

## PAPER

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[View Journal](#) | [View Issue](#)Cite this: *RSC Sustainability*, 2024, 2, 521Ammonium niobium oxalate (ANO) as an efficient catalyst in the Paal–Knorr synthesis of *N*-substituted pyrroles†Luiz H. Dapper,<sup>a</sup> Kethelyn M. da Rosa,<sup>a</sup> Viviane T. Mena,<sup>a</sup> Rodrigo O. M. A. de Souza,<sup>b</sup> Felipe L. N. da Silva,<sup>b</sup> Thiago Anjos,<sup>c</sup> Filipe Penteado \*<sup>c</sup> and Eder J. Lenardão \*<sup>b</sup>

Ammonium niobium oxalate (ANO) has been proven to be an outstanding cheap, low-toxicity and readily available Lewis acid catalyst for carbonyl activation reactions. Herein, we describe the use of ANO as a catalyst in the Paal–Knorr pyrrole synthesis. The reactions were conducted under mild conditions, not requiring heating or special apparatus, allowing the synthesis of the desired products in up to 99% yield in just 30 min. Additionally, ANO could be reusable up to seven times, without remarkable loss of efficiency. The batch protocol was successfully translated to a continuous-flow environment, with 96% conversion of the starting dione and aniline to the desired pyrrole in 2 min of residence time (a STY of 2.5 g h<sup>-1</sup>). The main protocol's features meet important green chemistry bases, making it a sustainable method to prepare *N*-substituted pyrrole derivatives.

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## Sustainability spotlight statement

The five-membered heterocycle pyrrole is an important commodity, widely used in the production of pharmaceuticals and agrochemicals, for example. In the form of the polymer polypyrrole (ppy), it has important application in electronics, such as organic photovoltaics (OPVs) and field-effect transistors (OFETs) and optical apparatus due to its conducting properties. Besides, pyrrole is the core structure of several natural and biologically important macrocycles, such as porphyrins (heme), chlorins (chlorophyll), and vitamin B<sub>12</sub> and a building block for other organic compounds. The global pyrrole market is expected to reach multimillion US dollars and has shown constant growth in recent years. For this reason, the development of efficient and sustainable approaches to construct these compounds is quite desirable. Industrially, pyrrole is obtained mainly by two approaches: the reaction of ammonia gas with furan or butadiene and by the dehydrogenation of pyrrolidine. These approaches are energy intensive (temperatures up to 500 °C) and low atom-efficient (up to 60% yield). In this sense, the possibility of using an abundant, cheap, non-toxic and reusable catalyst in the synthesis of such valuable scaffolds is featured in this manuscript. It was demonstrated that ammonium niobium oxalate (ANO) is an excellent catalyst to promote the Paal–Knorr reaction between easily available diketones and primary amines. The procedure is conducted using bioethanol as solvent at room temperature for just 30 min, and the catalyst can be reused without previous treatment for up to seven consecutive reactions with a good performance. Besides, the strategy was successfully used in gram-scale and continuous-flow experiments, demonstrating its suitability to be easily used in preparative synthesis of *N*-substituted pyrroles.

## Introduction

Agenda 2030 established new paradigms in the development of processes in the chemical industry, pointing out the intense progress in the advancement of sustainable technologies and

aligning the establishment of highly efficient chemical protocols, which also present pollution-prevention features.<sup>1–4</sup> In this context, since the late 90s, green chemistry has been proven to be an outstanding tool to design sustainable chemical protocols, by outlining the guidelines to reach ecofriendly approaches based on its twelve principles. Among them, principles #6 and #9 (design for energy efficiency and catalysis), which claim important sustainable aspects, can be highlighted. These bases point out circumventing the use of reagents/promoters in stoichiometric amounts, as well as avoiding energy-intensive processes, preferring the application of alternative, low-power and efficient energy sources.<sup>5–9</sup>

On the other hand, *N*-based heterocycles are a class of fascinating compounds, which besides being largely found in nature, are widely present in several pivotal economic sectors, including the fine chemical, pharmaceutical and agrochemical industries.<sup>10–15</sup> Among these compounds, pyrrole derivatives are

