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Article

N-formylsaccharin: a sweet(able) formylating agent in mechanochemistry

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Abstract: The acylation of amines has always attracted a deep interest as a synthetic route due to its high versatility in organic chemistry and biochemical processes. The purpose of this article is to depict a mechanochemical acylation procedure based on the use of acyl-saccharin derivatives, namely *N*-formylsaccharin, *N*-acetylsaccharin and *N*-propionylsaccharin. This protocol furnishes a valuable solventless alternative to the existing processes and aims to be highly beneficial in multi-step procedures due to its rapid and user-friendly workup.

Keywords: formamides; formylation; acylation; mechanochemistry; saccharin

1. Introduction

The derivatization of heteroatoms has recently gained a high degree of interest in the organic and pharmaceutical fields. It is crucial to converting some unrefined starting materials into something different, emphasizing molecules having a potential drug design. Regarding this, it was found that the attachment of a formyl or acetyl group often conferred biological or pharmacological properties, as they can create a more active drug or what could be termed as a *pro-drug* [1,2]. Several pharmaceuticals having different therapeutical effects can be numbered among these two classes: paracetamol and other NSAID's [3] and Oseltamivir [4] as antiviral are the prominent representatives in the case of the *N*-acetyl group. The *N*-formylated compounds, instead, have been less explored, probably due to some handling complications in their preparation. However, this does not suggest that their importance is negligible: as a matter of fact, some noteworthy drugs are available in the market, namely Formoterol and Arformoterol [5,6] for pulmonary diseases and Orlistat for the treatment of obesity [7] Fig. 1.

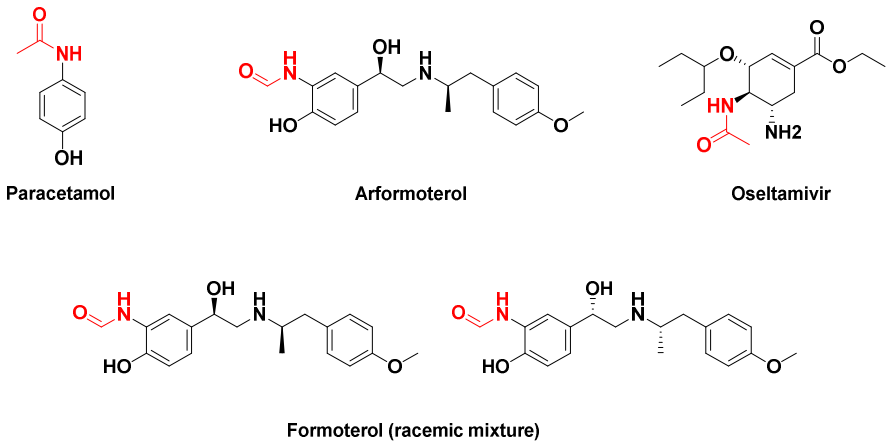

Fig. 1. Some examples of acetylated and formylated commercially available drugs.

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Anyway, the utility of these formylated compounds is considerably beyond the pure pharmaceutical use. Indeed, different types of reactions involve the use of formamides as starting materials, but one of the main concerns is the production of isocyanide [8,9,10,11,12,13,14]. Alongside the traditional solution-based chemistry behind isocyanide synthesis, a recent publication by our team depicts an efficient mechanochemical synthesis of isocyanides starting from formamides [15], proving the strength of the methodology and the importance of focusing on their production. Other potential applications are the synthesis of amidines [16], symmetrical and not symmetrical ureas [17,18], isocyanates [19], and heterocycles [20,21].

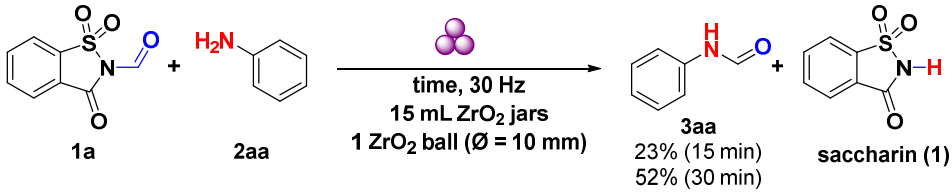
While acetylation is a general and effortless procedure to deal with, some operational issues instantly emerge when facing a formylation. The primary problem of the existing approaches lies in the required challenging conditions: for instance, the employment of gaseous CO_2 under reductive conditions [22]. Other methodologies involve the utilization of an acidic media, whose acid source could be represented by SiO_2 [23] or ZrO_2 [24] as Lewis's acids and sulfuric acid [25] or formic acid [26] as Brønsted's ones. Similarly, microwave reactions involving the use of ethyl formate suffer from the high temperature required (around 100 °C) despite being entirely performing as a method [27]. Other pathways involve using small molecules such as thiamine hydrochloride in combination with formic acid [28]. Finally, some other formylating agents have been recently proposed, such as DMF [29], sodium formate [30] and CDMT [31].

