

Cite this: *RSC Mechanochem.*, 2024, 1, 189

Protecting-group-free mechanosynthesis of amides from hydroxycarboxylic acids: application to the synthesis of imatinib†

Tatsiana Nikonovich,¹ Tatsiana Jarg,¹ Jevgenija Martõnova,¹ Artjom Kudrjašov,^{1,2} Danylo Merzhyievskiy,^{1,3} Marina Kudrjašova,¹ Fabrice Gallou,⁴ Riina Aav^{1*} and Dzmitry Kananovich^{1*}

Despite considerable advancements in mechanochemical amide couplings, there is a paucity of studies addressing chemoselective issues in these transformations, such as the tolerance of unmasked hydroxyl groups. In view of the high practical significance of amide coupling reactions in the synthesis of active pharmaceutical ingredients (APIs), we aimed to investigate the tolerance of unprotected hydroxyls in carboxylic acids towards various reported mechanochemical amide coupling conditions. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) in combination with ethyl acetate as a liquid-assisted grinding (LAG) additive was revealed as the most selective amide coupling system that delivers 76–94% yields of amides from a range of hydroxycarboxylic acids, including *N*-Boc-protected amino acids serine and tyrosine. The EDC-mediated amide coupling protocol was employed in the synthesis of imatinib, an anticancer drug included in the World Health Organization's List of Essential Medicines. The target API was synthesized in an overall 86% yield and 99% HPLC purity through a two-step mechanochemical C–N bond assembling reaction sequence starting from 4-(hydroxymethyl)benzoic acid.

Received 1st February 2024
Accepted 11th March 2024

DOI: 10.1039/d4mr00006d

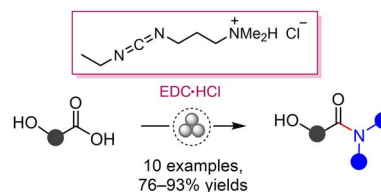
rsc.li/RSCMechanochem

Introduction

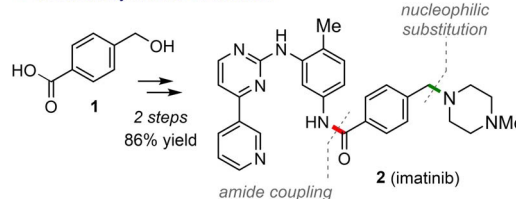
Mechanochemistry has shown great potential as a powerful tool for advancing the sustainability goals in the synthesis of active pharmaceutical ingredients (APIs).^{1–5} Focusing on the applications of mechanochemical C–N bond forming reactions,^{6,7} our objective was to develop a mechanochemical method for the synthesis of imatinib, an anti-cancer drug included in the World Health Organization's List of Essential Medicines.⁸ The planned synthetic route involved the amide coupling of 4-(hydroxymethyl)benzoic acid (**1**), followed by a subsequent nucleophilic substitution reaction at the benzylic hydroxyl (Scheme 1). In our previous work,⁷ we noticed that amide coupling of **1** with *N*-Boc piperazine mediated by the TCFH reagent (chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate) did not affect the hydroxyl group of **1**. However, regarding the synthesis of

imatinib, we were uncertain whether using a poorly nucleophilic aromatic amine would be equally successful, considering that competitive esterification reactions can be facilitated by common coupling reagents.^{9–15} While numerous mechanochemical amide coupling protocols have been reported,^{6,16–25} limited attention has been given to studying the chemoselectivity issues in these transformations. In particular, the amide bond formation in the presence of a free hydroxyl group in starting materials has not

Protecting-group-free amide coupling of hydroxycarboxylic acids



Mechanosynthesis of imatinib



Scheme 1 Outline of the work.

¹Department of Chemistry and Biotechnology, Tallinn University of Technology, Akadeemia tee 15, 12618, Tallinn, Estonia. E-mail: riina.aav@taltech.ee; dzmitry.kananovich@taltech.ee

²Tallinna Tõnismäe Realkool, Pärnu mnt 50, Tallinn, Estonia

³Department of Chemistry of Bioactive Nitrogen-containing Heterocyclic Bases, V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Academician Kukhar Str. 1, 02094 Kyiv, Ukraine

⁴Novartis Pharma AG, Novartis Campus, 4056 Basel, Switzerland

† Electronic supplementary information (ESI) available. CCDC 2287665. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4mr00006d>



been systematically explored, with only sporadic instances of such reactions reported.^{7,26–30} As a prerequisite for the synthesis of imatinib, we aimed to perform a systematic screening of previously reported protocols^{6,16,17,21} on a model amide coupling reaction of **1**. The goal was to identify a coupling reagent with the best tolerance to the unmasked hydroxyl functionality of **1** and to outline the limits of such tolerance by exploring amines with varying nucleophilicities.