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a privileged molecular framework, found in a plethora of natural compounds (including chlorophyll and vitamin B<sub>12</sub>), which also compose the core structure of several marketed drugs.<sup>16–23</sup> Some remarkable examples are (1) sunitinib, used in the treatment of pancreatic cancer;<sup>24–27</sup> and (2) atorvastatin, widely used to control blood cholesterol levels (Scheme 1, bioactive pyrrole-based compounds).<sup>28,29</sup> These compounds can be classically prepared through Paal–Knorr reactions, by reacting primary amines with 1,4-dicarbonyl compounds. Over the years, this important reaction has undergone some changes in the experimental conditions, making it more general and versatile. Although improvements have been achieved in the last few years, many of the new protocols face some significant drawbacks, such as the use of toxic and volatile solvents (DCM, THF, and MeOH), the need for long reaction times (up to 36 h) and high reaction temperatures (up to 160 °C), the use of strongly acidic conditions (H<sub>2</sub>SO<sub>4</sub>, HCl, H<sub>3</sub>PO<sub>4</sub>, and TsOH), specific reaction apparatus (MW or US reactors), and expensive reagents and catalysts (Scheme 1, typical drawbacks faced in Paal–Knorr reactions).<sup>30–40</sup>

Niobium-based catalysts have been extensively applied in organic synthesis, being able to conduct several important transformations towards many classes of organic compounds. The two most widely studied Nb-based catalysts are niobium pentachloride (NbCl<sub>5</sub>) and niobium pentoxide (Nb<sub>2</sub>O<sub>5</sub>).<sup>41–46</sup> In this context, niobium ammonium oxalate (ANO,

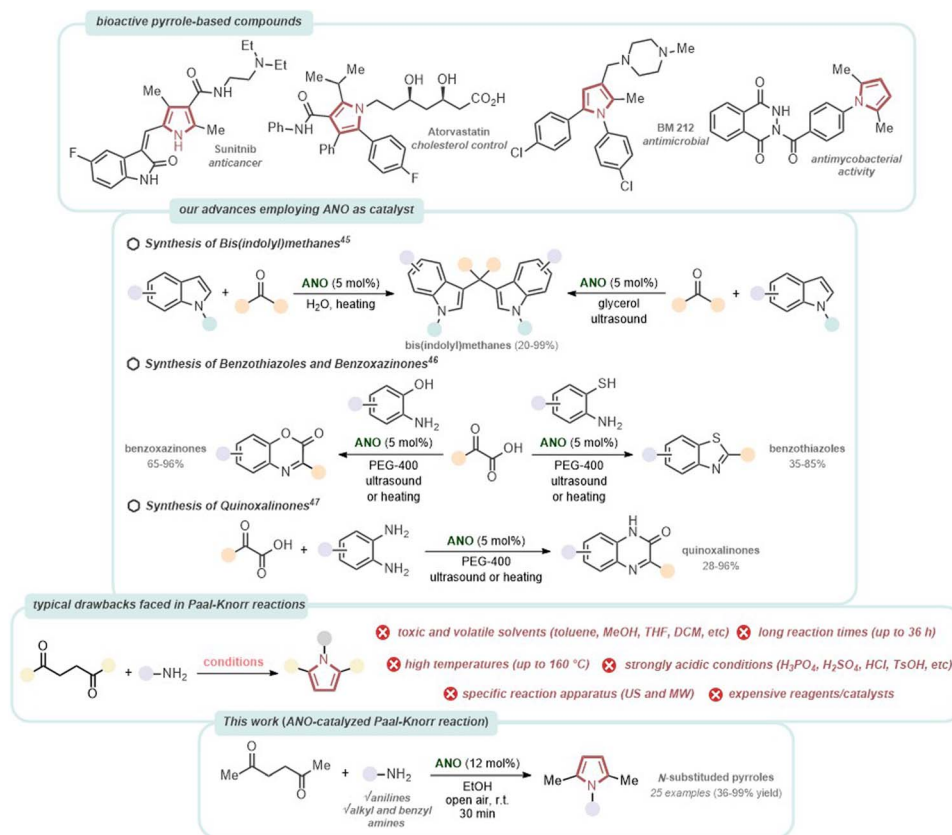
NH<sub>4</sub>[NbO(C<sub>2</sub>O<sub>4</sub>)<sub>2</sub>](H<sub>2</sub>O)<sub>2</sub>·xH<sub>2</sub>O) is widely used as an industrial precursor to access many important materials, including highly pure niobium oxides. Besides, ANO is a very cheap, bench stable and easy to handle Nb-based species, which presents a very low toxicity and no air- or moisture sensitivity.<sup>47</sup> Considering its fabulous properties, since 2015 we have been devoting our efforts to the development of reaction models employing ANO as a catalyst, exploring the synthesis of N-based heterocycles and aiming to expand the scope of application of this salt (Scheme 1, our advances employing ANO as a catalyst).<sup>48–50</sup>

Thus, considering our recent efforts in the development of ecofriendly synthetic protocols using ANO as a catalyst, we have disclosed herein an efficient approach to access *N*-substituted pyrroles through an ANO-catalyzed Paal–Knorr reaction. The protocol is very simple and consists of just stirring the reaction mixture in ethanol at room temperature for few minutes.