Analyzing the literature, we observed a relevant interest in developing better formylating/acylating agents. Taking inspiration from a recent paper by Cossy and coworkers, we chose *N*-formylsaccharin as a suitable solid reagent for running formylation reactions in a ball mill [32]. Furthermore, because this topic is almost unexplored but unobtrusively relevant, we also decided to expand the scope to the *N*-acylation reactions by exploiting the intriguing reactivity of other *N*-acylsaccharin compounds - namely the *N*-acetyl and *N*-propionyl derivatives. The considerable interest in producing such derivatives lies in the possibility of accessing to many different moieties, laying the groundwork for synthesizing anti-inflammatory drugs and analgesics, such as paracetamol-like compounds [33] and fentanyl derivatives [34].

In this article, we focused our attention on the neat synthesis of primary and secondary formamides by exploiting the mechanical force as the energy source and the reactivity of a green reagent. Moreover, we developed a mechanochemical workup of the reaction crude to limit the solvent employment at the sole recovery of the desired product.

2. Results and Discussion

At first, we explored the mechanochemical reaction using experimental conditions close to the classical referral procedure, to draw a direct comparison with the solvent-based method. We performed the initial mechanochemical reactions on a mmol scale, milling aniline **2aa** (1 mmol) and *N*-formyl saccharin (1 mmol) inside a 15 mL ZrO_2 vessel equipped with one ball (10 mm of diameter) of the same material (Scheme 1). We ran the mechanochemical reaction at a frequency of 30 Hz for 15 min. Unfortunately, the reaction gave only a 23% yield of compound **3aa**, whereas, when the reaction time was doubled (30 min), we obtained up to 52% yield of the desired product. Therefore, we investigated the influence of other parameters, such as the presence of Lewis' bases, to achieve an almost complete conversion and avoid tedious workups.



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Scheme 1. General scheme of the reaction.

In this context, we tested the effect of different carbonates to evaluate the cation (Na, K, Cs) influence and whether the anhydrous or moist form could give better outcomes. Unluckily, apart from a slight increase in specific cases, none of these bases showed beneficial effects by shortening the reaction time. Metal oxides did not bring any advantage as well. Other solid o liquid organic bases such as imidazole, *N*-methylimidazole and potassium *tert*-butylate failed to improve the conversion yields.

Several theories could be depicted in this regard, even if some doubts remain unsolved. For example, one of the possible explanations could be that such bases significantly modify the rheology of the system, forming a sort of "cake".

When ascertained that the base's nature was almost irrelevant, we turned our attention to stoichiometry, especially in cases where the yield seemed to slightly increase. Once again, the results were unsatisfactory on all sides, even in a ratio of 1:3 between the starting material and the base (Tab. 1). Lastly, we verified some LAG conditions. The solvents designated for these experiments were THF and CPME, allowing us to compare the solution approach in the former case and to give a greener alternative in the latter. Different η values were tested, ranging from 0.1 μL/mg to 0.5 μL/mg. The results indicated that small amounts of solvent (LAG) did not enhance the reactivity, at least under our experimental conditions.

Tab 1. Screening of different bases and ratios.

