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Mechanochemical synthesis of tetramic acids and their biomimetic ring expansion to 4-hydroxy-2-pyridones

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Mechanochemistry has emerged as a powerful tool for enabling solvent-free, energy-efficient, and sustainable chemical transformations. Herein, we report a concise mechanochemical strategy for the synthesis of 3-acyl-tetramic acids and their subsequent biomimetic ring expansion to 5-arylated-4-hydroxy-2-pyridones—privileged heterocycles with broad biological and synthetic relevance. Inspired by biosynthetic pathways, our approach utilizes iodine-mediated activation of the 5-arylidene moiety on tetramic acids to initiate a ring expansion under mild conditions.

Green foundation

1. Advancing the field: this work introduces a mechanochemical, solvent-free synthesis of tetramic acids and their biomimetic ring expansion to 4-hydroxy-2-pyridones—heterocycles with broad biological relevance—demonstrating a sustainable route to complex structures *via* clean energy input.

2. Specific green chemistry achievement: the methodology avoids bulk solvents and harsh reagents and uses mechanical energy at room temperature, achieving higher yields compared to solution-based protocols. The iodine-mediated rearrangement proceeds without initiators such as light or external heating, aligning with multiple green chemistry principles.

3. Greener potential: further greening could include developing fully solvent-free Knoevenagel condensations and extending the scope to continuous-flow mechanochemical systems, enhancing scalability and life cycle sustainability.


4-Hydroxy-2-pyridones constitute a privileged class of heterocycles found in numerous biologically potent secondary metabolites, important for pharmaceutical and agrochemical applications.[1] The structural diversity and biological activity have rendered them valuable synthetic targets; however, the synthetic accessibility of 4-hydroxy-2-pyridone heterocycles remains limited, often requiring multi-step protocols or harsh conditions that constrain the scalability, sustainability, and functional group tolerance of these methods.[2] Consequently, the 4-hydroxy-2-pyridone core is frequently introduced into synthetic targets as a preformed unit, relying on multistep, non-green synthetic protocols or on bespoke late-stage functionalization, rather than being constructed *de novo* (Scheme 1A).[3] This limitation underscores the need for new methodologies that allow for efficient, selective, and environmentally benign access to this heterocycle.

Closely related to pyridones, tetramic acids are five-membered nitrogen-containing heterocycles that are widespread in nature[4] and share a biosynthetic lineage with many 4-hydroxy-2-pyridone alkaloids through their oxidative ring expansion (Scheme 1B).[5] Despite this correlation, the unique reactivity of tetramic acids, stemming from their highly stabilized enol forms and tendency to tautomerize, complicates their synthesis and limits their use as biomimetic precursors of 4-hydroxy-2-pyridones. Over the past decade, our group has been actively developing divergent total syntheses, focusing on common scaffolds to access structurally diverse classes of natural products.[6] In this context, the biosynthetic transformation of tetramic acids into 4-hydroxy-2-pyridones presents a compelling opportunity for a divergent strategy, wherein an amino acid can serve as a common synthetic scaffold for both heterocyclic frameworks (Scheme 1C).[7]

In recent years, mechanochemistry has emerged as a transformative approach for chemical synthesis, offering an alternative to traditional solution-phase methods.[8] By harnessing mechanical force—typically *via* ball milling—reactions can

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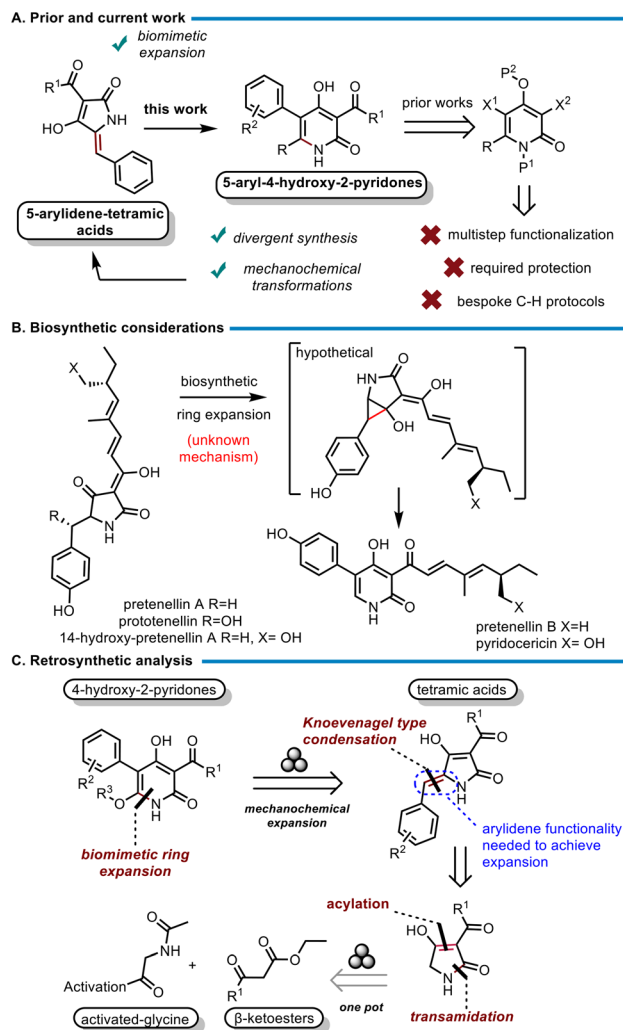
Scheme 1 Prior and current work; biosynthetic pathways towards and the proposed retrosynthetic analysis for 5-arylidene tetramic acids and 5-aryl-4-hydroxy-2-pyridones.

