude reaction mixture with EtOAc and removing imidazole by an aqueous acid washing provided pure imidazole carboxylic ester **5** with an 80% yield (Scheme 3).

Then, the reaction with ImSyd was optimized. The first attempt to react the ImSyd salt precursor **2** neat with an excess of **5** in a ball-mill failed. A complex mixture, including both starting materials, a low amount of **6** and unidentified by-products, was obtained (Table 1, entry 1). Applying liquid-assisted grinding (LAG)^[12c,19] by mixing a small amount of EtOAc with **2** and 1.1 equiv. of **5** for 2 hours in a vbm gave an encouraging conversion to molsidomine **6** with a low 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 the use of MeCN as a 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.^[14f,20] Gratifyingly, full conversion was obtained when reacting **2** and **5** for 12 cycles of 40 min in a pbm (Table 1, entry 5). Lowering the amount of liquid additive to $0.5 \mu\text{L}\cdot\text{mg}^{-1}$ did not have any influence on the conversion (Table 1, entry 5 vs 6). By adapting the isolation procedure, pure molsidomine **6** was finally isolated with a satisfactory yield of 65% (Table 1,



Scheme 3. Straightforward mechanochemical preparation of **5**.

Table 1. Optimized mechanochemical synthesis of molsidomine.



Entry	5 (equiv.)	Additive ^[a] (μL.mg ⁻¹)	Milling conditions	Conv. (%) ^[b]	Yield (%)
1	2.0	–	vbm, 30 Hz 90 min	n.d. ^[c]	n.d. ^[c]
2	1.1	EtOAc (0.2)	vbm, 30 Hz 2x60 min	n.d. ^[c]	27
3	1.4	EtOAc (0.5)	vbm, 30 Hz 5x60 min	80	42
4	3.3 ^[d]	MeCN (0.5)	vbm, 30 Hz 7x60 min	< 100	43
5	1.2	EtOAc (0.6)	pbm, 10 Hz 12x40 min	100	86 (45) ^[e]
6	1.2	EtOAc (0.5)	pbm, 10 Hz 12x40 min	100	65

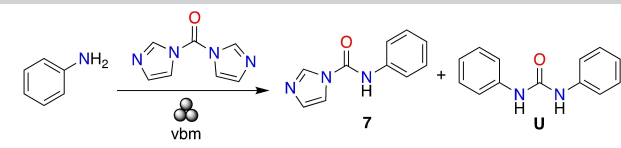
^[a] Amount of additive given against solid reagent. ^[b] Determined by HPLC. ^[c] n.d.: not determined. ^[d] Added in 3 portions of 1.5, 1.0 and 0.8 equiv. ^[e] Contamination by residual Im.HPF₆ after flash chromatography, final yield of pure **6** after precipitation of side products in CHCl₃ is given in brackets.

entry 6). Hence, this mechanochemical synthesis of molsidomine is more straightforward and safer than previous preparations of this API, avoiding an activation step with *p*-nitrophenyl chloroformate. Furthermore, while ImSyds are known to be poor nucleophiles and always require deprotonation prior to their N6-functionalization,^[6a] it is notable that, under solvent-less conditions, no base was necessary to achieve such a reaction. This remarkable result could be explained either by an exacerbated reactivity of the exocyclic nitrogen of ImSyd **2** in mechanochemical conditions, and/or by a favorable effect of the non-coordinating PF₆⁻ counter-ion. Noteworthy, the same reaction, starting with the chloride form of **2** led only to the formation of traces of **6**.

Next, with these fruitful results in hands, the mechanochemical preparation of the mesocarb analog **8** was undertaken. Because of the problematic availability of amphetamine, needed as starting material to prepare the ImSyd core of mesocarb, we chose to target its demethylated analog **8**. This compound is formally a phenyl-iminosydnone urea and 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 was obtained with good yields, although the formation of urea cannot be totally ruled out.^[16c,e]

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

Table 2. Mechanochemical conditions of reaction of CDI with aniline.