## Materials and methods

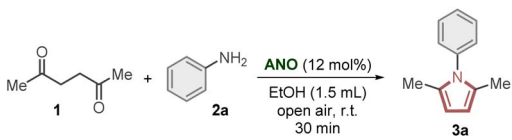
### General procedure for the synthesis of the *N*-substituted 2,5-dimethylpyrrole derivatives (3a–ad)

In a round-bottomed flask equimolar amounts (0.5 mmol) of aniline or amine derivative **2** and hexan-2,5-dione **1** and EtOH (1.5 mL) as solvent were added. In the sequence, ANO (0.023 g, 12 mol%) was added and the resulting mixture was vigorously stirred at room temperature for 30 min. After this time, the



**Scheme 1** Bioactive pyrrole-based compounds, our advances employing ANO as a catalyst, typical drawbacks of the Paal–Knorr reaction, and this work.



Table 1 Reaction optimization study for the synthesis of **3a**<sup>a</sup>


Entry	Deviation from the standard conditions	Yield of <b>3a</b> (%)
1	None	93
2	30 mol% of ANO instead of 12 mol%	95
3	20 mol% of ANO instead of 12 mol%	94
4	10 mol% of ANO instead of 12 mol%	88
5	60 °C instead of r.t.	94
6	80 °C instead of r.t.	94
7	MeCN instead of EtOH	65
8	EtOAc instead of EtOH	38
9	Acetone instead of EtOH	61
10	DCE instead of EtOH	52
11	1 h instead of 30 min	94
12	15 min instead of 30 min	89
13	Absence of ANO	34
14 <sup>b</sup>	Absence of ANO	39

<sup>a</sup> In a round-bottomed flask hexan-2,5-dione **1** (0.5 mmol), aniline **2a** (0.5 mmol), ANO (mol%) and the solvent (1.5 mL) were added. The resulting mixture was stirred for the tabled time at room temperature. Isolated yields were determined after column chromatography. <sup>b</sup> The reaction was conducted for 20 h.

mixture was concentrated under vacuum, and the crude was purified by column chromatography (silica gel) employing a mixture of hexane/ethyl acetate (99 : 1) as an eluent. Alternatively, the crude product can be recrystallized from methanol, to give pure pyrrole **3**.

## Results and discussion

Based on our previous reports on the use of ANO, our first experiment was carried out employing 0.5 mmol of hexan-2,5-dione **1** and aniline **2a** as substrates, EtOH (1.5 mL) as solvent and ANO (12 mol%) as a Lewis acid catalyst. Satisfactorily, after stirring the resulting solution for 30 min at room temperature, the desired product **3a** was isolated in 93% yield (Table 1, entry 1). Therefore, aiming to reach the best reaction conditions, several reaction parameters were systematically studied. Initially, different catalyst loads were tested (30 mol%, 20 mol%, and 10 mol%); however, none of them caused substantial improvement compared to using 12 mol% of ANO (Table 1, entries 2–4).

Following this, the reaction temperature was increased from room temperature to 60 °C and 80 °C, which allowed the preparation of **3a** in 94% yield in both cases, similarly to that observed at room temperature (Table 1, entries 5 and 6). Then, the reaction was carried out in the presence of polar aprotic solvents (MeCN, EtOAc, acetone, and DCE); however, the reaction efficiency decreased remarkably, which may be related to the low solubility of ANO in these solvents (Table 1, entries 7–10). Then, the

reaction time effect was investigated, by performing reactions for 1 h and for 15 min; the desired product **3a** was accessed in 94% and 89% yield, respectively (Table 1, entries 11 and 12).

Finally, aiming to prove the pivotal role played by ANO, two experiments were conducted in its absence, being carried out for 30 min and 20 h (Table 1, entries 13 and 14). Curiously, the reaction yields were very close, affording the product **3a** in 34% and 39% yield, respectively. Thus, the best reaction conditions were set by stirring a mixture of equimolar amounts (0.5 mmol) of substrates **1** and **2a** in the presence of ANO (12 mol%) as the catalyst in EtOH (1.5 mL) for 30 min at room temperature in an open flask (Table 1, entry 1).

