Green Chemistry

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Metal-free Knorr pyrrole synthesis by electrochemical reduction of oximes using carbon-based electrodes

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A new variation of the Knorr pyrrole synthesis was developed, which proceeds by the cathodic reduction of readily available oximes. In contrast to existing methodologies, the developed system remains completely metal-free by employing reusable carbon-based electrodes, greatly improving sustainability. In addition, the supporting electrolyte is formed *in situ* from inexpensive acetic acid and triethylamine. This protocol is easy to conduct in a simple two-electrode divided cell set-up under constant current conditions and provides direct access to a broad range of highly substituted pyrroles. The broad functional group tolerance was demonstrated on 48 diverse examples with up to 87% yield including precursors of highly relevant APIs. Furthermore, the applicability of the method was demonstrated by a gram-scale electrolysis.

Green foundation

1. Conventionally, the Knorr pyrrole synthesis uses over-stoichiometric amounts of reducing agents, typically zinc, generating large amounts of heavy metal waste by this process, or expensive transition metal catalysts with pressurised hydrogen. With electricity as a renewable reducing agent, the reported protocol circumvents the need for hazardous redox reagents and catalysts, minimising waste.
2. The developed method operates under ambient conditions in a simple galvanostatic set-up, utilising carbon-based electrodes and an *in situ* generated electrolyte, which results in a completely metal-free system. Only electricity is used as a reagent, leading to minimised amounts of side-products and waste.
3. Further efforts should be made to transfer the protocol to a larger scale, preferably in combination with flow technology. This would also allow the development of more efficient ways for downstream processing (*e.g.* isolation of product and reuse of electrolyte) that further enhance the sustainability.

Introduction

Pyrroles are distinct scaffolds that appear in a large number of natural products as well as pharmaceutical agents and exhibit a diverse range of biological activities.[1–3] Naturally occurring molecules containing a pyrrole moiety include vitamin B_{12}, bile pigments such as bilirubin and biliverdin, and the porphyrins of heme, chlorophyll, chlorins and porphyrinogens.[4–8] In addition, numerous pyrrole-bearing alkaloids of varying complexity and activity have been isolated from marine organisms, insects, fungi, bacteria and plants.[9–11] In drug discovery, the pyrrole is a widespread structural motif due to its broad spectrum of therapeutic applications.[12,13] Pyrrole derivatives exhibit anticancer,[14,15] antidiabetic,[16] antitubercular,[17] antimalarial,[18] antiviral,[19] antibacterial,[20] anti-inflammatory,[21,22] anti-Parkinsonian,[23] and anti-Alzheimer's properties.[24] Among the marketed drugs with a pyrrole system are the anti-cancer medication Sunitinib,[25] the nonsteroidal anti-inflammatory drug Tolmetin[26] and the cholesterol lowering agent Atorvastatin (Fig. 1), which was the most prescribed drug in the United States in 2023.[27,28] Furthermore, pyrrole-derived molecules are applied as conductive polymers for energy storage[29,30] and corrosion control,[31] as high-performance pigments and dyes for optoelectronics and fluorescent probes,[32–35] and as biomimetic catalysts, *e.g.* for hydrogen generation.[36–38]

Structure–activity relationship studies of bioactive pyrrole derivatives have shown the pharmacophoric properties to be dependent on the various functionalities, substituents, and halogen(s) at specific positions of the pyrrole ring.[39] Therefore, strategies for the regioselective, sustainable and industry-oriented synthesis of highly substituted pyrroles are in great demand. One of the oldest and most established routes towards pyrroles is the Knorr pyrrole synthesis. The method