The study identified 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) as the most efficient amide coupler for **1** and other examples of hydroxycarboxylic acids. Subsequently, we demonstrate the application of the established chemoselective amide coupling methodology in the two-step synthesis of imatinib **2**.

Results and discussion

The mechanochemical amidation protocols have been screened for the model coupling reaction of hydroxycarboxylic acid **1** with 4-bromo-3-methylaniline **3** as a poorly nucleophilic aromatic amine³¹ (Table 1).

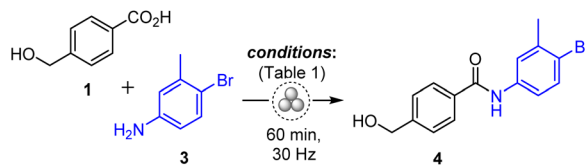
Initially, we expected that free hydroxyl of **1** could act as a competitive nucleophile,^{9–15} thereby leading to the formation of ester by-products. However, we observed a variety of side processes, the prevalence of which was influenced by the specific coupling conditions employed. The combination of

TCFH with K₂HPO₄ (Table 1, entry 1)⁷ afforded amide **4** in low 26% yield due to a competitive reaction between TCFH and amine **3** with the formation of a guanidinium derivative **3a**. 1,1'-Carbonyldiimidazole (CDI, entry 4)¹⁶ demonstrated a low 10% yield of **4** since the process was accompanied by self-condensation of **1** that delivered ester-type by-products. Several other reported methodologies^{17,21} failed to provide the amide product at all. The highest yield of **4** (90% by ¹H NMR) was attained with the EDC·HCl reagent (entry 7) and ethyl acetate as a green LAG additive.³² The use of EDC·HCl for the mechanochemical amide coupling in combination with nitromethane as a LAG additive was first reported by Štrukil and co-workers,²¹ which was followed by several examples of peptide couplings, where nitromethane was replaced by ethyl acetate.^{22,33} In our case, ethyl acetate demonstrated comparable efficacy to nitromethane and sulfolane as LAG additives (Table S1, entries 1–3 in the ESI†). This is particularly important from a safety perspective, as it is essential to avoid the use of hazardous nitromethane³² under mechanochemical conditions. Pure amide **4** was isolated in 89% yield by following an operationally simple work-up protocol, which involved treatment with water, filtration and drying.

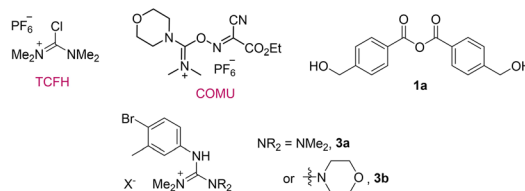
The results demonstrate that the amide coupling is generally more favoured with many of the tested reagent systems compared to the ester capping of the hydroxyl group. To further clarify the respective chemoselectivity concerns, certain amide

Table 1 Screening experiments for amide coupling of **1** and **3**^a

Entry	Coupling reagent/base	LAG additive, η ($\mu\text{L mg}^{-1}$)	Yield of 4 ^b , %
1	TCFH/K ₂ HPO ₄	EtOAc (0.19)	26 ^c
2	COMU/K ₂ HPO ₄	EtOAc (0.19)	83 ^{d,e}
3	TCFH/NMI	Without	74 ^c
4	CDI	Without	10 ^e
5	<i>t</i> -BuOK	Without	0 ^{f,g}
6	EDC·HCl/DMAP	CH ₃ NO ₂ (0.25)	0 ^g
7	EDC·HCl	EtOAc (0.25)	90 ^h



Structures of the reagents and identified by-products:



NMI = 1-methylimidazole, CDI = carbonyldiimidazole.

^a General conditions: acid **1** (0.66 mmol, 100 mg), amine **3** (0.9–1 equiv.), coupling reagent (1–1.1 equiv.), base (0.85–3 equiv.), LAG additive (η = 0.19–0.25 $\mu\text{L mg}^{-1}$), and ball milling at 30 Hz for 60 min (see the ESI for the details). ^b Yields are determined by ¹H NMR with an internal standard (1,3,5-trimethoxybenzene). ^c Guanidinium derivative **3a** was formed by the reaction of TCFH with **3**. ^d Guanidinium derivative **3b** was formed as a by-product. ^e Ester by-products resulting from self-condensation of **1** were observed. ^f The reaction was performed with ethyl ester of **1**. ^g Almost no reaction: starting materials with a trace of unidentified by-products. ^h Anhydride **1a** was formed in a reaction without amine **3**.