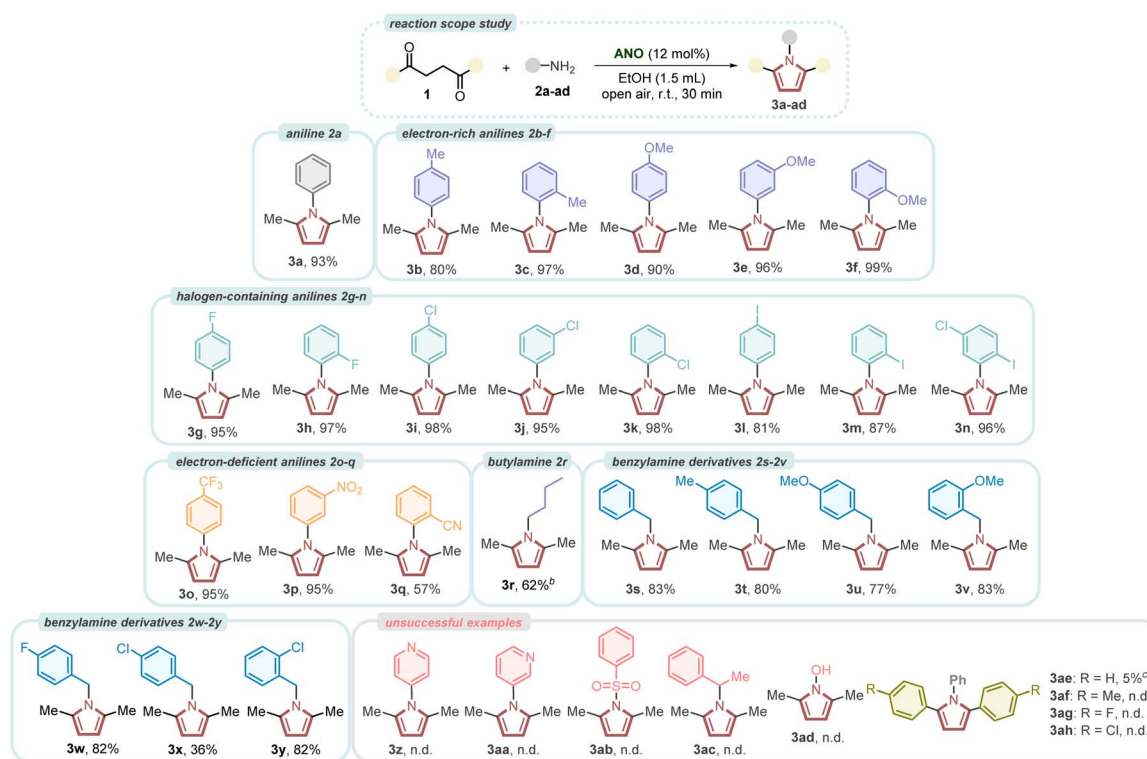
With the best reaction conditions in hand, a reaction scope study was performed, delivering a wide library of *N*-substituted 2,5-dimethyl pyrroles **3a–y**, by reacting hexan-2,5-dione **1** with several substituted anilines **2a–2q**, butylamine **2r**, and with substituted benzylamines **2s–2y** (Table 2).

Initially, electron-rich anilines **2b–f** were employed, delivering the products **3b–f** in very good to excellent yields. Regarding these examples, it is worth mentioning that *ortho*-toluidine **2c** and 2-methoxyaniline **2f** were suitable substrates, affording products **3c** and **3f** in 97% and 99% yield, respectively, without the expected drawbacks due to the presence of *ortho*-substituents. Additionally, a series of halogen-containing anilines **2g–n** was also employed, delivering the respective halogen-containing *N*-phenyl 2,5-dimethyl pyrroles **3g–n** in very good to excellent yields. Considering these derivatives, an excellent substrate tolerance was observed, since drawbacks were not faced even with *ortho*-substituted and iodine-substituted anilines **2h**, **2k**, **2m**, and **2n**. These results are quite important, opening opportunities for further functionalization of the obtained pyrroles by transition-metal catalyzed cross-coupling processes. Following this, electron-deficient anilines **2o–q** were satisfactorily submitted to the optimized reaction conditions. Among these derivatives, downsides were found when 2-aminobenzonitrile **2q** was used as the substrate, and the respective product **3q** was obtained in just 57% yield. In contrast, the nitro- and trifluoromethyl-containing derivatives **2o** and **2p** reacted smoothly to afford the products **3o** and **3p** in 95% yield, in both cases (Table 2).