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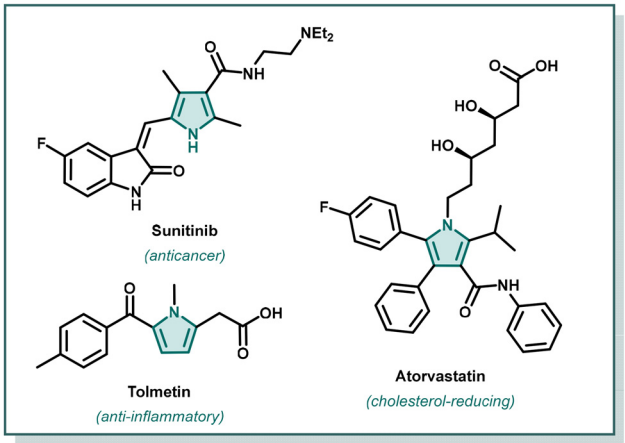
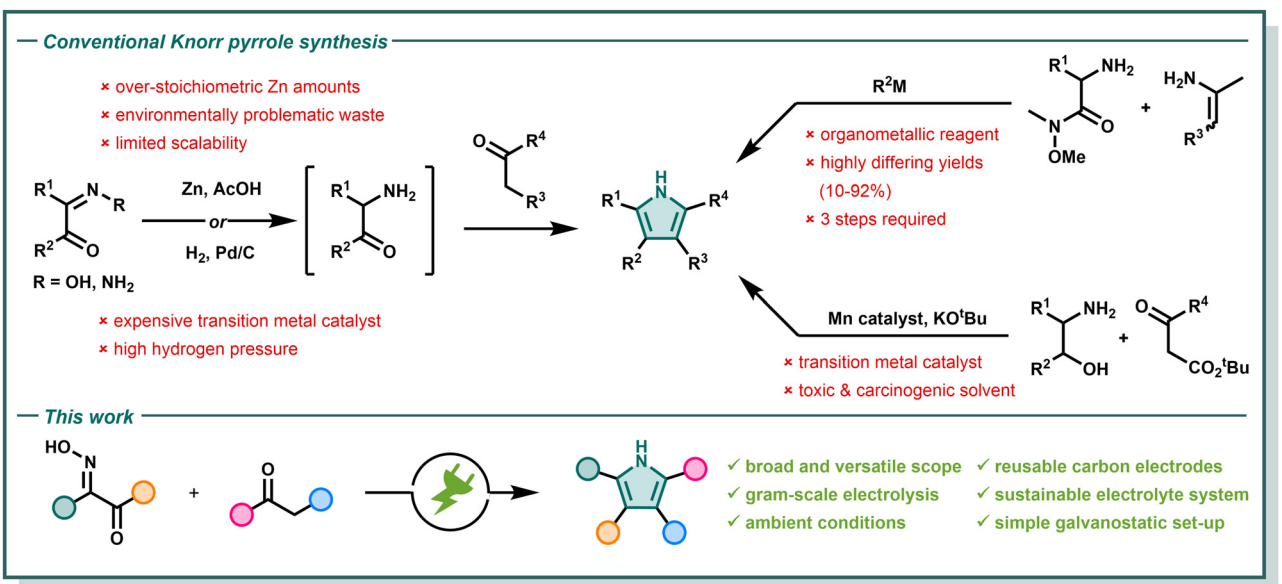


Fig. 1 Selected examples of approved drugs containing a pyrrole scaffold: the anticancer agent Sunitinib, the nonsteroidal anti-inflammatory drug Tolmetin, and the cholesterol-reducing agent Atorvastatin.

was first reported in 1884 and involves condensation between an α-amino ketone and a carbonyl compound with an active α-methylene unit, typically β-ketoesters.[40–42] Usually, the reaction is conducted at elevated temperatures under acidic conditions and gives tetrasubstituted *N*–H pyrroles with high regioselectivity. Since α-amino ketones are highly susceptible to self-condensation, they are generated *in situ* by reduction of oximes or hydrazones using over-stoichiometric amounts of zinc dust and acetic acid. However, the use of zinc dust is associated with several drawbacks: it can be pyrophoric, poses a risk of dust explosions and excess zinc needs to be removed and quenched after the reaction.[43] The zinc waste is also toxic for water organisms and thus it must be handled with special precautions.[44] All of these points greatly limit the sustainability and applicability of zinc dust in large-scale processes.[45] Therefore, several variations of the Knorr pyrrole synthesis have been developed with the aim of making the process more sustainable (Scheme 1).[46] In some examples, the reduction with zinc was substituted with catalytic hydrogenation over palladium on charcoal.[47,48] The separation of products and work-up in these protocols is simple because the palladium catalyst can be separated by filtration, but the method still suffers from the safety requirements due to hydrogen and the high cost of the palladium catalyst and high pressure equipment. Other approaches avoid the reduction step altogether by using Weinreb α-aminoamides or β-hydroxy enamines as substrates instead of α-amino ketones.[49,50] However, these methods require organometallic reagents or metal catalysts, resulting in more complex reaction conditions, the need for hazardous solvents such as tetrahydrofuran or 1,4-dioxane, and long reaction times.[46] Further approaches to greener pyrrole synthesis include microwave irradiation, solvent-free synthesis or multicomponent reactions; however, these techniques have not been applied to Knorr-type reactions.[51,52] Electrosynthesis offers a novel, highly attractive approach to replacing the use of hazardous reducing agents and metals with electricity. The intrinsic advantages of organic electrochemistry have led to its increasing integration into fundamental research and industrial applications.[53–56] Since electrons serve as reagents, stoichiometric amounts of hazardous or toxic redox agents are avoided, which in turn minimizes reagent waste. If the electricity is generated from renewable sources, electro-organic chemistry can be regarded as almost waste- and pollutant-free.[57,58] In addition, electrochemical processes are inherently safe because switching off the electricity stops the reaction and prevents a thermal runaway.[59,60]