Entry	Bases	R-NH_2/Base ratio	Yields[a]
1	none	-	52%
2	Li_2CO_3 (anhydrous)	1:1	35%
3	Li_2CO_3 (wet)	1:1	32%
4	Li_2CO_3 (anhydrous)	1:3	29%
5	Li_2CO_3 (wet)	1:3	29%
6	**K_2CO_3 (anhydrous)**	**1:1**	**56%**
7	K_2CO_3 (wet)	1:1	40%
8	K_2CO_3 (anhydrous)	1:3	35%
9	K_2CO_3 (wet)	1:3	32%
10	Na_2CO_3 (anhydrous)	1:1	53%
11	Na_2CO_3 (wet)	1:1	42%
12	Na_2CO_3 (anhydrous)	1:3	39%
13	Na_2CO_3 (wet)	1:3	40%
14	Cs_2CO_3 (anhydrous)	1:1	46%
15	Cs_2CO_3 (wet)	1:1	43%
16	Cs_2CO_3 (anhydrous)	1:3	45%
17	Cs_2CO_3 (wet)	1:3	45%
18	MgO	1:1	26%
19	CaO	1:1	15%
20	*N*-methylimidazole	1:1	36%
21	Imidazole	1:1	33%
22	*t*-BuOK	1:1	23%

The reactions were all carried out with the same experimental parameters unless otherwise specified: aniline (1 mmol), *N*-formyl saccharin (1.1 mmol), base (1 mmol), 15 mL ZrO_2 jar and 1 ball (Ø = 10 mm), 30 Hz for 30 min. [a] Yields are calculated by GC-MS analysis.

Gratifyingly, we found the complete conversion of amine **2aa** into the desired formamide **3aa** as we increased the reaction time up to 60 minutes without adding a base. So, in

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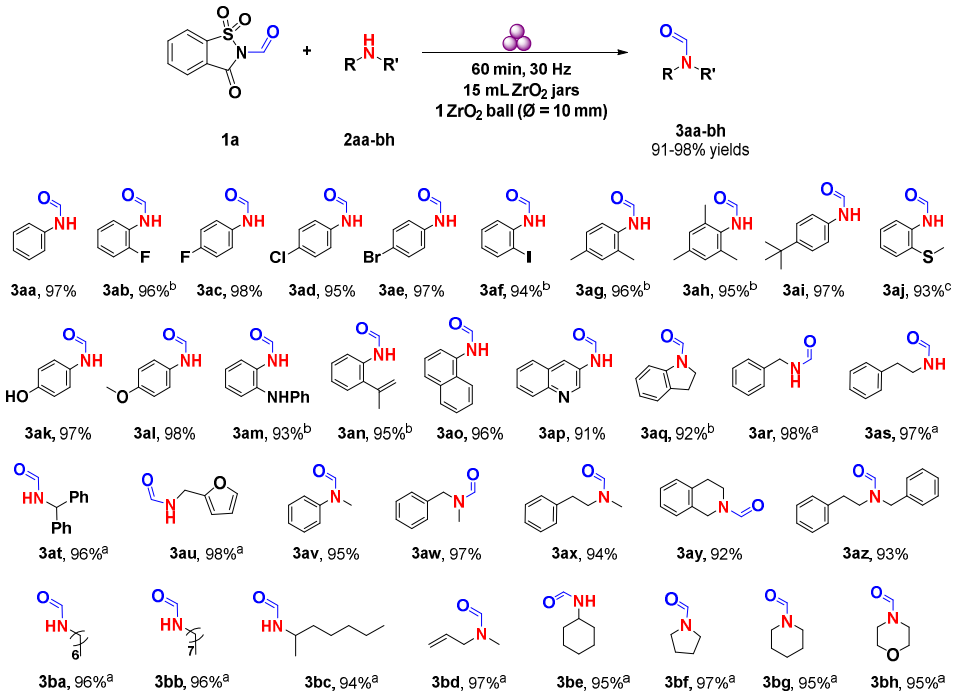
the case of aromatic amines and secondary benzylic ones, namely compounds **2aa**, **2ac**, **2ad**, **2ae**, **2ai**, **2ak**, **2al**, **2ao**, **2ap**, **2av**, **2aw**, **2ax**, **2ay**, **2az,** the reaction proceeded to a complete conversion in 1h (Scheme 2).

