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Article

Highly Selective Electrosynthesis of 1*H*-1-Hydroxyquinol-4-ones—Synthetic Access to Versatile Natural Antibiotics

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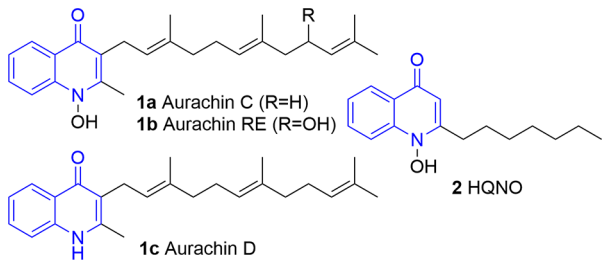
ABSTRACT: 1*H*-1-Hydroxyquinolin-4-ones represent a broad class of biologically active heterocycles having an exocyclic N,O motif. Electrosynthesis offers direct, highly selective, and sustainable access to 1-hydroxyquinol-4-ones by nitro reduction. A versatile synthetic route starting from easily accessible 2-nitrobenzoic acids was established. The broad applicability of this protocol was demonstrated on 26 examples with up to 93% yield, highlighted by the naturally occurring antibiotics Aurachin C and HQNO. The practicability and technical relevance were underlined by multigram scale electrolysis.

KEYWORDS: *electrochemistry, electro-organic synthesis, N-heterocycles, quinolones, aurachin, reduction, cyclo-condensation*

INTRODUCTION

Nitrogen containing heterocycles are ubiquitous in pharmaceuticals and biomolecules as core motifs.[1,2] One particular example is the family of quinol-4-ones, which are represented in a variety of drugs and biomolecules with anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive properties (Chart 1).[3−6] In recent years, natural antibiotics such as

Chart 1. Important Biologically Active Compounds Involving Quinol-4-one Motif



the aurachins (**1a−c**), first isolated from myxobacteria like *stigmatella aurantiaca*, have taken the center stage in research.[7−12] Due to the structural similarity of aurachins to vitamin K, they can inhibit the electron transport chains in living organisms and therefore also have a number of antimicrobial properties.[13,14]

Functionalization and modification of aurachins by biosynthetic processes gained access to a large substance library in the field of quinolone antibiotics.[15−22] Furthermore, 1*H*-2-heptyl-2-hydroxyquinol-4-one (**2**, HQNO) acts as an NADH oxidase inhibitor and shows antibiotic and antimicrobial properties, making it an ideal candidate for antimalaria and anticancer drugs or as caries prophylaxis.[23−30] In addition to the biosynthetic approaches, a number of syntheses are reported that provide access to this unique structural motif of *N*-hydroxy quinolinones with its exocyclic N,O bond (Scheme 1).[20,31−35] HQNO (**2**) is synthesized by oxidation of the corresponding quinolone using equimolar amounts of *m*CPBA (Scheme 1A).[36] However, this method requires the use of a hazardous oxidant and protection with ethyl chloroformate, resulting in a poor atom economy.

In contrast, reduction of nitro arenes and subsequent cyclo-condensation enables direct access to the *N*-hydroxyquinolines (Scheme 1B).[37−42] Selective reduction of the nitro group to the corresponding hydroxylamines is crucial. By using stoichiometric amounts of reagent and an acidic additive, the selectivity of the reduction can be controlled, and reducing agents such as tin(II) chloride,[43] red phosphorus,[44] and zinc[45] enable the synthesis in moderate to good yields. Furthermore, the desired products can be obtained in high yields by hydrogenation with H_2 and $NaBH_4$.[46,47] However, this requires expensive transition-metal catalysts and precisely controlled conditions, as this approach is widely used for reduction to anilines.[45,48,49] Organic electrosynthesis can address these challenges, as selective reduction to hydroxylamine is well-established under appropriate conditions (Scheme 1C). In 1969, Lund reported the cathodic synthesis of the *N*-hydroxy quinolinone **5c** in a divided cell under potential controlled conditions using a mercury cathode with hydrochloric acid.[50] Furthermore, an electrochemical protocol for the synthesis of 1*H*-1hydroxy-2-methylquinol-4-one (**5a**) was described by Tallec and co-workers using a mercury cathode with sulfuric acid as the supporting electrolyte.[51] Both protocols enable in electroanalytic studies the access to a single example using highly toxic metal electrodes, which is nowadays banned in