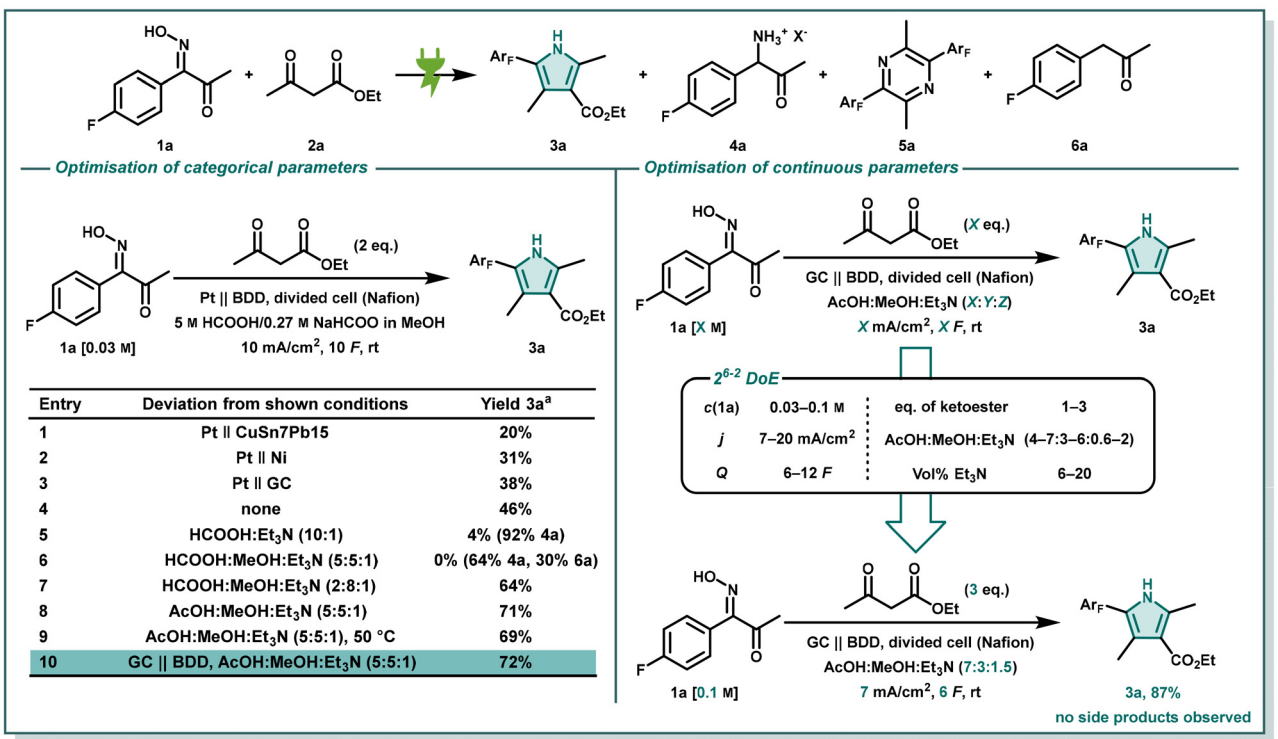
Scheme 1 Conventional conditions for the Knorr pyrrole synthesis and modern approaches in comparison with the electrochemical Knorr pyrrole synthesis.

Moreover, electro-synthetic reactions can often be conducted under ambient conditions without expensive and rare metal catalysts, while still enabling unique reactivity and selectivity.[61–63] Therefore, organic electrochemistry is a valuable tool for the green synthesis of value-added products, also in industrial contexts.[64–66] Electrochemical strategies have already been extensively employed for the formation of nitrogen-containing heterocycles through the reduction of nitro arenes.[67–71] Meanwhile, research on the reduction of oximes has been scarce, especially with the direct use of the generated amine in two- or multi-component reactions.[72]