proceed under solvent-free or minimal-solvent conditions, improving atom economy, energy efficiency, and environmental compatibility. Mechanochemical methods often exhibit unique reactivity and selectivity profiles, enabling transformations that are difficult or inaccessible using conventional techniques.[9] As such, mechanochemistry aligns closely with the principles of green chemistry and is particularly well-suited for exploring sustainable routes to complex molecules.[10]

Given the need for more sustainable synthetic methodologies, the combination of biosynthetically inspired transformations with mechanochemical techniques presents a promising frontier. Developing such approaches could not only expand the toolbox for accessing 4-hydroxy-2-pyridone derivatives but also provide deeper insights into reactivity, selectivity, and the role of reaction conditions in governing complex rearrangements.

Guided by biosynthetic pathways, we focused on synthesizing a series of 3-acyl-tetramic acids bearing 5-arylidene substituents. We hypothesized that the arylidene moiety could stabil-

ize a cationic or radical intermediate, facilitating the desired ring expansion (Scheme 1C). To achieve this transformation, we initially targeted a one-pot procedure for synthesizing 5-arylidene-tetramic acids using β-keto esters in the presence of glycine whose carboxyl group was chemically activated (Scheme 1C). Azalactone (**1**) was initially used as the activated congener in the presence of anions of β-ketoesters **2–7** (Scheme 2A; route A).[11] Depending on the β-keto ester employed, the method yielded either the desired product **8** or a complex mixture of products with major compound **9**, attributed to the soft character of the enolate, which favored addition to the alkene of the azalactone congener (Scheme 2; route A). These findings prompted the utilization of a more general and robust synthetic procedure. Utilization of acetylglycine succinimide ester **10** instead of azalactone **1** provided a convenient alternative for the synthesis of 3-acylated tetramic acids **17–22** (Scheme 2A; route B).[12] The synthesis involved anion formation of β-keto esters (**2–7**) with sodium hydride or sodium ethoxide, in THF followed by acetyl-glycine succinimide ester **10**. The reaction resulted in the synthesis of compounds **11–16**, which were isolated and subsequently cyclized by overnight stirring with sodium ethoxide in ethanol to **17–22**, albeit in low overall yields (Scheme 2A). Similarly, low yields for tetramic acid preparation are commonly reported in the literature,[12] primarily due to the inherent instability of intermediate C-acylation compounds **11–16**. These intermediates are prone to inter- and intramolecular cyclisations as well as rapid hydrolysis. Furthermore, during the subsequent deprotection step with sodium ethoxide, cyclisation of the deprotected amine onto the ketone alkyl chain can occur, forming hemiaminal byproducts that are difficult to isolate and characterize, thereby further contributing to the low overall yields of tetramic acids.

With tetramic acids **17–22** at our disposal, the introduction of an arylidene substituent at the 5-position was next examined. The Knoevenagel condensation of 3-acyl-tetramic acids **17–22** with aryl aldehydes in the presence of HCl in MeOH under reflux conditions afforded the corresponding 5-arylidene-tetramic acids **23–31** in moderate yields (Scheme 2A).[12]

With these 5-arylidene tetramic acids in hand, their biomimetic expansion to 5-aryl-4-hydroxy-2-pyridones was investigated. Pleasingly, when compounds **23–31** were heated with N-iodo-succinimide (NIS) in methanol at 80 °C, the transformation to the corresponding 5-aryl-6-methoxy-4-hydroxy-2-pyridone **32** and **35–42** proceeded smoothly, affording products in 41–62% yields (Scheme 2A). Interestingly, using different alcohols such as EtOH or iPrOH also gave comparable results, whereas other nucleophiles failed to initiate the reaction.