Aiming to prove the protocol suitability, an alkyl- and several benzylamines **2r–2y** were selected to react as substrates. Butylamine (**2r**) demonstrated good fittingness to the protocol, being satisfactorily converted into **3r** in 62% yield after 3 h, which shows a slightly lower reactivity in comparison to the aniline derivatives. A wide diversity of electron-rich and halogen-containing benzylamine derivatives were reacted with hexan-2,5-dione **1**. Among them, the products **3s–3w** and **3y** could be prepared in good yields (77–83%), while (4-chlorophenyl) methanamine **3x** was less reactive, affording the product **3x** in just 36% yield (Table 2).

Unfortunately, the developed protocol presented limitations, and some specific  $-NH_2$  sites failed under the present conditions. Initially, pyridinamine derivatives **2z** and **2aa** could not be converted into the desired products **3z** and **3aa**. Regrettably, the benzenesulfonamide **2ab** was not suitable for the present protocol and the product **3ab** could not be obtained. The failure



Table 2 Reaction scope study for the synthesis of the **3a–3ad** compounds<sup>a</sup>

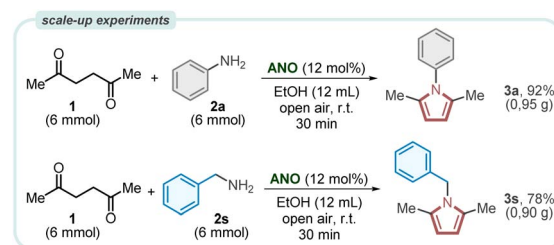
<sup>a</sup> In a round-bottomed flask hexan-2,5-dione **1** (0.5 mmol), amine **2** (0.5 mmol), ANO (12 mol%) and EtOH (1.5 mL) were added. The resulting mixture was stirred for 30 min at room temperature. Isolated yields were determined after column chromatography or recrystallization from methanol. <sup>b</sup> The reaction was conducted for 3 h. <sup>c</sup> The reaction was conducted for 20 h. Obtained as an inseparable mixture with aniline. The presence of **3ae** was confirmed by <sup>1</sup>H and <sup>13</sup>C-NMR analyses.

may be related to the lower nucleophilicity of the  $\text{--NH}_2$  site due to the strong electron withdrawing mesomeric effect caused by the adjacent S=O double bonds. Additionally, 1-phenylethan-1-amine **2ac** could not be converted into the desired product **3ac**. The lower reactivity of this substrate may be related to a steric hindrance effect caused by the methyl group. Similarly, hydroxylamine **2ad** also failed to act as a substrate in this protocol. The presence of two nucleophilic reaction sites may establish a competition between the  $\text{--OH}$  and the  $\text{--NH}_2$  groups. Finally, 1,4-dicarbonyl aryl derivatives **1b–e** were also employed as substrates, aiming to achieve 2,5-diaryl decorated *N*-aryl pyrrole derivatives **3ae–ah**. However, unfortunately the whole experiment failed, and only the product **3ae**, derived from 1,4-diphenylbutane-1,4-dione, could be observed, even if in a very low amount (Table 2). This could be due, at least in part, to steric hindrance by the aromatic ring.

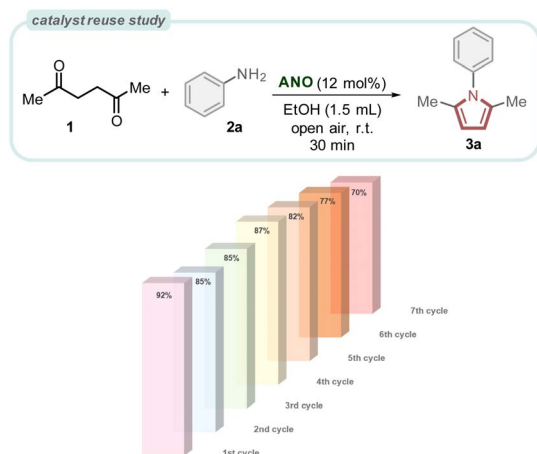
Aiming to demonstrate the protocol utility, scale-up experiments to prepare the products **3a** and **3s** in gram amounts were performed. Thus, the amounts of substrates were increased from 0.5 mmol to 6 mmol (12-fold higher). The amount of EtOH was increased, while the reaction time and temperature were maintained. Satisfactorily, in both cases, the protocol has been demonstrated to be very robust, delivering the products **3a** and **3s** in 92% (0.95 g) and 78% (0.90 g) yield, respectively. These results highlight

a very important protocol feature, which can be easily scaled, without major changes in the reaction parameters (Scheme 2).