The results considerably differed as the amine's nucleophilicity changed. Due to their enhanced nucleophilicity, both primary (aliphatic and benzylic **2ar**, **2as**, **2at**, **2au**, **2ba**, **2bb**, **2bc**, **2be)** and secondary aliphatic amines **2bd**, **2bf**, **2bg**, **2bh**, only needed 30 min of reaction (Scheme 2). Instead, the more hindered ortho-substituted anilines **2ab**, **2af**, **2ag**, **2am**, **2an**, and some heterocycles such as the indoline **2aq** required a longer reaction time (2h) to reach the complete conversion. The *o*-methylthio aniline **2aj** takes up to 3h of milling to for being fully converted into its corresponding formamide **3aj**. (Scheme 2)



Scheme 2. Mechanosynthesis of aryl, alkyl and heterocyclic formamides. a) 30 minutes of reaction time; b) 120 min of reaction time; c) 180 min of reaction time. Yields refer to pure isolated compounds.

These experimental results show that the reaction follows a definite trend, a logical behavior intrinsic to each substrate's chemical characteristics, briefly summarized in Figure 2.

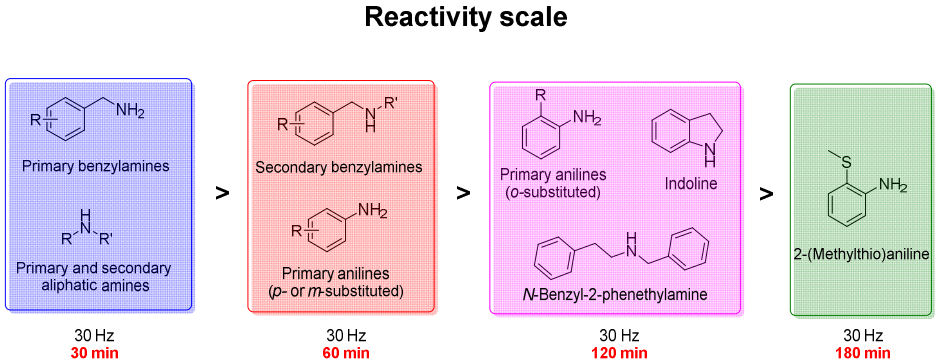


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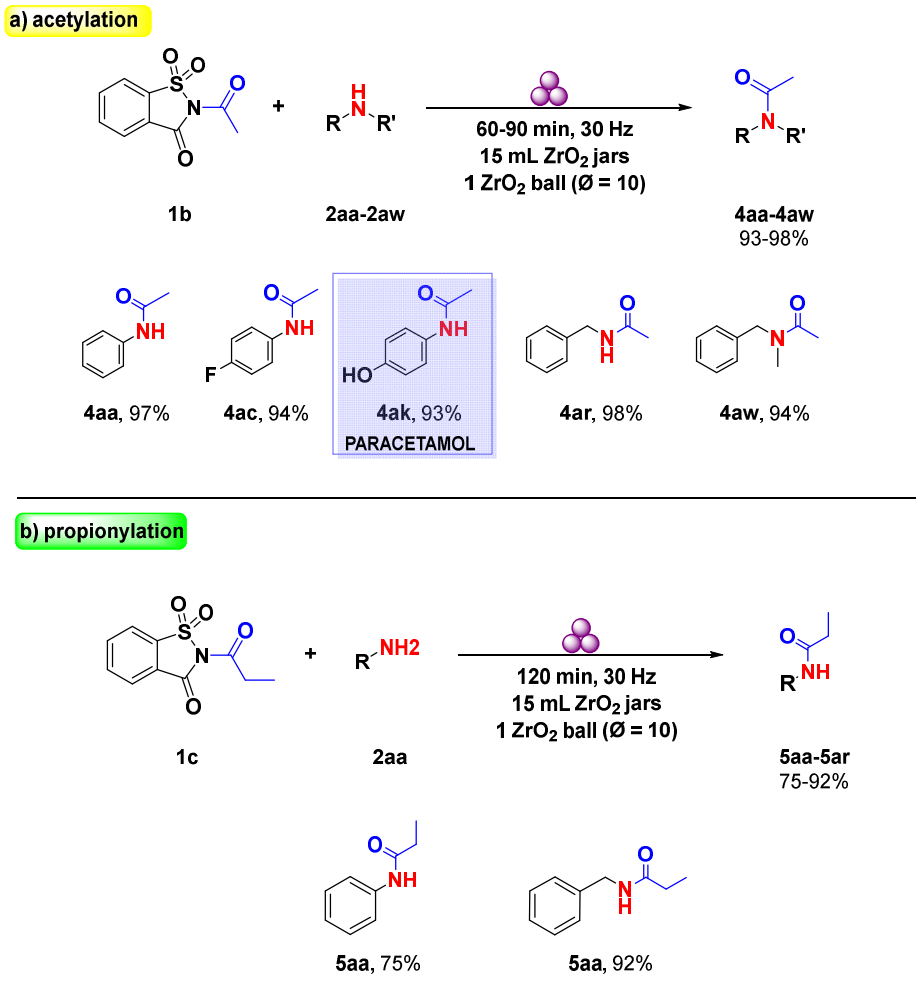
Fig. 2. The general reaction trend related to the substrate's structure.