Results and discussion

Optimisation of electrolysis conditions

Oxime **1a** was chosen as the test substrate to enable quantification by ^{19}F NMR and was easily synthesised from 4-fluorophenylacetone in a single step. With inexpensive ethyl acetoacetate **2a** as a reagent, pyrrole **3a** is formed as the desired product. However, three major side products were observed during early investigations: the ammonium salt **4a**, which under suitable conditions can further react accomplishing pyrrole **3a**, self-condensation product **5a** and deamination product **6a** (Scheme 2), formed by overreduction of **4a**. For the optimisation of the electrochemical Knorr pyrrole synthesis of **3a**, a one-variable-at-a-time (OVAT) approach was employed, changing only one parameter while the others were kept constant. Using this approach, the categorical parameters were screened, *i.e.* variables that do not take on numerical values (Scheme 2).[73] The reaction was conducted in a divided cell using a Nafion™ N324 membrane as the separator. Undivided and quasi-divided cell designs were also tested in preliminary experiments, but led to a decreased yield of **3a** and decomposition of the starting material due to oxidative polymerisation of the pyrrole and oxidation of the starting material (see the SI for further information).[74] Leaded bronze was used as a more stable and sustainable alternative to unalloyed lead cathodes exhibiting high overpotential for hydrogen evolution, which competes with the reduction of the substrate in acidic media.[75,76] As a sustainable electrolyte, a formic acid/formate buffer in methanol was employed, utilising the oxidation of formic acid to CO_2 as a convenient counter reaction. Under these initial conditions, the desired pyrrole **3a** was obtained in 20% yield (entry 1). With nickel as the cathode material, the yield could be slightly improved to 31% (entry 2), while zinc, tin and lead were also investigated as cathode materials, but were excluded from further experiments due to their severe corrosion and/or toxicity (see the SI for further information). Fortunately, the yield of pyrrole **3a** was increased using carbon-based cathodes, reaching 38% with glassy carbon (GC) and 46% with boron-doped diamond (BDD) (entries 3 and 4). BDD is an innovative electrode material known for its high stability which is produced in a sustainable way with methane as a carbon source.[77–79] In addition, BDD exhibits high overpotentials for hydrogen and oxygen evolution and shows unique



Entry	Deviation from shown conditions	Yield 3a[a]
1	Pt ‖ CuSn7Pb15	20%
2	Pt ‖ Ni	31%
3	Pt ‖ GC	38%
4	none	46%
5	HCOOH:Et_3N (10:1)	4% (92% 4a)
6	HCOOH:MeOH:Et_3N (5:5:1)	0% (64% 4a, 30% 6a)
7	HCOOH:MeOH:Et_3N (2:8:1)	64%
8	AcOH:MeOH:Et_3N (5:5:1)	71%
9	AcOH:MeOH:Et_3N (5:5:1), 50 °C	69%
10	GC ‖ BDD, AcOH:MeOH:Et_3N (5:5:1)	72%

Scheme 2 Desired product and observed side products in the electrochemical Knorr pyrrole synthesis and 2-stage optimisation of reaction parameters. Ar_F = 4-fluorophenyl. [a] Yields were determined by ^{19}F NMR with 4-fluorotoluene as the internal standard.

reactivity towards the electrochemical conversion of various substrates.[80] Changing the electrolyte to a ternary mixture of formic acid, methanol and triethylamine led to a more efficient reduction, as indicated by a higher conversion of **1a**. This electrolyte system provides the advantage that no specialised and expensive supporting electrolyte is required as the triethylammonium salt is formed *in situ*. However, with higher ratios of formic acid, the ammonium salt **4a** was formed as the dominant product and did not condense further to **3a** (entries 5 and 6). This demonstrates the pH dependency of the reaction: at low pH, the acid–base equilibrium is shifted strongly toward the ammonium salt, which suppresses the nucleophilic attack at the dicarbonyl species due to the negligible availability of free amine. By decreasing the amount of formic acid in methanol to a 1 : 4 ratio, pyrrole **3a** was obtained in 64% yield after overnight stirring of **4a** (entry 7). Switching to acetic acid, a weaker acid, enabled the formation of pyrrole **3a** to proceed more smoothly with only trace amounts of ammonium salt remaining. In addition, triethylammonium acetate which serves as the *in situ*-generated supporting electrolyte in this system can be regenerated through distillation.[81,82] Using a 1 : 1 ratio of acetic acid in methanol, a yield of 71% was achieved (entry 8). Conducting electrolysis at 50 °C did not significantly alter the yield with 69% of **3a** (entry 9). Finally, with glassy carbon as a more cost and resource efficient anode material, pyrrole **3a** was obtained in 72% yield (entry 10), resulting in a completely metal-free system.