Aiming to investigate the ability of ANO to be employed in several successive reactions, a reuse study was performed in the reaction between **1** and aniline **2a**. Pleasingly, the catalyst proved to be very efficient and reusable, driving the reaction efficiently for up to seven times. Initially, from the second reuse a slight decrease in the formation of **3a** to a range of 87% to 82% yield was observed, which was kept up until the fifth recycle. In the sixth and seventh reuses a sharp drop in the catalyst efficiency was observed, but that even so allowed the process to be driven to the formation of the product **3a** in 77% and 70% yield, respectively (Scheme 3).

Scheme 2 Scale-up experiments for the synthesis of **3a** and **3s**.



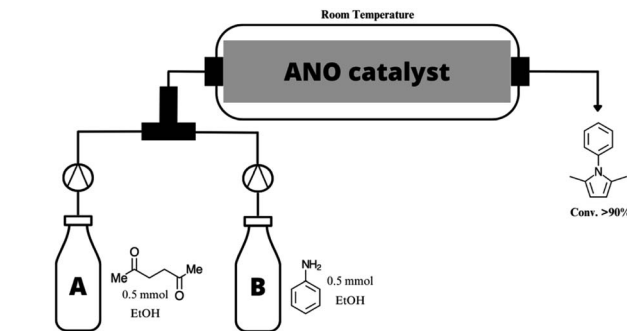
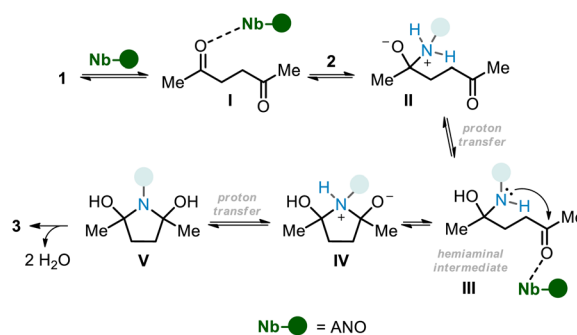


Scheme 3 Catalyst reuse study.

After the batch scaling-up and the catalyst recyclability studies, we have decided to explore the potential of translating the developed batch protocol to a continuous-flow environment. We have decided not to re-optimize the reaction conditions to the continuous-flow system and different reaction times were evaluated to obtain the best conversion possible. Reagents were introduced using two different pumps (A and B) through a T-mixer into a packed bed reactor filled with ANO (1.1 g) at room temperature (Scheme 4).

Our previous experience in developing continuous-flow heterogeneous reactions by using packed bed reactors has shown us how fast the reactions can be under such conditions. Based on that, we have started evaluating a 5-min residence time where conversions up to 92% were obtained ( $STY = 0.9 \text{ g h}^{-1}$ ). Reduction of residence time to 3 min still allows the conversion to maintain values up to 96% and gives an interesting increment in space-time-yield (STY) to  $1.6 \text{ g h}^{-1}$ . An additional reduction in residence time to 2 min was evaluated and the results have shown that 96% of conversion can still be obtained leading to a STY of  $2.5 \text{ g h}^{-1}$ . Recyclability of the packed bed reactor was also evaluated, and we have been able to recycle the packed bed 6 times without significant loss of activity.

Based on the results of the studies in the reaction optimization and on our early studies reporting the reactivity of ANO as a Lewis acid catalyst,<sup>45–50</sup> we propose a plausible reaction mechanism for the transformation, through a hemiaminal reaction pathway. Initially, a Lewis acid–base complexation between a non-bonding oxygen lone pair from hexan-2,5-dione **1** and the niobium coordination sphere occurs, to give the strong electrophilic complex **I**. Once formed, **I** undergoes a nucleophilic attack from the non-bonding lone pair of the nitrogen atom in **2**, to form the zwitterionic intermediate **II**. Then, a proton transfer process drives the transformation towards the hemiaminal intermediate **III**, which can also be activated by the niobium-based catalyst. This C=O double bond activation allows an intramolecular annulative event to afford the zwitterionic species **IV**, which also undergoes a proton transfer process to be converted into the diol intermediate **V**. Finally, a dehydration process drives the reaction towards the highly stable aromatic pyrrole core **3** (Scheme 5).