Once the formylation reaction was explored, we pursued the idea of extending the methodology to other potential acylating systems. According to the limited literature previously reported on the topic, we moved to the synthesis of *N*-acetyl and *N*-propionyl saccharin [35].

With an efficient and green amine formylation procedure in hand, we extended this methodology to the mechanosynthesis of acetamides **4aa-4aw** and propionamide **5aa-5ar** from the corresponding amines. The mechanochemical approach allowed a ready synthesis of the target amides, avoiding the need for an aqueous acid purification or the requirement for tedious chromatographic techniques. In contrast, analogous solvent-based processes usually require an additional post-synthesis purification stage. The remarkable results can be seen from the data summarized in Scheme 3.



Scheme 3. The other acylation scope.

It is noteworthy that we were also able to obtain an Active Pharmaceutical Ingredient (API) of considerable interest, such as paracetamol **4ak**, an evergreen drug of worldwide use (Scheme 3). Not only is our methodology straightforward and solvent-free, but it also highlights an often-undervalued aspect, namely the purification process. At the end of the reactions, our by-product is a non-toxic compound such as saccharin, which can be easily converted into sodium saccharinate salt through a rapid grinding with moist $NaHCO_3$. This base is strong enough to deprotonate the resulting saccharin but not to hydrolyze our

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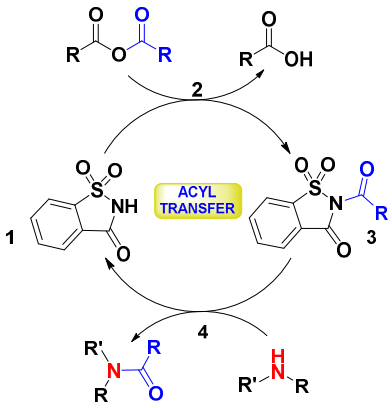
newly formed amide. This was the main issue with the moist form of Na_2CO_3, which decomposed about 30% of our product. Therefore, we are firmly convinced that this methodology is suitable for an industrial scale-up and production.

Lastly, aniline was chosen for the propionylation reaction because of the nature of the relative product **5aa**. This decision was mainly based on the premise that this amine can represent a perfect building block for fentanyl derivatives, a well-known and widespread pain therapy drug.

All the syntheses depicted throughout this article are easy to accomplish and proceed with the exact reaction mechanism, which could be defined as an acyl transfer. It is a mere transamidation between the *N*-acylsaccharin and a different amine. Naturally, the larger the steric hindrance of the acyl group, the lower the yields will be, as can be readily displayed by the schemes reported above. The reaction mechanism is shortly described in Scheme 4. It is worthy to underline that, at the end of each reaction, the residual saccharinate salt inside the jar can be recovered as a solid to be recycled.



Scheme 4. The assumed mechanism for this mechanochemical promoted acyl transfer reaction.

4. Materials and Methods

4.1. Materials

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, and TCI Europe and used as received. All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualised under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade. Mechanochemical reactions were carried out using a FormTech FTS-1000 Shaker Mill® apparatus. The reagents were milled using a zirconia SmartSnap™ grinding jar (15 mL) equipped with balls Ø 10 mm) of the same material. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 600 MHz NMR spectrometer at 298 K. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to as the residual hydrogen in the solvent ($CDCl_3$, 7.27 ppm or DMSO-d_6 2.54 ppm). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, 77.0 ppm or DMSO-d_6 39.5 ppm). GC-MS analyses were performed on an Agilent 5977B MS interfaced to the GC 7890B equipped with a DB-5ms column (J & W). Yields refer to pure isolated materials.