Table 2 Esterification of **4** with 4-(hydroxymethyl)benzoic acid **1**^a

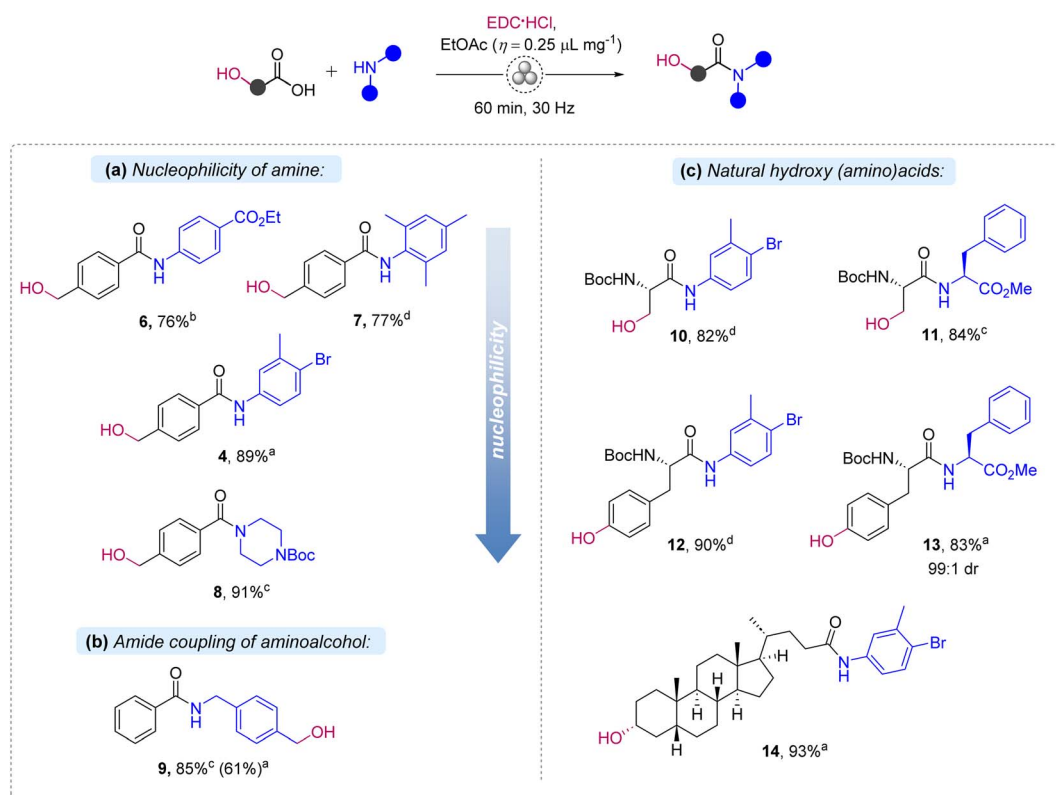
Entry	Coupling reagent/base	LAG additive, η ($\mu\text{L mg}^{-1}$)	Yield of 5 ^b , %
1	COMU/ K_2HPO_4	EtOAc (0.19)	31
2	TCFH/NMI	Without	40
3	TCFH/ K_2HPO_4	EtOAc (0.19)	5 ^c
4	EDC·HCl	EtOAc (0.25)	<1 ^d

^a General conditions: amide **4** (0.19 mmol, 60 mg), acid **1** (1 equiv.), coupling reagent (1–1.1 equiv.), base (3 equiv.), LAG additive ($\eta = 0.19$ – $0.25 \mu\text{L mg}^{-1}$), and ball milling at 30 Hz for 60 min. ^b Yields are determined by $^1\text{H NMR}$. ^c Anhydride **1a** was formed in 70% yield. ^d Starting materials are left and anhydride **1a** was formed in 30% yield.

coupling conditions were also tested for producing ester **5** through the reaction of **4** with **1** (Table 2). Both COMU/ K_2HPO_4 and TCFH/NMI systems afforded **5** at moderate yields of 31% and 40%, respectively (Table 2, entries 1 and 2). However, using TCFH/ K_2HPO_4 or EDC·HCl (entries 3 and 4) resulted in only trace amounts of **5**, with the predominant process being the generation of anhydride **1a**.

This suggests that COMU/ K_2HPO_4 and TCFH/NMI systems are equally effective for synthesizing both esters and amides, thus requiring to incorporate protecting groups in the starting materials to achieve optimal yields. Conversely, EDC·HCl can be reliably used for amide synthesis in the presence of unprotected hydroxyls.