Scheme 4 Continuous-flow synthesis of **3a**.Scheme 5 Plausible reaction mechanism for the synthesis of **3**.

## Conclusions

In conclusion, herein an ecofriendly methodology was developed to prepare *N*-substituted pyrrole derivatives efficiently, employing ammonium niobium oxalate (ANO) as a cheap and highly effective catalyst. The transformation was conducted at room temperature and in the presence of EtOH as a green, environmentally benign solvent. By the developed approach, twenty-five *N*-substituted pyrrole derivatives, decorated with several substituents (strong and moderately electron-donating and electron-withdrawing groups, and halogens), were satisfactorily prepared in short reaction time. Additionally, gram-scale and continuous-flow experiments demonstrated the protocol suitability to be easily used in preparative synthesis. Despite this, ANO has proven its catalytic activity through a wide reuse study, in which it could be reused seven times with high catalytic efficiency (92–70% yield). Taken together, these features highlight the protocol's greenness, going to meet important green chemistry principles, including the #6 and #9 ones (design for energy efficiency and catalysis), allowing the synthesis of important organic frameworks under very mild reaction conditions.

## Author contributions

Methodology, L. H. D., V. T. M., K. M. R. and F. L. N. S.; writing—original draft preparation, L. H. D. and F. P.; writing—review and editing, R. O. M. A. S., F. P. and E. J. L.; supervision, R. O. M.