4.2. General procedure for N-formamides synthesis from primary and secondary amines.

A 15 mL ZrO_2 jar equipped with one ZrO_2 milling ball (10 mm diameter) was filled with amine **2aa-bh** (1 mmol) and **1a** (1.1 mmol). The vessel was then closed, and the mechanochemical reaction was conducted from 30-180 min at a frequency of 30 Hz. At the end of the reaction, an additional 10 min grinding was made with $NaHCO_3$ to purify the reaction mixture. The crude was then recovered as a solid in a beaker, dissolved in EtOAc (10

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mL) and filtered on paper. The solvent was removed under reduced pressure to afford the pure formamide **3aa-bh**.

^{1}H and ^{13}C NMR data of compounds are reported in the Supplementary Material file.

4.3. General procedure for N-acetamides synthesis from primary and secondary amines

A 15 mL ZrO_2 jar equipped with one ZrO_2 milling ball (10 mm diameter) was filled with amine **2aa**, **2ac**, **2ak**, **2ar** or **2aw** (1 mmol) and **1b** (1.1 mmol). The vessel was then closed, and the mechanochemical reaction was conducted from 60-90 min at a frequency of 30 Hz. At the end of the reaction, an additional 10 min grinding was made with $NaHCO_3$ to purify the reaction mixture. The crude was then recovered as a solid in a beaker, dissolved in EtOAc (10 mL) and filtered on paper. The solvent was removed under reduced pressure to afford the pure acetamide **4aa**, **4ac**, **4ak**, **4ar**, or **4aw**.

4.4. General procedure for N-propionamide synthesis from aniline

A 15 mL ZrO_2 jar equipped with one ZrO_2 milling ball (10 mm diameter) was filled with amine **2aa** or **2ar** (1 mmol) and **1c** (1.1 mmol). The vessel was then closed, and the mechanochemical reaction was conducted for 120 min at a frequency of 30 Hz. At the end of the reaction, an additional 10 min grinding was made with $NaHCO_3$ to purify the reaction mixture. The crude was then recovered as a solid in a beaker, dissolved in EtOAc (10 mL) and washed with a citric acid solution (5% p/p). After that, it was dried on Na_2SO_4 and filtered on paper. The solvent was removed under reduced pressure to afford the pure propionamide **5aa** or **5ar**.

5. Conclusions

To conclude, a mechanochemical protocol for the formylation of amines has been described in this work, involving a solid formylated reagent such as *N*-formyl saccharin. The reaction is easy to set and allows to obtain almost quantitative yields of products. The purification method is robust and *green*, performed as much as possible in the solid phase, and limits the solvent employment at the sole recovery of the desired compounds. $NaHCO_3$ proved to be a *green* and efficient inorganic salt useful in a facile acid-base purification process. With this method, we could also provide an alternative pathway for synthesizing APIs, such as paracetamol, and valuable building blocks with potential application in the design of fentanyl-like drugs.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1.

Author Contributions: Conceptualization, writing—review and editing, C.F. and A.P.; validation, formal analysis, investigation, data curation, F.C. and F.B.; supervision, funding acquisition, A.P. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Not applicable here.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1 . Wu, K. M., A new classification of prodrugs: Regulatory perspectives. *Pharmaceuticals*, **2009**, *2*, 77–81. https://doi.org/10.3390/ph2030077.

2. Stella, V. J., Borchardt, R. T., Hageman, M. J., Oliyai, R., Maag, H., Tilley, J. W., *Prodrugs: Challenges and Rewards*, **2007**, ISBN 978-0-387-49785-3. https://doi.org/10.1007/978-0-387-49785-3.