Seeking to optimize the synthetic sequence for tetramic acids and their biomimetic expansion while minimizing the use of environmentally impactful reagents and solvents (e.g. NaH, THF, etc.), a mechanochemical protocol was considered.

Initially, the synthesis of tetramic acids **17–22** under mechanochemical conditions was examined. Ethyl acetoacetate (**2**) was chosen as the model β-ketoester for reaction optimization (Table 1). When compound **2** was ground with azalac-
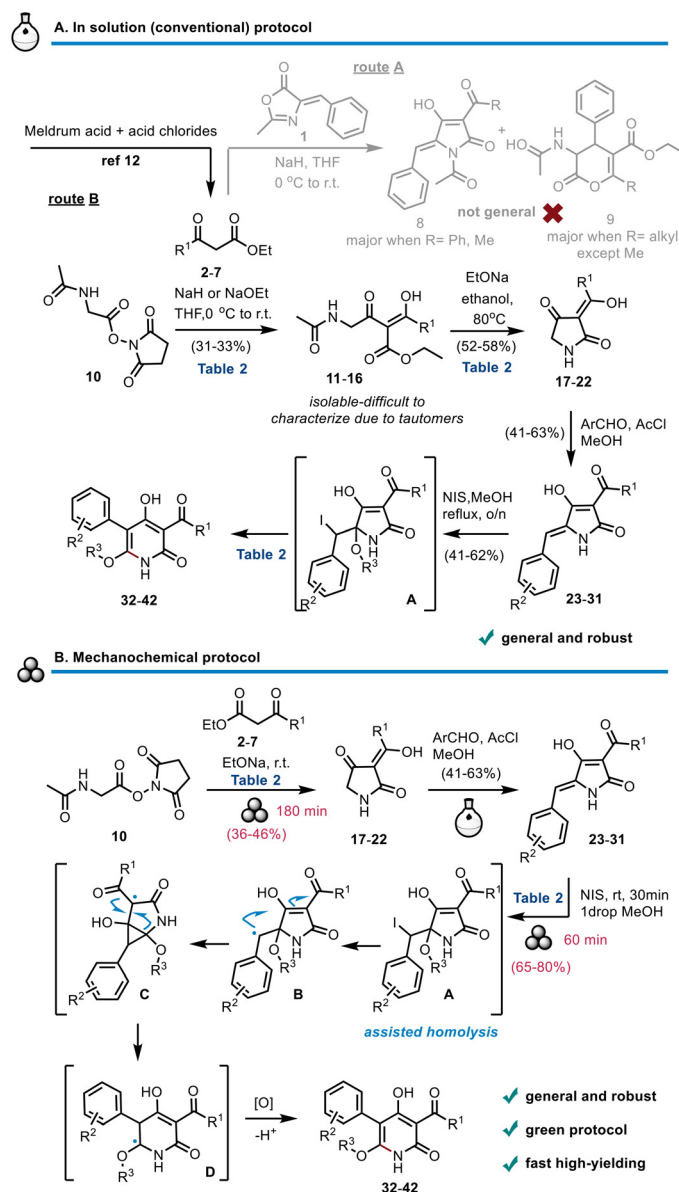
Scheme 2 Conventional and mechanochemical synthesis of 5-arylidene-3-acyl-tetramic acids **23–31** and 5-aryl-4-hydroxy-3-acyl-2-pyridones **32–42**.

tone **1** in the presence of an equimolar amount of sodium ethoxide, no reaction was observed (Table 1; entry 1). Milling the same substrates with pyrophoric sodium hydride under an argon atmosphere also failed to afford any acylation products (Table 1, entry 2). However, when succinimide ester **10** was used with one equivalent of sodium ethoxide as a base, compound **11** was isolated in 15% yield after 1 h of milling at 40 Hz, along with unidentified byproducts (Table 1; entry 3). Increasing the equivalents of sodium ethoxide to two equivalents improved the formation of both **11** and **17**, albeit in low yields (Table 1, entries 7 and 8). Finally, using three equivalents of sodium ethoxide split into two equal portions ($t_1 = 0$ and $t_2 = 1.5$ h) and milling at 25 Hz resulted in the highest yield of compound **17** (42%) in a single step (Table 1, entry 9).

In most cases, minimal starting material was recovered, suggesting that hydrolytic side reactions also occur under these conditions.