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

^[a] Complete conversion was checked and ratio 7/urea determined by ¹H 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] PhNH₂.HCl was used instead of aniline.

prone to hydrolysis by atmospheric moisture, and batches of CDI often contain a variable proportion of imidazole, measurable by ¹H NMR.^[21]

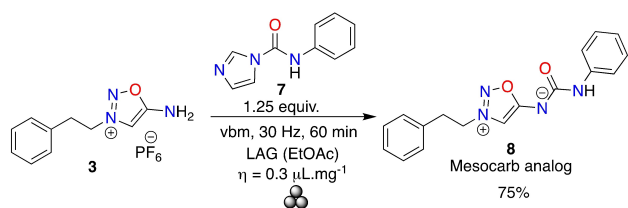
Thus, working with 1 equivalent of CDI might mean working with an excess of aniline that could favor the formation of urea.^[22] However, increasing the amount of CDI to 1.2 equiv. did not bring a significant improvement (Table 2, entry 2). Similar results were obtained when increasing the milling frequency 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.^[16a] 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 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 an inert additive allowed to reduce the molar percentage of urea to 5%, regardless of the amount of CDI (Table 2, entries 8, 9 and 10). Doubling the amount of NaCl gave slightly better results, especially with an excess of CDI (Table 2, entry 13). Finally, using 10 equiv. of NaCl with 1.2 equiv. of CDI proved to be the best combination (Table 2, entry 11). Two work-up protocols were tested to isolate the carbamoylimidazole: either suspending the crude mixture in cold water followed by filtration and drying, as reported

previously,^[14g] or extracting the product in EtOAc followed by aqueous washings to remove imidazole. Although the latter method avoids the partial hydrolysis of **7**, the former, more environmentally friendly, was found to be more efficient. 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 mechanochemical synthesis of **7** represents a significant improvement in terms of sustainability and efficiency in comparison with results reported in the literature for this compound,^[23] 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 hand, 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, using a slight excess of carbamoyl derivative **7** in LAG conditions with EtOAc. After purification by flash chromatography to remove residual urea, the desired analog **8** was obtained with a very good yield of 75% (Scheme 4). This new solventless method was found to be direct, easy to set up, and safer than procedures previously reported using phenylisocyanate in pyridine.^[9]

Conclusions

In summary, we have developed a new, straightforward, efficient, and eco-friendly mechanochemical synthesis 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 iminosydones could be performed successfully, with an inferior number of steps compared to solution, 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 innovative solventless procedure demonstrates the strong potential of mechanochemistry to access original heterocyclic structures useful in medicinal chemistry and chemical biology.



Scheme 4. Mechanochemical mesocarb analog synthesis.

Supporting Information

Experimental procedures, including data characterization and copies of ^1H and ^{13}C NMR spectra, are given in Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: green chemistry · solid-state reactions · iminosydones · mechanochemistry · API