Then, the scope of the EDC-promoted coupling was briefly investigated (Scheme 2). First, we explored the effect of the nucleophilicity of the amine partner on the amide coupling of **1** (Scheme 2a). As a result, more nucleophilic *N*-Boc piperazine smoothly delivered amide **8** in a high 91% yield, while the least nucleophilic electron-deficient ethyl 4-aminobenzoate and sterically hindered 2,4,6-trimethylaniline formed the corresponding amides **6** and **7** in reduced 76% and 77% yields, respectively. These results confirm that poor nucleophilic amines are less reactive, but still amenable substrates. Besides the hydroxycarboxylic acid **1**, the amino group in (4-(aminomethyl)phenyl)methanol was selectively acylated with benzoic acid, affording amide **9** in 85% yield, with no ester isomer of **9**



Scheme 2 Scope of EDC-mediated mechanochemical amide coupling: (a) influence of amine's nucleophilicity; (b) amide coupling of aminoalcohol; (c) synthesis of amides and dipeptides from natural hydroxy (amino)acids. ^aYield of the isolated product after treatment with water, filtration and drying in air. ^bYield determined by $^1\text{H NMR}$ with an internal standard. ^cYield of the isolated product after extraction work-up. ^dProduct isolated by silica gel column chromatography.

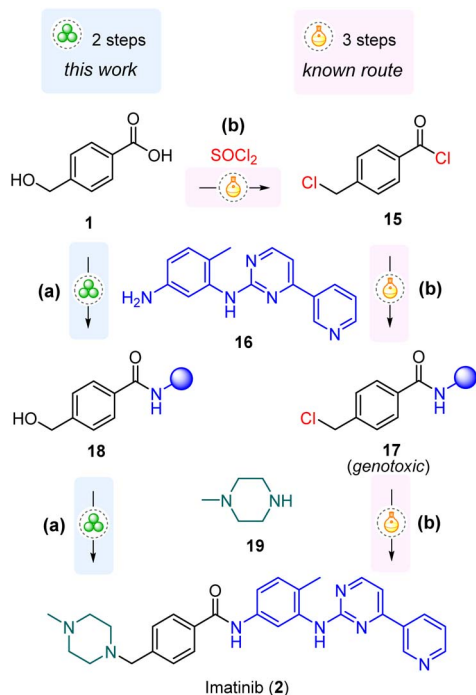


being formed (Scheme 2b). The outcome complies with the analogous reactions in solution^{34,35} and by mechanochemistry.^{26–28} Next, we explored hydroxyl group containing amino acids, namely *N*-Boc-*L*-serine and *N*-Boc-*L*-tyrosine, in the reaction with aniline **3** and *L*-phenylalanine methyl

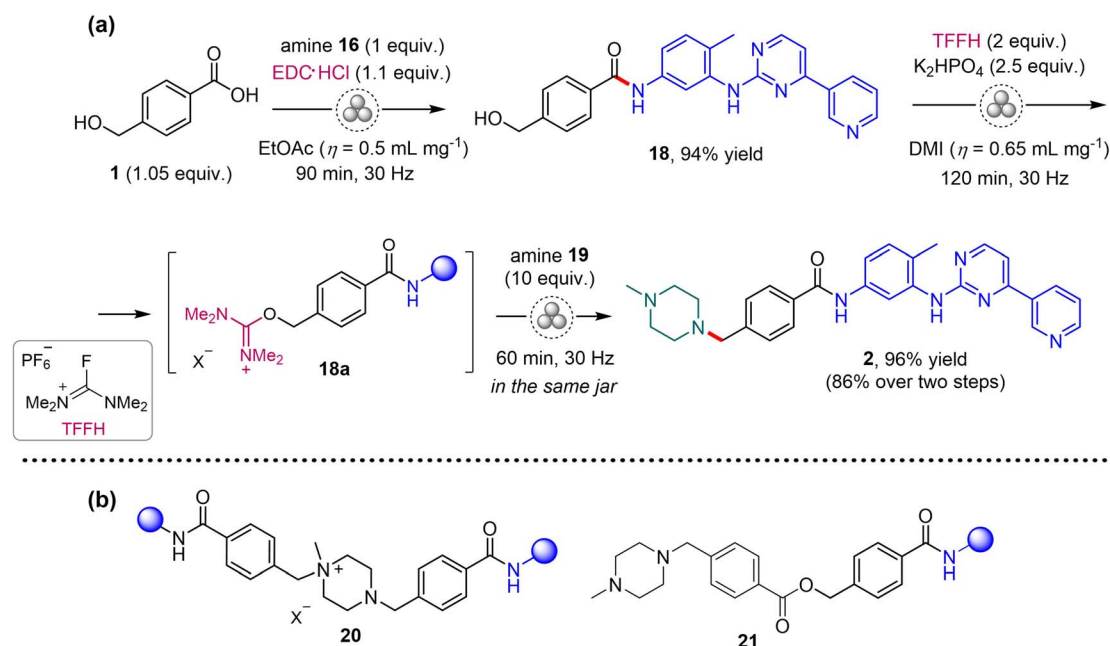
ester (Scheme 2c). Notably, previous examples of mechanochemical peptide coupling reactions relied on the use of hydroxyl-protecting groups in serine and tyrosine.^{18,19} Amides **10** and **12** were prepared in good 82% and 90% yields in the reactions with **3**. However, column chromatography purification was needed in these cases to separate unreacted amine **3**. Dipeptides **11** and **13** were flawlessly prepared by coupling with *L*-phenylalanine methyl ester. Pure products were isolated in 84% and 83% yields after extractive workup. Importantly, dipeptide **13** was obtained with high diastereomeric purity (99 : 1 dr), indicating the absence of notable epimerization. Lithocholic acid in its coupling with **3** produced amide **14** in a high 93% yield, after simple treatment of the reaction mixture with water and drying in air. To compare the mechanochemical protocol with solution synthesis, dipeptide **11** was additionally prepared in CH₂Cl₂ solution. The solution-based reaction followed by extractive workup also afforded pure **11** in 90% yield, demonstrating that the chemoselectivity of the amide coupling is attributable to the coupling reagent rather than the mechanochemical conditions applied.