With optimized conditions established, the scope of the mechanochemical reaction was surveyed and compared with the conventional method (Table 2). Specifically, when β-dicarbonyl compounds **2–7** were reacted with the acetyl-glycine succinimide ester **10** in the presence of excess sodium ethoxide under milling at 25 Hz for 3 h, the corresponding tetramic acids **17–22** were obtained in moderate yields (Scheme 2 and Table 2).

In contrast, performing the same transformation under conventional solution-phase conditions as a one-pot procedure resulted in poor conversion, yielding less than 10%. In all

Table 1 Optimization of mechanochemical conditions for the synthesis of tetramic acids[a]

Entry	Activated amino acid	Base (equiv.)	Milling[b] (Hz)/time (min)	Conv. (%)	% yield **11**; **17**
1	**1**	EtONa (1)	40/120	60	0; 0
2	**1**	NaH (1)	40/120	100	0; 0
3	**10**	EtONa (1)	40/120	65	15; 0
4	**10**	t-BuOK (1)	40/120	67	10; 0
5	**10**	MeONa (1)	40/120	70	Complex mixture
6	**10**[c]	EtONa (1)	40/120	65	Complex mixture
7	**10**	EtONa (2)	25/180	100	12; 18
8	**10**	EtONa (2)	30/180	100	14; 20
9	**10**	**EtONa (3)**[d]	**25/180**	**100**	**0; 42**
10	**10**	EtONa (3)[d]	25/240	100	0; 42

[a] Conditions: 1.5 mmol of the activated amino acid and 2.25 mmoles of ethyl acetoacetate were used in all indicated optimization attempts. [b] All mechanochemical reactions were conducted under milling at indicated Hz for 3 h. [c] Glycine and succinimide ester were used instead of **10** in an attempt at its *in situ* preparation. [d] Two equal portions of the base was added at t_1 = 0 and t_2 = 90 min.

Table 2 Synthesis of tetramic acids **17–22** and 4-hydroxy-2-pyridones **32–42** under conventional and mechanochemical conditions

Substrate (–R^1)	Product	% yield[a] (2 steps)	% yield[b]	Substrate (–R^1 and R^2)	Product (–R^1, R^2 and R^3)	% yield[c]	% yield[d]
		A. Synthesis of 3-acyl tetramic acids **17–22**			B. Expansion of tetramic acids **23–31** to 4-hydroxy-2-pyridones **32–42**[a]		
2 (–CH$_3$)	**17**	18	42	**23** (–CH$_3$ and –H)	**32** (–CH$_3$, –H, and –OMe)	41	55
				23 (–CH$_3$ and –H)	**33** (–CH$_3$, –H, and –OEt)	62	70
				23 (–CH$_3$ and –H)	**34** (–CH$_3$, –H, and –OiPr)	56	74
3 (–CH$_2$CH$_3$)	**18**	18	39	**24** (–CH$_2$CH$_3$ and –H)	**35** (–CH$_2$CH$_3$, –H, and –OMe)	62	80
				25 (–CH$_2$CH$_3$ and –o-OMe)	**36** (–CH$_2$CH$_3$, –o-OMe, and –OMe)	61	79
4 (–CH$_2$(CH$_2$)$_5$CH$_3$)	**19**	17	46	**26** (–CH$_2$(CH$_2$)$_5$CH$_3$ and –H)	**37** (–CH$_2$(CH$_2$)$_5$CH$_3$, –H, and –OMe)	45	59
				27 (–CH$_2$(CH$_2$)$_5$CH$_3$ and –p-OH)	**38** (–CH$_2$(CH$_2$)$_5$CH$_3$, –p-OH, and –OMe)	42	57
5 (–CH$_2$(CH$_2$)$_9$CH$_3$)	**20**	17	43	**28** (–CH$_2$(CH$_2$)$_9$CH$_3$ and –H)	**39** (–CH$_2$(CH$_2$)$_9$CH$_3$, –H, and –OMe)	60	77
6 (–CH$_2$(CH$_2$)$_{14}$CH$_3$)	**21**	18	46	**29** (–CH$_2$(CH$_2$)$_{14}$CH$_3$ and –H)	**40** (–CH$_2$(CH$_2$)$_{14}$CH$_3$, –H, and –OMe)	53	65
7 (–CH$_2$(C$_6$H$_{11}$))	**22**	18	36	**30** (–CH$_2$(C$_6$H$_{11}$) and –H)	**41** (–CH$_2$(C$_6$H$_{11}$), –H, and –OMe)	58	72
				31 (–CH$_2$(C$_6$H$_{11}$) and –OMe)	**42** (–CH$_2$(C$_6$H$_{11}$), –OMe, and –OMe)	56	60