- [1] a) P. G. Wang, M. Xian, X. Tang, X. Wu, Z. Wen, T. Cai, A. J. Janczuk, *Chem. Rev.* **2002**, *102*, 1091–1134; b) K. Schönafinger, *Il Farmaco* **1999**, *54*, 316–320; c) Z. A. Olovyanishnikova, V. A. Parshin, V. V. Ogorodnikova, M. D. Mashkovskii, V. G. Yashunskii, *Pharm. Chem. J.* **1987**, *21*, 756–759; d) K. Kikuchi, M. Hirata, Y. Aramaki, *Jpn. J. Pharmacol.* **1970**, *20*, 23–43.
- [2] a) K. Porte, B. Renoux, E. Péraudeau, J. Clarhaut, B. Eddhif, P. Poinot, E. Gravel, E. Doris, A. Wijkhuisen, D. Audisio, S. Papot, F. Taran, *Angew. Chem. Int. Ed.* **2019**, *58*, 6366–6370; b) M. Riomet, E. Decuypere, K. Porte, S. Bernard, L. Plougastel, S. Kolodych, D. Audisio, F. Taran, *Chem. Eur. J.* **2018**, *24*, 8535–8541; c) S. Bernard, D. Audisio, M. Riomet, S. Bregant, A. Sallustrau, L. Plougastel, E. Decuypere, S. Gabillet, R. A. Kumar, J. Elyian, M. N. Trinh, O. Koniev, A. Wagner, S. Kolodych, F. Taran, *Angew. Chem. Int. Ed.* **2017**, *56*, 15612–15616.
- [3] a) L. Madegard, M. Girard, B. R. Yaw, K. Porte, D. Audisio, S. Papot, F. Taran, *Chem. Eur. J.* **2023**, *29*, e202301359; b) M. Feng, L. Madegard, M. Riomet, M. Louis, P. A. Champagne, G. Pieters, D. Audisio, F. Taran, *Chem. Commun.* **2022**, *58*, 8500–8503; c) K. Porte, M. Riomet, C. Figliola, D. Audisio, F. Taran, *Chem. Rev.* **2021**, *121*, 6718–6743; d) Z. Shao, W. Liu, H. Tao, F. Liu, R. Zeng, P. A. Champagne, Y. Cao, K. N. Houk, Y. Liang, *Chem. Commun.* **2018**, *54*, 14089–14092; e) E. Decuypere, S. Bernard, M. Feng, K. Porte, M. Riomet, P. Thuéry, D. Audisio, F. Taran, *ACS Catal.* **2018**, *8*, 11882–11888.
- [4] M. Riomet, K. Porte, L. Madegard, P. Thuéry, D. Audisio, F. Taran, *Org. Lett.* **2020**, *22*, 2403–2408.
- [5] M. Riberaud, K. Porte, A. Chevalier, L. Madegard, A. Rachet, A. Delaunay-Moisan, F. Vinchon, P. Thuery, G. Chiappetta, P. A. Champagne, G. Pieters, D. Audisio, F. Taran, *J. Am. Chem. Soc.* **2023**, *145*, 2219–2229.
- [6] a) K. Masuda, T. Kamiya, Y. Imashiro, T. Kaneko, *Chem. Pharm. Bull.* **1971**, *19*, 72–79; b) H. U. Daeniker, J. Druey, *Helv. Chim. Acta* **1962**, *45*, 2441–2462.
- [7] a) M. Vahermo, T. Suominen, A. Leinonen, J. Yli-Kauhaluoma, *Arch. Pharm.* **2009**, *342*, 201–209; b) V. G. Yashunskii, L. E. Kholodov, *Russ. Chem. Rev.* **1980**, *49*, 28–45.
- [8] a) A. Nortcliffe, I. N. Fleming, N. P. Botting, D. O'Hagan, *Tetrahedron* **2014**, *70*, 8343–8347; b) A. Nortcliffe, A. G. Ekstrom, J. R. Black, J. A. Ross, F. K. Habib, N. P. Botting, D. O'Hagan, *Bioorg. Med. Chem.* **2014**, *22*, 756–761; c) A. Nortcliffe, N. P. Botting, D. O'Hagan, *Org. Biomol. Chem.* **2013**,