Subsequently, the EDC-mediated amide coupling protocol was employed in the synthesis of anticancer drug imatinib **2** (the trade name Gleevec®) from the World Health Organization's List of Essential Medicines.⁸ The first synthetic route was patented in 1993 by Zimmermann,³⁶ followed by a number of improved protocols,^{37–48} including flow-based approaches,^{49–52} and microwave-assisted solid-phase synthesis.⁵³ However, mechanochemical preparations have not been reported yet.

Importantly, our planned route bypasses the formation of a chlorinated intermediate **17** with known genotoxic properties (Scheme 3), the content of which is strictly regulated (10 ppm)⁴¹ and which is commonly encountered in the mainstream synthetic strategies.^{38–40,44–47,49–51,53}



Scheme 3 The developed mechanochemical route (a) and previously reported mainstream solution-based (b) approach for the synthesis of imatinib (**2**).



Scheme 4 (a) Mechanochemical synthesis of imatinib (**2**). DMI = dimethyl isosorbide. (b) The main impurities identified in the crude **2**.



After short optimization of the reaction conditions (see Tables S4 and S5 in the ESI†), imatinib **2** was prepared by EDC-mediated amide coupling of **1** with amine **16**, followed by nucleophilic substitution of the hydroxyl group in the formed amide **18** with 1-methylpiperazine **19** *via* generation of reactive isouronium intermediate **18a** (Scheme 4a).⁷ The crude API was obtained in 86% overall yield, taking into account its 95% HPLC purity. The main impurities in **2** were identified as unreacted **18** (1.3%), quaternary salt **20** (2%) and **21** (1.4%; Scheme 4b). Purification of the crude **2** was achieved through recrystallization from a methanol-ethyl acetate mixture (1 : 1 ratio), yielding the target API with an HPLC purity of 99%. Crystals of intermediate **18** suitable for single-crystal X-ray diffraction analysis were obtained by crystallization from methanol solution and its solid-state structure was revealed, in a form of methanol solvate (CCDC 2287665, see Section 5 in the ESI†).

The genotoxic potential of intermediate **18** was checked by performing *in silico* assessment. Knowledge-based and statistical systems were used to predict potential mutagenicity following the recommendations of the ICH M7 (R1) (2018) guideline. As a result, **18** displayed no structural concern for mutagenicity. However, genotoxic amine **16** was still present in

the product, in a content of *ca.* 560 ppm (see the ESI† for the details). This is similar to the content in the crude imatinib obtained by other methods and could be minimized during the downstream processing (see Section 6.2 in the ESI†).⁵⁴

Next, we applied the CHEM21 toolkit⁵⁵ to reveal the advantages of the developed mechanochemical synthesis in comparison to the similar early-stage development solution protocol described by Liu *et al.*³⁹ (extended data and calculations for other similar routes are shown in Table S6 in the ESI†).

The main advantages of the mechanochemical protocol compared to the benchmarking solution-based approach included reduced process mass intensity (PMI, 221 *vs.* 564), the use of green and sustainable solvents (ethyl acetate, dimethyl isosorbide, and water) and room temperature operation (Fig. 1a). The exclusion of the genotoxic intermediate **17** (Scheme 3) was another important improve.