In order to optimise the continuous parameters, *i.e.* variables that can take on numerical values over a continuous range, we employed Design of Experiments (DoE), a statistical approach that gives valuable insight into the effects and interactions of the parameters with a minimal number of experiments.[73,83,84] A 2^{6-2} fractional factorial design was applied to investigate the influence of the concentration of substrate **1a**, the equivalents of dicarbonyl **2a**, the ratio of acetic acid/methanol, the amount of added triethylamine, the current density and the amount of applied charge (Scheme 2). The results showed that only the substrate concentration and the equivalents of dicarbonyl compound have a significant influence on the yield of **3a**, with higher concentration and more equivalents being beneficial. A higher amount of triethylamine led to a significantly decreased cell voltage and allowed the reaction to proceed with an improved faradaic efficiency of 57%. This can be attributed to a higher concentration of charged species, increasing conductivity while also increasing the concentration of acetate, which is consumed on the counter electrode in the Kolbe reaction. The conditions obtained after response optimisation yielded pyrrole **3a** in

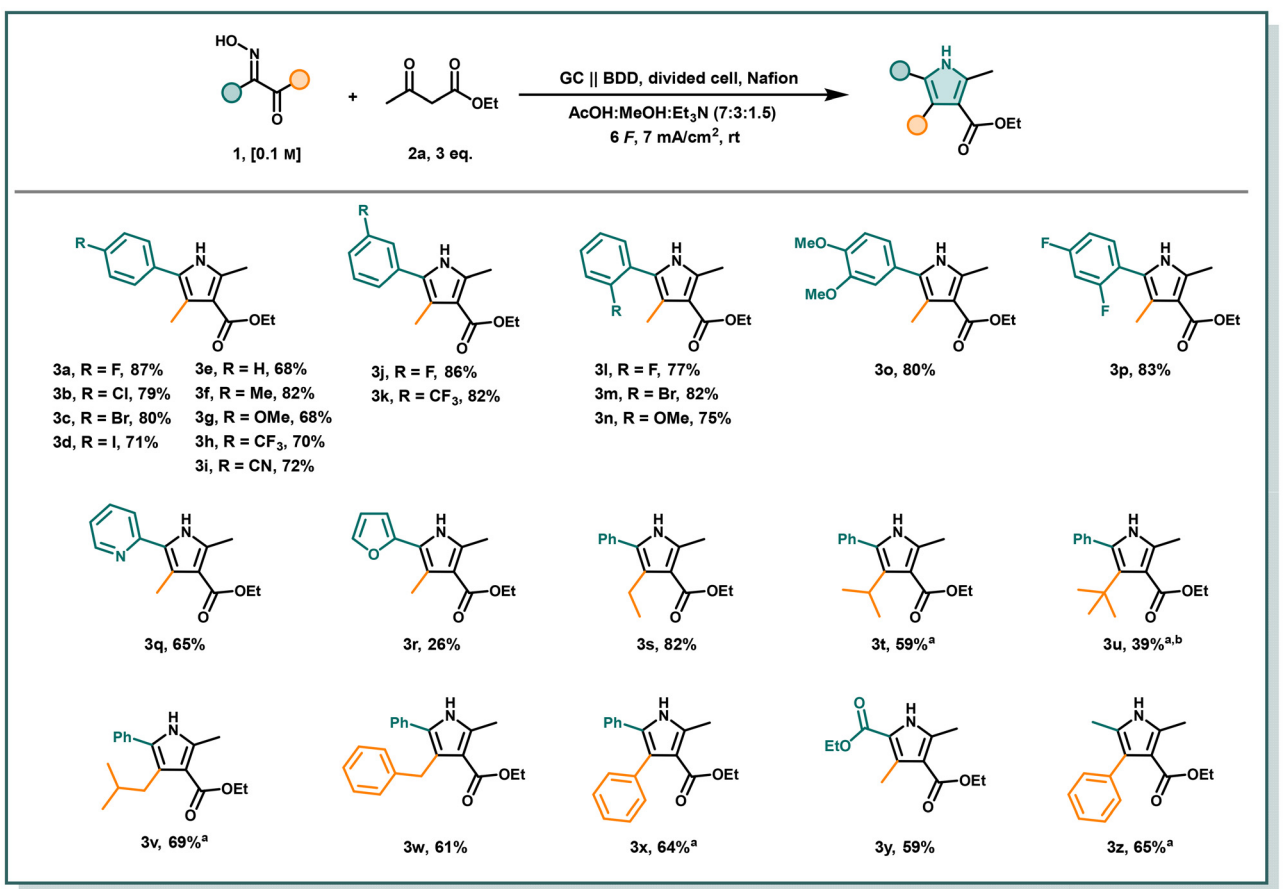


Fig. 2 Scope of oximes employed in the electrochemical Knorr pyrrole synthesis; yields of the isolated product. [a] T = 70 °C; [b] Q = 11 *F*.

89% NMR yield and 87% isolated yield. Only trace amounts of the self-condensation product **5a**, were observed and the formation of the other side products **4a** and **6a** was fully suppressed. To avoid polyfluorinated equipment, a glass frit (P4) could also be used as a separator instead of the Nafion membrane, resulting only in a slightly lower NMR yield of 83% for **3a**. Albeit, the same set of membranes could be reused without any sign of deterioration throughout the whole course of the project.