3. Warwick, C., Paracetamol and fever management. *Journal of The Royal Society for the Promotion of Health*, **2008**, *128*, 320–323. https://doi.org/10.1177/1466424008092794.
4. Ebell, M. H., Call, M., Shinholser, J. A.. Effectiveness of oseltamivir in adults: A meta-analysis of published and unpublished clinical trials. *Family Practice*, **2013**, *30*, 125–133. https://doi.org/10.1093/fampra/cms059.
5. LaCrone, M. E., Buening, N., Paul, N. A Retrospective Review of an Inhaler to Nebulizer Therapeutic Interchange Program Across a Health System. *Journal of Pharmacy Practice*, **2022**, *0*, 1–6. https://doi.org/10.1177/08971900221101761.
6. Loh, C. H., Donohue, J. F., Ohar, J. A., Review of drug safety and efficacy of arformoterol in chronic obstructive pulmonary disease. *Expert Opinion on Drug Safety*, **2015**, *14*, 463–472. https://doi.org/10.1517/14740338.2015.998196.
7. Bodkin, J. A., Humphries, E. J., McLeod, M. D.. The total synthesis of (-)-tetrahydrolipstatin, *Australian Journal of Chemistry*, **2003**, *56*, 795–803. https://doi.org/10.1071/CH03121.
8 .Lieke, W., Ueber das Cyanallyl, *Ann. der Chemie und Pharm.* **1859**, *112*, 316–321. https://doi.org/10.1002/jlac.18591120307.
9. Ugi, I., Fetzer, U., Eholzer, U., Knupfer, H. and Offermann, K., Isonitrile Syntheses, *Angew. Chem. Int. Ed. Engl.*, **1965**, *4*, 472-484. https://doi.org/10.1002/anie.196504721.
10. A. W. Hofmann, Isonitrile, I. Darstellung von Isonitrilen aus monosubstituierten Formamiden durch Wasserabspaltung, *Grundlagen der organischem Chemie*, Verlag Sauerlander Aarau, Diesterweg, **1970.**
11. Ugi, I. and Meyr, R., *Chem. Ber.*, **1960**, *93*, 239-248. https://doi.org/10.1002/cber.19600930136.
12. Weber, W. P.; Gokel, G. W.; Ugi, I. K. Phase Transfer Catalysis in the Hofmann Carbylamine Reaction, *Angew. Chemie Int. Ed. English*, **1972**, *11*, 530– 531. doi:10.1002/anie.197205301.
13. Waibel, K. A.; Nickisch, R.; Möhl, N.; Seim, R.; Meier, M. A. R., A more sustainable and highly practicable synthesis of aliphatic isocyanides, *Green Chem.*, **2020**, *22*, 933–941. doi:10.1039/c9gc04070f.
14. Porcheddu, A.; Giacomelli, G.; Chimica, D. J., Microwave-Assisted Synthesis of Isonitriles: A General Simple Methodology, *Org. Chem.* **2005**, *70*, 2361–2363.
15. Basoccu, F.; Cuccu, F.; Casti, F.; Mocci, R.; Fattuoni, C.; Porcheddu, A., A Trustworthy Mechanochemical Route to Isocyanides: The Handyman of Chemistry, *Beilstein Arch.* **2022**, pre-print. doi:10.3762/bxiv.2022.21.v1.
16. P. Oxley, D. A. Peak, W. F. Short, Amidines. Part X. Preparation of amidines from substituted amides, a sulphonyl chloride, and an amine, *J. Chem. Soc.*, **1948**, 1618-1619.
17. Kotachi, S., Tsuji, Y., Kondo, T., Watanabe, Y., Ruthenium catalysed N,N′-Diarylurea Synthesis from N-Aryl substituted Formamides and Aminoarenes, *J. Chem. Soc., Chem. Commun.*, **1990**, 549-550.
18. Lane, E. M., Hazari, N., Bernskoetter, W. H., Iron-catalyzed urea synthesis: Dehydrogenative coupling of methanol and amines, *Chemical Science*, **2018**, *9*, 4003–4008. https://doi.org/10.1039/c8sc00775f.
19 . Lyons, J. E., Conversion of formamides to isocyanates, U.S. Patent, **1976**, US3960914A, https://worldwide.espacenet.com/patent/search?q=pn%3DUS3960914A.
20. Bonin, M. A., Giguère, D., Roy, R., N-Arylimidazole synthesis by cross-cycloaddition of isocyanides using a novel catalytic system. *Tetrahedron*, **2007**, *63*, 4912–4917. https://doi.org/10.1016/j.tet.2007.03.152.
21. Mishra, K., Datta Khanal, H., & Rok Lee, Y. (2021). Facile N-Formylation of Amines on Magnetic Fe3O4–CuO Nanocomposites, *Eur. J.Org. C.*, **2021**, *31*, 4477–4484. https://doi.org/10.1002/ejoc.202100872.
22. Kuhlmann, R., Künnemann, K. U., Hinderink, L., Behr, A., Vorholt, A. J., CO_2 Based Synthesis of Various Formamides in Miniplant Scale: A Two-Step Process Design. *ACS Sustainable Chemistry and Engineering*, **2019**, *7*, 4924–4931. https://doi.org/10.1021/acssuschemeng.8b05477.
23. Ghorbani-Vaghei, R., Veisi, H., Amiri, M, Disulfonamide Catalyzed Formylation of Amines and Alcohols Using Ethyl Formate under Microwave Irradiation, *Chem. Soc* **2009**, *6*, 761-768.