In order to expose the green chemistry-related innovations of the developed method even more clearly, we applied the “innovation Green Aspiration Level” (iGAL) methodology⁵⁶ by using the respective scorecard web calculator.⁵⁷ The mechanochemical method demonstrated an excellent relative process greenness (RPG) of 77%, which is much higher when compared to the RPG (30%) of the solution-based method by Liu *et al.*, used as a benchmark early-stage development process (Fig. 1b). Importantly, the mechanochemical approach exhibits a lower waste output of 2.22 times when compared to the average value at the early development stage. However, the developed methodology still relies on the use of stoichiometric coupling reagents (EDC·HCl and TFFH), which may pose environmental, safety or health hazards⁵⁸ and reduce the atom economy of the reaction. Consequently, there is a need for further development of mechanochemical amidation methods with improved atom efficiency through the avoidance of stoichiometric amide coupling reagents.⁵⁹

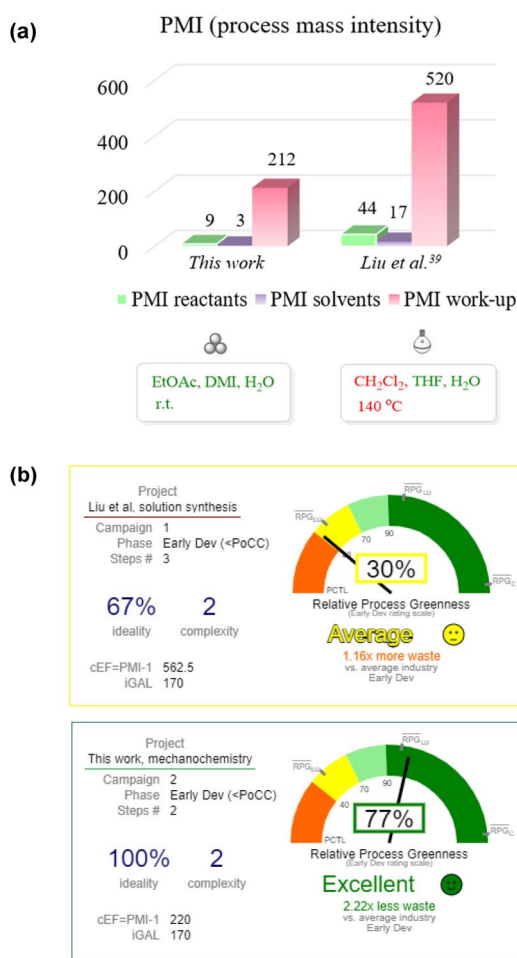


Fig. 1 (a) Comparison of PMI values for the mechanochemical and a benchmarking solution-based method.³⁹ (b) Graphical illustration of green chemistry innovation using the iGAL scorecard.

Conclusions

Here we demonstrated that mechanochemical amide coupling can be performed with unprotected hydroxycarboxylic acids by using EDC·HCl as a coupling reagent in combination with ethyl acetate as a LAG additive. High 76–94% yields of amides can be achieved, while the use of poor nucleophilic amines results in reduced coupling efficacy. The presence of an unmasked hydroxyl group in the obtained amide products allows their straightforward functionalization in a step-economical manner, such as nucleophilic substitution of the hydroxyl group. The application is illustrated by the first mechanochemical synthesis of imatinib, an anticancer drug included in the World Health Organization's List of Essential Medicines. The target API was prepared in 86% total yield and HPLC purity of 99% through a two-fold mechanochemical C–N bond construction sequence.

Conflicts of interest

The authors declare no conflict of interest.



Acknowledgements

The research was supported by the Estonian Research Council grant PRG399 and COST Action CA18112 “Mechanochemistry for Sustainable Industry”. This project has received funding from the European Union’s Horizon 2021–2027 research and innovation programme under grant agreement No. 101057286 (IMPACTIVE). Danylo Merzhyievskiy is grateful to the Education and Youth Board of Estonia for financial support of his research stay at the Tallinn University of Technology.