Scope of pyrroles

The applicability of the established protocol was explored by applying the optimised conditions to a versatile scope of substrates. First, various aromatic oximes were employed to investigate the influence of their substitution pattern on the electroreduction (Fig. 2). Oximes with fluoro, chloro, bromo and iodo substituents in the *para*-position afforded the desired pyrroles **3a–d** in very good yields between 71% and 86%, without dehalogenation. Pyrrole **3e** with an unsubstituted phenyl moiety was obtained in a slightly lower yield of 68% and the methyl-substituted **3f** was isolated in 82% yield. Both electron-donating and electron-withdrawing groups were well tolerated as demonstrated by yields between 68% and 72% for **3g–i**. Of special note is that a cyano moiety was also tolerated, which is also prone to electrochemical reduction in acidic media.[85,86] At the *meta*-position, fluoro and trifluoro moieties achieved very good yields of 86% and 82% for **3j** and **3k**, respectively. Substituents at the *ortho*-position as in **3l–n** were tolerated in yields between 82% and 75%. Disubstituted, highly electron-rich and electron-deficient derivatives **3o** and **3p** were also obtained in very good yields of 80% and 83%, respectively. Furthermore, heterocyclic substrates were also susceptible to the reaction. Pyrrole **3q** with a pyridine moiety was afforded in 65% yield, while furan-substituted pyrrole **3r** was obtained in a lower yield of 26%, probably due to the insufficient stability of furan in acidic media.

Next, the influence of the acyl moiety adjacent to the oxime was investigated. An ethyl chain was well tolerated affording **3s** in 82% yield, whereas the isopropyl derivative **3t** resulted in a low yield of 32%. This can be attributed to the steric effect of the isopropyl group, which hinders the condensation step while the electrochemical reduction is unaffected, indicated by full conversion of the oxime. A high sensitivity towards steric hindrance is a known downside of the Knorr pyrrole synthesis, which can be partially compensated for by increasing the reaction temperature. Thus, reactions with sterically demanding substrates were carried out at 70 °C, which led to an improved yield of 59% for pyrrole **3t**. The *tert*-butyl moiety hindered not only the condensation step, but also the reduction, necessitating a high amount of applied charge of 11 *F* for nearly complete conversion. Combined with a reaction temperature of 70 °C, a moderate yield of 39% of **3u** could be achieved. Isobutyl substituted pyrrole **3v** also required 70 °C for 69% yield. The benzyl derivative **3w** was obtained in 61% yield under ambient conditions and the phenyl derivative **3x** in 64% yield at 70 °C. Aliphatic oximes were also investi-