24. Takahashi, K., Shibagaki, M., & Matsushita, H.. Formylation of Amines by Di-methylformamide in the Presence of Hydrous Zirconium Oxide, *Biol. Chem*, **1988**, *52*, 853-854.
25. Karami, B., Farahi, M., Pam, F., A green protocol for the N-formylation of amines using molybdate sulfuric acid as a reusable solid catalyst. *Tetrahedron Letters*, **2014**, *55*, 6292–6296. https://doi.org/10.1016/j.tetlet.2014.09.114.
26. Chandra Shekhar, A., Ravi Kumar, A., Sathaiah, G., Luke Paul, V., Sridhar, M., & Shanthan Rao, P., Facile N-formylation of amines using Lewis acids as novel catalysts, *Tetrahedron Letters*, **2009**, *50*, 7099–7101. https://doi.org/10.1016/j.tetlet.2009.10.006.
27. Kajanus, J., Jacobson, I., Åstrand, A., Olsson, R. I., Gran, U., Björe, A., Fjellström, O., Davidsson, Ö., Emtenäs, H., Dahlén, A., Löfberg, B., Yuan, Z. Q., Sundell, J., Cassel, J., Gyll, J., Iliefski, T., Högberg, Å., Lindhardt, E., Malmberg, J., Isoindolinone compounds active as Kv1.5 blockers identified using a multicomponent reaction approach, *Bioorganic and Medicinal Chemistry Letters*, **2016**, *26*, 2023–2029. https://doi.org/10.1016/j.bmcl.2016.02.081.
28. Lei, M., Ma, L., & Hu, L., A convenient one-pot synthesis of formamide derivatives using thiamine hydrochloride as a novel catalyst. *Tetrahedron Letters*, **2010**, *51*, 4186–4188. https://doi.org/10.1016/j.tetlet.2010.06.005.
29. Zhang, F., Li, L., Ma, J., & Gong, H., MoS 2 -Catalyzed transamidation reaction. *Scientific Reports*, **2019**, *9*. https://doi.org/10.1038/s41598-019-39210-5.
30. Brahmachari, G., & Laskar, S. A very simple and highly efficient procedure for N-formylation of primary and secondary amines at room temperature under solvent-free conditions. *Tetrahedron Letters*, **2010**, *51*, 2319–2322. https://doi.org/10.1016/j.tetlet.2010.02.119.
31. de Luca, L., Giacomelli, G., Porcheddu, A., Salaris, M., A new, simple procedure for the synthesis of formyl amides, *Synlett*, **2004**, *14*, 2570–2572. https://doi.org/10.1055/s-2004-834788.
32. Cochet, T., Bellosta, V., Greiner, A., Roche, D., Cossy, J., N-Formylsaccharin: A new formylating agent. *Synlett*, **2011**, *13*, 1920–1922. https://doi.org/10.1055/s-0030-1260951.
33. Uzzaman, M., Shawon, J., & Siddique, Z. A. (2019). Molecular docking, dynamics simulation and ADMET prediction of Acetaminophen and its modified derivatives based on quantum calculations. *SN Applied Sciences*, *1*(11). https://doi.org/10.1007/s42452-019-1442-z
34. Vardanyan, R. S., Hruby, V. J. (2014). Fentanyl-related compounds and derivatives: Current status and future prospects for pharmaceutical applications. In *Future Medicinal Chemistry* 6, 385–412. Future Science. https://doi.org/10.4155/fmc.13.215
35. Choi, S.-Y., Lee, S.-G., Yoon, Y.-J., Kim, K.-W., Reaction of *N*-hydroxymethylsaccharin with aliphatic carboxylic acid derivatives: Synthesis of *N*-acylsaccharins and *N*-(saccharinylmethyl) aliphatic carboxylates *J. Heterocyclic Chem.*, **1989**, *26*, 1073, https://doi.org/10.1002/jhet.5570260430.