References

- P. Ying, J. Yu and W. Su, *Adv. Synth. Catal.*, 2021, **363**, 1246–1271.
- O. Bento, F. Luttringer, T. Mohy El Dine, N. Pétry, X. Bantreil and F. Lamaty, *Eur. J. Org. Chem.*, 2022, e202101516.
- X. Yang, C. Wu, W. Su and J. Yu, *Eur. J. Org. Chem.*, 2022, e202101440.
- M. Pérez-Venegas and E. Juaristi, *ACS Sustainable Chem. Eng.*, 2020, **8**, 8881–8893.
- O. Galant, G. Cerfeda, A. S. McCalmont, S. L. James, A. Porcheddu, F. Delogu, D. E. Crawford, E. Colacino and S. Spatari, *ACS Sustainable Chem. Eng.*, 2022, **10**, 1430–1439.
- T. Dalidovich, K. A. Mishra, T. Shalima, M. Kudrjašova, D. G. Kananovich and R. Aav, *ACS Sustainable Chem. Eng.*, 2020, **8**, 15703–15715.
- T. Dalidovich, J. V. Nallaparaju, T. Shalima, R. Aav and D. G. Kananovich, *ChemSusChem*, 2022, **15**, e202102286.
- World Health Organization, *WHO Model List of Essential Medicines 23rd List*, 2023.
- M. Tsakos, E. S. Schaffert, L. L. Clement, N. L. Villadsen and T. B. Poulsen, *Nat. Prod. Rep.*, 2015, **32**, 605–632.
- B. Neises and W. Steglich, *Angew. Chem., Int. Ed.*, 1978, **17**, 522–524.
- A. Chighine, S. Crosignani, M.-C. Arnal, M. Bradley and B. Linclau, *J. Org. Chem.*, 2009, **74**, 4753–4762.
- J. K. Twibanire and T. B. Grindley, *Org. Lett.*, 2011, **13**, 2988–2991.
- M. Pittelkow, F. S. Kamounah, U. Boas, B. Pedersen and J. B. Christensen, *Synthesis*, 2004, 2485–2492.
- N. R. Luis, K. K. Chung, M. R. Hickey, Z. Lin, G. L. Beutner and D. A. Vosburg, *Org. Lett.*, 2023, DOI: [10.1021/acscorglett.3c01611](https://doi.org/10.1021/acscorglett.3c01611).
- H. Nishikawa, M. Kuwayama, A. Nihonyanagi, B. Dhara and F. Araoka, *J. Mater. Chem. C*, 2023, **11**, 12525–12542.
- T.-X. Métro, J. Bonnamour, T. Reidon, J. Sarpoulet, J. Martinez and F. Lamaty, *Chem. Commun.*, 2012, **48**, 11781–11783.
- W. I. Nicholson, F. Barreteau, J. A. Leitch, R. Payne, I. Priestley, E. Godineau, C. Battilocchio and D. L. Browne, *Angew. Chem., Int. Ed.*, 2021, **60**, 21868–21874.
- L. Gonnet, T. Tintillier, N. Venturini, L. Konnert, J.-F. Hernandez, F. Lamaty, G. Laconde, J. Martinez and E. Colacino, *ACS Sustainable Chem. Eng.*, 2017, **5**, 2936–2941.
- J. Bonnamour, T.-X. Métro, J. Martinez and F. Lamaty, *Green Chem.*, 2013, **15**, 1116–1120.
- C. Bolm and J. G. Hernández, *ChemSusChem*, 2018, **11**, 1410–1420.
- V. Štrukil, B. Bartolec, T. Portada, I. Đilović, I. Halasz and D. Margetić, *Chem. Commun.*, 2012, **48**, 12100–12102.
- V. Porte, M. Thioly, T. Pigoux, T.-X. Métro, J. Martinez and F. Lamaty, *Eur. J. Org. Chem.*, 2016, 3505–3508.
- C. Duangkamol, S. Jaita, S. Wangngae, W. Phakhodee and M. Pattarawarapan, *RSC Adv.*, 2015, **5**, 52624–52628.
- T. Lainer, F. Czerny and M. Haas, *Org. Biomol. Chem.*, 2022, **20**, 3717–3720.
- J. G. Hernández, K. J. Ardila-Fierro, D. Crawford, S. L. James and C. Bolm, *Green Chem.*, 2017, **19**, 2620–2625.
- T. Portada, D. Margetić and V. Štrukil, *Molecules*, 2018, **23**, 3163.
- Q. Cao, D. E. Crawford, C. Shi and S. L. James, *Angew. Chem., Int. Ed.*, 2020, **59**, 4478–4483.
- F. Ravalico, S. L. James and J. S. Vyle, *Green Chem.*, 2011, **13**, 1778–1783.
- M. Anselmi, P. Stavole, E. Boanini, A. Bigi, E. Juaristi and L. Gentilucci, *Future Med. Chem.*, 2020, **12**, 479–491.
- F. Santino, R. Petruzzelli, J. Zhao, E. Boanini and L. Gentilucci, *Sustainable Chem. Pharm.*, 2021, **24**, 100540.
- T. Kanzian, T. A. Nigst, A. Maier, S. Pichl and H. Mayr, *Eur. J. Org. Chem.*, 2009, 6379–6385.
- D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.
- N. Pétry, H. Benakki, E. Clot, P. Retailleau, F. Guenoun, F. Asserar, C. Sekkat, T.-X. Métro, J. Martinez and F. Lamaty, *Beilstein J. Org. Chem.*, 2017, **13**, 2169–2178.
- D.-K. Kim, J. Y. Lee, J.-S. Kim, J.-H. Ryu, J.-Y. Choi, J. W. Lee, G.-J. Im, T.-K. Kim, J. W. Seo, H.-J. Park, J. Yoo, J.-H. Park, T.-Y. Kim and Y.-J. Bang, *J. Med. Chem.*, 2003, **46**, 5745–5751.
- M. Parmentier, M. K. Wagner, K. Magra and F. Gallou, *Org. Process Res. Dev.*, 2016, **20**, 1104–1107.
- J. Zimmermann, *EP Pat.*, 0564409, 1993.
- B. J. Deadman, M. D. Hopkin, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2013, **11**, 1766–1800.
- Y. Heo, D. Hyun, M. R. Kumar, H. M. Jung and S. Lee, *Tetrahedron Lett.*, 2012, **53**, 6657–6661.
- Y.-F. Liu, C.-L. Wang, Y.-J. Bai, N. Han, J.-P. Jiao and X.-L. Qi, *Org. Process Res. Dev.*, 2008, **12**, 490–495.
- X. Zhang, J. Sun, T. Chen, C. Yang and L. Yu, *Synlett*, 2016, 2233–2236.
- A. Kompella, B. R. K. Adibhatla, P. R. Muddasani, S. Rachakonda, V. K. Gampa and P. K. Dubey, *Org. Process Res. Dev.*, 2012, **16**, 1794–1804.
- K. C. Nicolaou, D. Vourloumis, S. Totokotsopoulos, A. Papakyriakou, H. Karsunky, H. Fernando, J. Gavrilyuk, D. Webb and A. F. Stepan, *ChemMedChem*, 2016, **11**, 31–37.
- C. Wang, X. Bai, R. Wang, X. Zheng, X. Ma, H. Chen, Y. Ai, Y. Bai and Y. Liu, *Org. Process Res. Dev.*, 2019, **23**, 1918–1925.
- Z. Szakács, S. Béni, Z. Varga, L. Örfi, G. Kéri and B. Noszál, *J. Med. Chem.*, 2005, **48**, 249–255.
- W. Szczepek, W. Luniewski, L. Kaczmarek, B. Zagrodzki, D. Samson-Lazinska, W. Szelejewski and M. Skarzynski, *World Pat.*, 2006071130A2, 2006.