[a] All conventional reactions were conducted using 1.2 mmol of the corresponding β-ketoester with 0.8 mmol **10** and 1.1 mmol NaH in THF at 50 °C. Then the resulting was heated with 2.5 equiv. of sodium ethoxide in refluxing ethanol for 3 h. [b] All mechanochemical reactions were conducted under milling at 25 Hz for 3 h using 2.25 mmol of the corresponding β-ketoester with 1.5 mmol **10** and 4.5 mmol sodium ethoxide in two equal portions (t_1 = 0 and t_2 = 90 min) under the optimized reaction conditions of entry 9, Table 1. [c] All conventional reactions were conducted using 0.1 mmol of the corresponding 5-benzylidene-3-aryl tetramic acid and 0.11 mmol of NIS. [d] All mechanochemical reactions were conducted using 0.3 mmol of the corresponding 5-benzylidene-3-aryl tetramic acid and 0.33 mmol of NIS.

cases examined, the mechanochemical protocol outperformed the conventional process in both yield and reaction time and could be easy scaled up to 3 mmol.

Attempts to adapt the conventional Knoevenagel reaction to mechanochemical conditions failed to provide optimized yields of products **23–31**, despite the extensive literature on mechanochemical Knoevenagel processes.[13] However, the reaction was successfully adapted to proceed efficiently under minimal solvation conditions (Scheme 2B). This limitation under neat milling is likely due to the high temperatures required to initiate the process even in solution, which led to decomposition applied under mechanochemical conditions without sufficient solvation.

On the other hand, adaptation of the tetramic acid ring expansion to mechanochemical conditions was unproblematic. Grinding 5-benzylidene-3-acyl tetramic acids (**23–31**) with NIS and a minimal amount of alcohol (1 drop) at 25 Hz for 1 h resulted in a clean rapid and high-yielding ring expansion to 4-hydroxy-2-pyridone derivatives **32–42** (Scheme 2B and

Table 2), outperforming the conventional method. This mechanochemical expansion could be scaled up to 1.5 mmol of tetramic acids and proceeded efficiently at room temperature.

The mechanism of this expansion is postulated to begin with iodination of the double bond by NIS, followed by nucleophilic opening by methanol. From this point, different pathways may be considered, involving either oxonium cation intermediates or homolytic cleavage of the C–I bond. Experiments conducted in the presence of TEMPO completely shut down the expansion process, indicating the involvement of a radical pathway (Scheme 2B). Thus, it is proposed that homolytic cleavage of the C–I bond may be facilitated by the destabilizing effect of the methoxy group at the α-position, potentially leading to radical cyclization to the enol. Subsequent cleavage of the cyclopropyl ring could then enable expansion to 4-hydroxy-2-pyridones.[14] In contrast to a recently reported light-induced expansion to 3-acyl-2-pyridones, where homolysis is triggered exclusively by photochemical activation, our

transformation proceeds at room temperature in the absence of light, suggesting that a different initiation mode may be operative despite the presence of a similarly positioned methoxy group.[15]

Green metrics analysis was conducted for both solution-phase and mechanochemical protocols. For the mechanochemical synthesis of tetramic acids, the process mass intensity (PMI) and E-factor were calculated in the 100–190 range while the reaction mass efficiency (RME) was between 10 and 15%, reflecting a significant improvement over solution-phase reactions, which typically exhibited PMI and E-factors greater than 1000 and RMEs below 5%.

Conclusions

In conclusion, we have developed a concise and sustainable mechanochemical strategy for the synthesis of 3-acyl-tetramic acids and their biomimetic ring expansion to 5-aryl-4-hydroxy-2-pyridones, structurally privileged heterocycles with significant biological and synthetic importance. By leveraging the inherent reactivity of tetramic acids and drawing inspiration from natural biosynthetic pathways, our method enables efficient, solvent-minimized access to complex pyridone frameworks under mild conditions. The use of mechanical force not only streamlines the synthesis but also unlocks unique reactivity, including an iodine-mediated radical rearrangement that proceeds without the need for initiators, light, or harsh reagents. This work exemplifies the synergy between biomimicry and mechanochemistry and underscores the potential of solvent-free methodologies in advancing green and scalable synthetic approaches to valuable heterocyclic architectures. Future development of continuous mechanochemical protocols is underway to further enhance the sustainability profile of this methodology.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI: Experimental procedures, compound characterization data, and NMR spectra are provided in the SI. See DOI: **https://doi.org/10.1039/d5gc03085d**.

Acknowledgements

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