- 11, 4657–4671; d) L. Soullère, P. Hoffmann, F. Bringaud, *J. Heterocycl. Chem.* **2003**, *40*, 943–947.
- [9] H. Chen, M. Liu, M. Sathyamoorthy, Q. Su, L. Leary, W. S. Zhong, Caliper Life Sciences, Inc., **2011**.
- [10] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice* **1998**, Oxford University Press: Oxford, U.K.
- [11] a) R. T. O'Neill, R. Boulatov, *Nat. Chem. Rev.* **2021**, *5*, 148–167; b) D. Tan, T. Friščić, *Eur. J. Org. Chem.* **2018**, 18–33; c) J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080–3094; d) J. Andersen, J. Mack, *Green Chem.* **2018**, *20*, 1435–1443; e) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007–4019; f) J. L. Do, T. Friscic, *ACS Cent. Sci.* **2017**, *3*, 13–19; g) G. W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700; h) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friscic, F. Grepioni, K. D. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413–447.
- [12] a) O. Bento, F. Luttringer, T. Mohy El Dine, N. Pétry, X. Bantreil, F. Lamaty, *Eur. J. Org. Chem.* **2022**, e202101516; b) P. Ying, J. Yu, W. Su, *Adv. Synth. Catal.* **2021**, *363*, 1246–1271; c) E. Colacino, A. Porcheddu, C. Charnay, F. Delogu, *React. Chem. Eng.* **2019**, *4*, 1179–1188.
- [13] a) N. Pétry, F. Luttringer, X. Bantreil, F. Lamaty, *Faraday Discuss.* **2023**, *241*, 114–127; b) N. Pétry, T. Vanderbeeken, A. Malher, Y. Bringer, P. Retailleau, X. Bantreil, F. Lamaty, *Chem. Commun.* **2019**, *55*, 9495–9498; c) X. Bantreil, N. Pétry, F. Lamaty, *Dalton Trans.* **2019**, *48*, 15753–15761.
- [14] a) L. Appy, A. Depaix, X. Bantreil, F. Lamaty, S. Peyrottes, B. Roy, *Chem. Eur. J.* **2019**, *25*, 2477–2481; b) T.-X. Métro, J. Martinez, F. Lamaty, *ACS Sustainable Chem. Eng.* **2017**, *5*, 9599–9602; c) L. Konnert, L. Gonnet, I. Halasz, J. S. Suppo, R. M. de Figueiredo, J. M. Campagne, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2016**, *81*, 9802–9809; d) L. Konnert, M. Dimassi, L. Gonnet, F. Lamaty, J. Martinez, E. Colacino, *RSC Adv.* **2016**, *6*, 36978–36986; e) T.-X. Métro, J. Bonnamour, T. Reidon, A. Duprez, J. Sarpoulet, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2015**, *21*, 12787–12796; f) M. Lanzillotto, L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *ACS Sustainable Chem. Eng.* **2015**, *3*, 2882–2889; g) T.-X. Metro, J. Bonnamour, T. Reidon, J. Sarpoulet, J. Martinez, F. Lamaty, *Chem. Commun.* **2012**, *48*, 11781–11783.
- [15] a) E. N. Beal, K. Turnbull, *Synth. Commun.* **1992**, *22*, 673–676; b) K. Masuda, Y. Imashiro, T. Kaneko, *Chem. Pharm. Bull.* **1970**, *18*, 128–132.
- [16] a) J. Bansagi, C. Wilson-Konderka, V. Debrauwer, P. Narayanan, R. A. Batey, *J. Org. Chem.* **2022**, *87*, 11329–11349; b) S. K. Verma, R. Ghorpade, A. Pratap, M. P. Kaushik, *Tetrahedron Lett.* **2012**, *53*, 2373–2376; c) T. Rawling, A. M. McDonagh, B. Tattam, M. Murray, *Tetrahedron* **2012**, *68*, 6065–6070; d) P. A. Duspara, M. S. Islam, A. J. Lough, R. A. Batey, *J. Org. Chem.* **2012**, *77*, 10362–10368; e) H. A. Staab, *Angew. Chem. Int. Ed.* **1962**, *1*, 351–367; f) H. A. Staab, *Justus Liebigs Ann. Chem.* **1957**, *609*, 83–88; g) H. A. Staab, *Justus Liebigs Ann. Chem.* **1957**, *609*, 75–83.
- [17] a) A. Velavan, S. Sumathi, K. K. Balasubramanian, *Org. Biomol. Chem.* **2012**, *10*, 6420–6431; b) J. A. Grzyb, R. A. Batey, *Tetrahedron Lett.* **2003**, *44*, 7485–7488; c) R. A. Batey, C. Yoshina-Ishii, S. D. Taylor, V. Santhakumar, *Tetrahedron Lett.* **1999**, *40*, 2669–2672; d) R. A. Batey, V. Santhakumar, C. Yoshina-Ishii, S. D. Taylor, *Tetrahedron Lett.* **1998**, *39*, 6267–6270; e) A. K. Saha, H. Rapoport, P. Schultz, *J. Am. Chem. Soc.* **1989**, *111*, 4856–4859.
- [18] R. A. Hernandez, I. Trakakis, J.-L. Do, L. A. Cuccia, T. Friščić, P. Forgione, *Eur. J. Org. Chem.* **2023**, *26*, e202300374.
- [19] G. A. Bowmaker, *Chem. Commun.* **2013**, *49*, 334–348.
- [20] a) L. Konnert, B. Reneaud, R. M. de Figueiredo, J.-M. Campagne, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2014**, *79*, 10132–10142; b) L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2014**, *79*, 4008–4017.
- [21] K. M. Engstrom, A. Sheikh, R. Ho, R. W. Miller, *Org. Process Res. Dev.* **2014**, *18*, 488–494.
- [22] A. Porcheddu, F. Delogu, L. De Luca, E. Colacino, *ACS Sustainable Chem. Eng.* **2019**, *7*, 12044–12051.
- [23] a) L. Chen, X. Zhou, Z. Chen, C. Wang, S. Wang, H. Teng, *Beilstein J. Org. Chem.* **2022**, *18*, 1032–1039; b) A. Lee, H. K. Kim, D. H. Thompson, *Bull. Korean Chem. Soc.* **2016**, *37*, 154–160; c) S. Perveen, N. Fatima, M. A. Khan, A. Dar, K. M. Khan, N. Afza, W. Voelter, *Med. Chem. Res.* **2011**, *21*, 2709–2715.

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