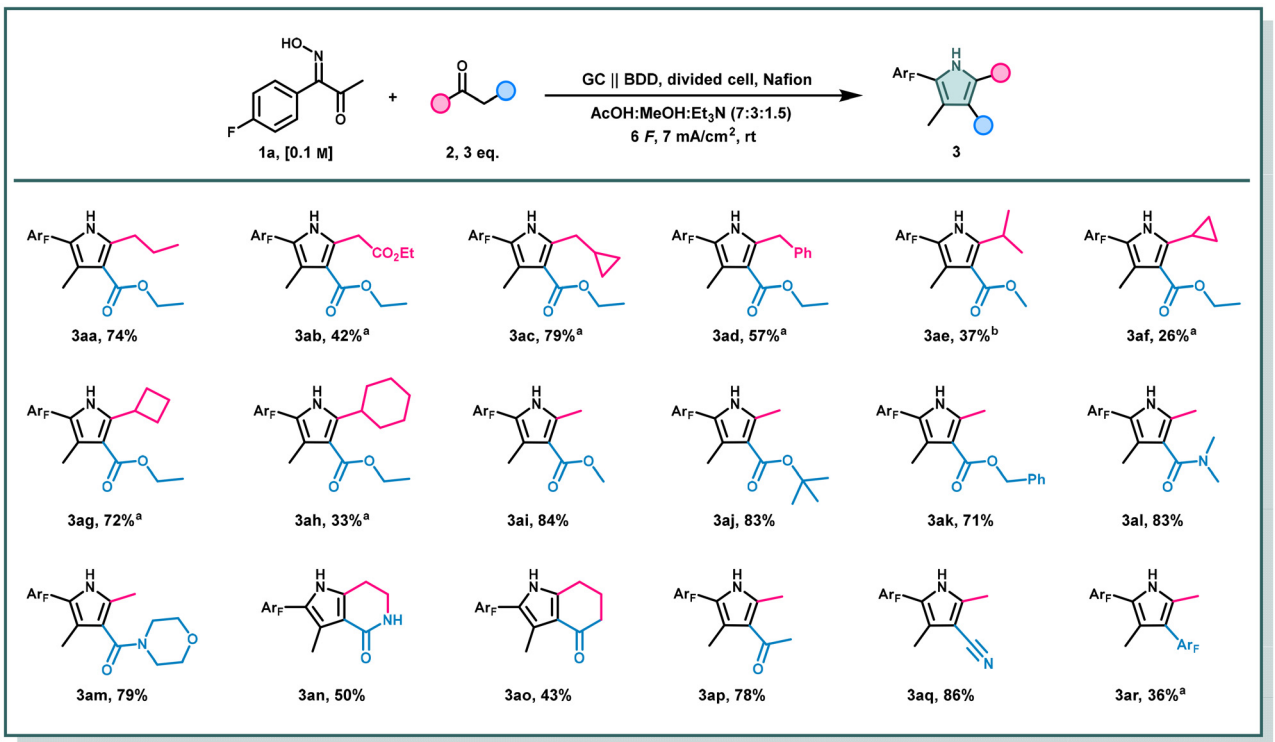


Fig. 3 Scope of dicarbonyl starting materials employed in the electrochemical Knorr pyrrole synthesis; yields of the isolated product; Ar_F = 4-fluorophenyl. [a] *T* = 70 °C; [b] *T* = 90 °C.

gated and gave classic *Knorr's pyrrole* **3y** derived from ethyl acetoacetate in a yield of 59%, while the reaction with α-isonitrosopropiophenone afforded pyrrole **3z** in a yield of 65%.

Next, we investigated the scope of the β-activated ketone (Fig. 3). A derivative of 3-oxohexanoate could be successfully transformed to pyrrole **3aa** in a yield of 74%. An adipic acid derivative resulted in the formation of **3ab** in a yield of 42%, with the decarboxylation product **3a** as a major side product in 52% yield. Methyl cyclopropyl and benzyl derivatives **3ac** and **3ad** could be synthesised in yields of 79% and 57%. An isopropyl group adjacent to the ketone resulted in a sluggish condensation due to steric hindrance, favouring the formation of dimer **5a**. Even at elevated temperatures of 90 °C, the yield of pyrrole **3ae** remained moderate with a yield of 37%. The same effect resulted in moderate yields of cyclopropyl and cyclohexyl derivatives **3af** and **3ah** with yields of 26% and 33%. Surprisingly, the cyclobutyl-containing pyrrole **3ag** could be accessed in a good yield of 72%. Modifications of the ester residue in the 3-position led only to small differences in yield. Satisfyingly, *tert*-butyl ester **3aj** and benzyl ester **3ak** resulted in good yields of 83% and 71%, which allows for deprotection with either acid hydrolysis or catalytic hydrogenolysis. Amides also participated well in the reaction, leading to derivatives **3al** and **3am** in high yields of 83% and 79%. Notably, polycyclic pyrrole **3an** was also obtained in a moderate yield of 50%. Simple diketones also gave the desired products in moderate to good yields, again with the formation of polycyclic compounds **3ao**, which did not auto-oxidise to the corresponding hydroxy indole. Pleasingly, the use of unstable β-ketonitrile also resulted in the clean formation of cyanopyrrole **3aq** in a very good yield of 85%. Phenones also participate in the reaction, enabling access to 2,4-diarylated pyrrole **3ar** albeit in a lower yield of 36%.

To showcase the high versatility and the ability to access pharmaceutically relevant targets, we synthesised precursors and derivatives of APIs (Fig. 4). A precursor of Atorvastatin was synthesised in a yield of 30%, which only lacks the final substituent at the 1-position. The modest yield of **3as** can be attributed to the high steric demand of the isopropyl and the phenyl group, which already led to diminished yields of pyrroles **3x** and **3ae**. Furthermore, the direct precursor of Sitagliptin, a valuable drug used to treat type 2 diabetes, which can also be synthesised electrochemically, was used as the ketone component.[87,88] It afforded highly complex pyrrole **3at** in a yield of 23%, likely due to steric demand and competing reduction of the electron-deficient triazole. Next, precursor **3au** used for the large-scale synthesis of Sunitinib by Manley *et al.* was synthesised in a yield of 54%. It can be converted in two more steps to Sunitinib and was previously accessed only by Pd catalysis.[47] To further prove the versatility of the reaction, **3av** was synthesised in a yield of 60%. This reaction proceeds *via* the divergent Fischer–Fink pathway discovered in 1944, which results in a different connection and thus a different substitution pattern of the pyrrole product.[89–92] Using oxime **1av** derived from malonic acid promotes this reaction pathway and is termed the Kleinspehn modification, which has found wide applications in the synthesis of porphyrins.[93]