A. S, F. P. and E. J. L.; project administration, F. P. and E. J. L. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- W. Colglazier, *Science*, 2015, **349**, 1048–1050.
- B. Soergel, E. Kriegler, I. Weindl, S. Rauner, A. Dirnaichener, C. Ruhe, M. Hofmann, N. Bauer, C. Bertram, B. L. Bodirsky, M. Leimbach, J. Leininger, A. Levesque, G. Luderer, M. Pehl, C. Wiggins, L. Baumstark, F. Beier, J. P. Dietrich, F. Humpenöder, P. von Jeetze, D. Klein, J. Koch, R. Pietzcker, J. Streffer, H. Lotze-Campen and A. Popp, *Nat. Clim. Change*, 2021, **11**, 656–664.
- P. Anastas, M. Nolasco, F. Kerton, M. Kirchhoff, P. Licence, T. Pradeo, B. Subramaniam and A. Moores, *ACS Sustainable Chem. Eng.*, 2021, **9**, 8015–8017.
- S. A. Matlin, G. Mehta, H. Hopf and A. Krief, *Nat. Chem.*, 2016, **8**, 393–398.
- P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
- R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43.
- P. Anastas, B. Han, W. Leitner and M. Poliakoff, *Green Chem.*, 2016, **18**, 12–13.
- R. A. Sheldon, M. L. Bode and S. G. Akakios, *Curr. Opin. Green Sustainable Chem.*, 2022, **33**, 100569.
- H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata and P. T. Anastas, *Green Chem.*, 2018, **20**, 1929–1961.
- L. D. Quin and J. A. Tyrell, *Fundamentals of Heterocyclic Chemistry*, Wiley-VCH, Weinheim, 2010.
- J. Alvarez-Builla, J. J. Vaquero and J. Barluenga, *Modern Heterocyclic Chemistry*, Wiley-VCH, Weinheim, 2010.
- A. R. Katritzky, C. W. Rees and E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II*, Pergamon Press, Oxford, 1996.
- A. R. Katritzky, C. W. Rees and E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry III*, Pergamon, Oxford, 1999.
- R. Vardanyan and V. Hruby, *Synthesis of Best-Seller Drugs*, Academic Press, London, 2016.
- C. Lamberth and J. Dinges, *Bioactive Heterocyclic Compound Classes: Agrochemicals*, Wiley-VCH, Weinheim, 2012.
- H. Fan, J. Peng, M. T. Hamann and J. F. Hu, *Chem. Rev.*, 2008, **108**, 264–287.
- V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233–15266.
- S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 10–144.
- B. T. Parr, C. Economou and S. B. Herzon, *Nature*, 2015, **525**, 507–510.
- A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582–3603.
- M. Biava, G. C. Porretta, D. Deidda, R. Pompei, A. Tafi and F. Manetti, *Bioorg. Med. Chem.*, 2003, **11**, 515–520.
- D. Deidda, G. Lampis, R. Fioravanti, M. Biava, G. C. Porretta, S. Zanetti and R. Pompei, *Antimicrob. Agents Chemother.*, 1998, **42**, 3035–3037.
- I. K. Khanna, R. M. Weier, Y. Yu, P. W. Collins, J. M. Miyashiro, C. M. Koboldt, A. W. Veenhuizen, L. L. Currie, K. Seibert and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1619–1633.
- B. Carlisle, N. Demko, G. Freeman, A. Hakala, N. MacKinnon, T. Ramsay, S. Hey, A. J. London and J. Kimmelman, *J. Natl. Cancer Inst.*, 2016, **108**, djv292.
- A. Z. Dudek, J. Zolnieriek, A. Dham, B. R. Lindgren and C. Szczylik, *Cancer*, 2008, **115**, 61–67.
- L. Q. M. Chow and S. G. Echhardt, *J. Clin. Oncol.*, 2007, **25**, 884–896.
- E. D. Deeks and G. M. Keating, *Drugs*, 2006, **66**, 2255–2266.
- A. P. Lea and D. McTavish, *Drugs*, 1997, **53**, 828–847.
- S. I. van Leuven and J. J. P. Kastelein, *Expert Opin. Pharmacother.*, 2005, **6**, 1191–1203.
- B. Emayavaramban, M. Sen and B. Sundararaju, *Org. Lett.*, 2017, **19**, 6–9.
- L. Liu, C. Tan, R. Fan, Z. Wang, H. Du, K. Xu and J. Tan, *Org. Biomol. Chem.*, 2019, **17**, 252–256.
- S. C. Philkhana, F. O. Badmus, I. C. Dos Reis and R. Kartika, *Synthesis*, 2021, **53**, 1531–1555.
- T. Shi, G. Yin, X. Wang, Y. Xiong, Y. Peng, S. Li, Y. Zeng and Z. Wang, *Green Synth. Catal.*, 2023, **4**, 20–34.
- A. Balakrishna, A. Aguiar, P. J. M. Sobral, M. Y. Wani, J. A. Silva and A. J. F. N. Sobral, *Catal. Rev.*, 2019, **61**, 84–110.
- S. C. Philkhana, F. O. Badmus, I. C. dos Reis and R. Kartika, *Synthesis*, 2021, **53**, 1531–1555.
- P. N. Rakendu, T. Aneja and G. Anilkumar, *Asian J. Org. Chem.*, 2021, **10**, 2318–2333.
- A. Sharma and P. Piplani, *J. Heterocycl. Chem.*, 2017, **54**, 27–34.
- S. D. Joshi, U. A. More, V. H. Kulkarni and T. M. Aminabhavi, *Curr. Org. Chem.*, 2013, **17**, 2279–2304.
- M. Leonardi, V. Estévez, M. Villacampa and J. C. Menéndez, *Synthesis*, 2019, **51**, 816–828.
- D. Akbaslar, O. Demirkol and S. Giray, *Synth. Commun.*, 2014, **44**, 1323–1332.



- 41 I. Nowak and M. Ziolk, *Chem. Rev.*, 1999, **99**, 3603–3624.
- 42 K. Tanabe, *Catal. Today*, 2003, **78**, 65–77.
- 43 M. Ziolk, *Catal. Today*, 2003, **78**, 47–64.
- 44 M. O. Guerrero-Pérez, *Catal. Today*, 2020, **354**, 19–25.
- 45 M. Ziolk and I. Sobczak, *Catal. Today*, 2017, **285**, 211–225.
- 46 M. O. Guerrero-Pérez and M. A. Bañares, *Catal. Today*, 2009, **142**, 245–251.
- 47 J. C. Barros, L. Fortes, P. M. Monte, A. P. P. M. Silva, J. C. Barros and T. L. Silva, *SynOpen*, 2021, **3**, 252–254.
- 48 S. R. Mendes, S. Thurow, F. Pentead, M. S. da Silva, R. A. Gariani, G. Perin and E. J. Lenardão, *Green Chem.*, 2015, **17**, 4334–4339.
- 49 F. Pentead, M. M. Vieira, G. Perin, D. Alves, R. G. Jacob, C. Santi and E. J. Lenardão, *Green Chem.*, 2016, **18**, 6675–6680.
- 50 C. Ebersol, N. Rocha, F. Pentead, M. S. Silva, D. Hartwig, E. J. Lenardão and R. G. Jacob, *Green Chem.*, 2019, **21**, 6154–6160.