- 46 A. Kompella, A. K. S. Bhujanga Rao, N. Venkaiah Chowdary and R. Srinivas, *World Pat.*, 2004108699A1, 2004.
- 47 O. Loiseleur, D. Kaufmann, S. Abel, H. M. Buerger, M. Meisenbach, B. Schmitz and G. N. Sedelmeier, *World Pat.*, 2003066613, 2003.
- 48 M. D. Khunt, N. S. Patil, H. S. Pagire and N. S. Pradhan, *World Pat.*, 2011095835A1, 2011.
- 49 M. D. Hopkin, I. R. Baxendale and S. V. Ley, *Chem. Commun.*, 2010, **46**, 2450–2452.
- 50 J. C. Yang, D. Niu, B. P. Karsten, F. Lima and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2016, **55**, 2531–2535.
- 51 N. Collins, D. Stout, J.-P. Lim, J. P. Malerich, J. D. White, P. B. Madrid, M. Latendresse, D. Krieger, J. Szeto, V.-A. Vu, K. Rucker, M. Deleo, Y. Gorfú, M. Krummenacker, L. A. Hokama, P. Karp and S. Mallya, *Org. Process Res. Dev.*, 2020, **24**, 2064–2077.
- 52 W. C. Fu and T. F. Jamison, *Org. Lett.*, 2019, **21**, 6112–6116.
- 53 F. Leonetti, C. Capaldi and A. Carotti, *Tetrahedron Lett.*, 2007, **48**, 3455–3458.
- 54 E. Grendele and A. Soldà, *Eur. Pat.*, 2927223B1, 2015.
- 55 C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111–3121.
- 56 F. Roschangar, Y. Zhou, D. J. C. Constable, J. Colberg, D. P. Dickson, P. J. Dunn, M. D. Eastgate, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg, U. Scholz, A. G. Smith, M. Henry, J. Mulder, J. Brandenburg, J. R. Dehli, D. R. Fandrick, K. R. Fandrick, F. Gnad-Badouin, G. Zerban, K. Groll, P. T. Anastas, R. A. Sheldon and C. H. Senanayake, *Green Chem.*, 2018, **20**, 2206–2211.
- 57 <https://www.acs.org/green-chemistry-innovation-scorecard>, 2023.
- 58 J. C. Graham, A. Trejo-Martin, M. L. Chilton, J. Kostal, J. Bercu, G. L. Beutner, U. S. Bruen, D. G. Dolan, S. Gomez, J. Hillegass, J. Nicolette and M. Schmitz, *Chem. Res. Toxicol.*, 2022, **35**, 1011–1022.
- 59 T. Stolar, J. Alić, G. Talajić, N. Cindro, M. Rubčić, K. Molcanov, K. Užarević and J. G. Hernández, *Chem. Commun.*, 2023, **59**, 13490–13493.