Scale-up

The synthetic utility and scalability of the developed protocol were demonstrated by a gram-scale electrolysis of **1a**. The scale-up afforded 1.21 g (84%) of the desired pyrrole **3a**, pro-

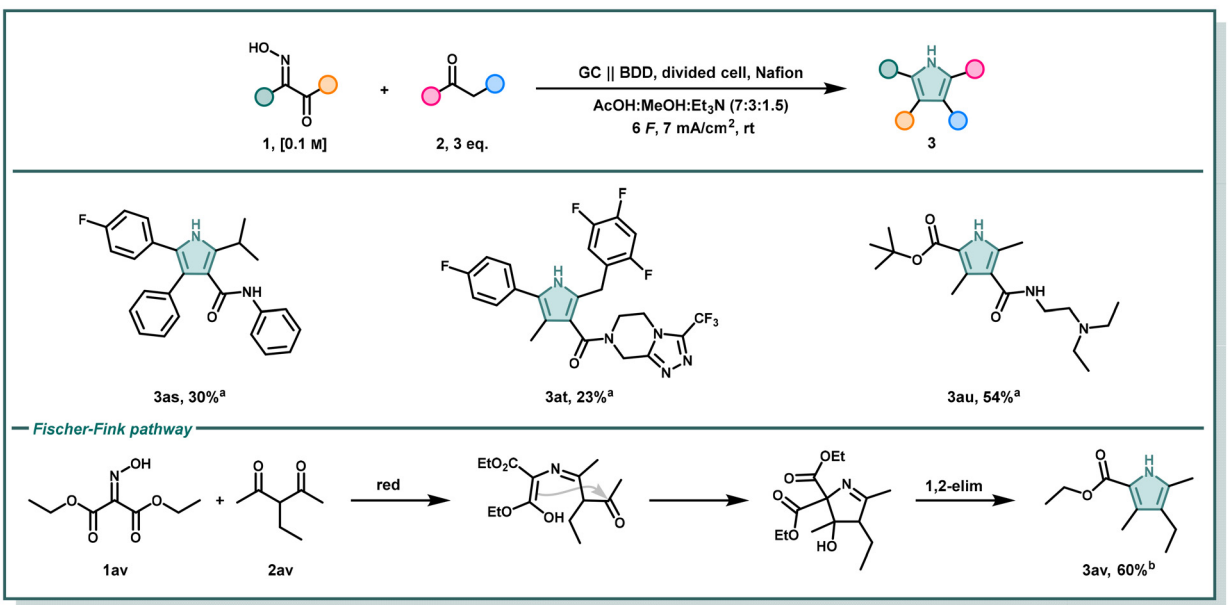
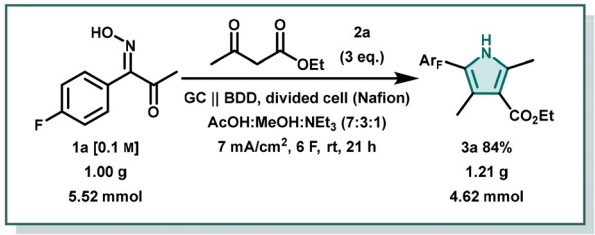


Fig. 4 Synthesis of API-related molecules and compound **3av** obtained *via* the Fischer–Fink pathway; yields of the isolated product. [a] T = 70 °C; [b] T = 90 °C.



Scheme 3 Electrochemical Knorr pyrrole synthesis of **3a** on a gram scale. Ar_F = 4-fluorophenyl.

ceeding without loss in yield or faradaic efficiency (Scheme 3) with a reaction time of 21 h.

Conclusions

An electrochemical modification of the Knorr pyrrole synthesis was developed, which proceeds in a completely metal-free system in a simple, galvanostatic cell set-up. While conventional methods rely on the use of over-stoichiometric amounts of heavy metals or precious metal catalysts, the presented method significantly increases the sustainability of the reaction. Furthermore, a ternary electrolyte system with renewable components is used, which generates the required conductivity by itself without the need for any additional supporting electrolyte. The versatility and applicability of the reaction were demonstrated with a broad scope of 48 pyrroles, demonstrating high functional group tolerance. Also, highly substituted pyrroles with increased steric bulk could be accessed in moderate to good yields. The applicability of the developed protocol was demonstrated through the synthesis of API precursors and derivatives showing a high degree of functionalisation and complexity. Furthermore, the process was conducted on a gram scale to prove the robustness of the method.

Author contributions

F. M. conceptualised the project. M. S. L. and F. M. carried out the investigation and analysis of the generated data and wrote the original draft. S. R. W. supervised the project and reviewed the draft. All authors discussed the results and approved the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): experimental and analytical data (CV studies, NMR and HRMS). See DOI: https://doi.org/10.1039/d6gc03267b.

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