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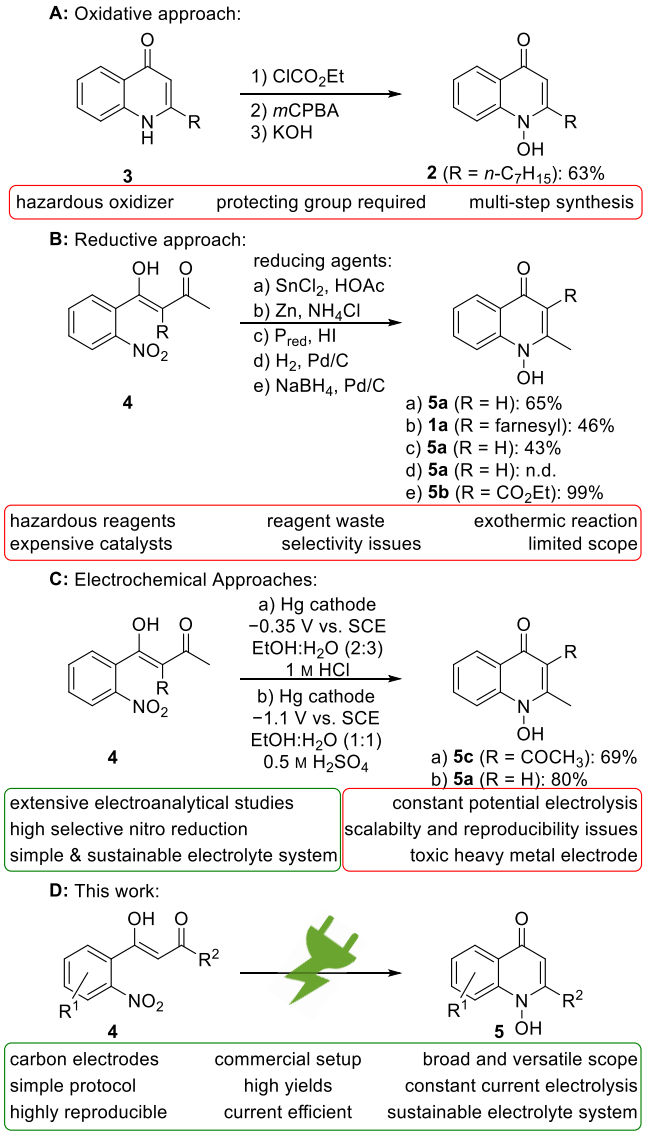
Scheme 1. Synthetic Access to 1*H*-1-hydroxyquinol-4-ones



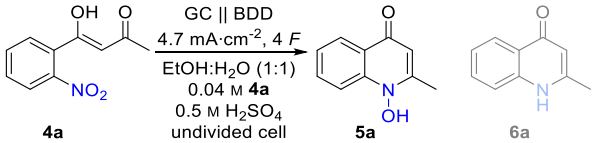
most countries for sensitive technical applications. Due to cathodic corrosion, heavy metal contamination of the product cannot be avoided.[52]

In this work, a simple, scalable, and versatile electrochemical method for the reductive cyclization of easy to prepare nitro arenes into 1*H*-1-hydroxyquinol-4-ones **5** is established (Scheme 1D). The electrolysis was performed in a commercially available electrochemical setup with commonly used sustainable carbon-based electrode materials to ensure high reproducibility and applicability.[53−55] Organic electrosynthesis is experiencing a renaissance as an alternative to conventional synthetic protocols by considering sustainable aspects.[56−60] This methodology can easily pay off as a key discipline for future synthetic applications for high value-added products, especially, in the synthesis of APIs.[61,62] The use of electric current as an alternative to conventional reagents proves to be almost waste- and pollutant-free due to the absence of toxic and hazardous reagents, especially when solvents and supporting electrolytes are reused. Furthermore, these processes prove to be inherently safe due to the precise reaction control, as the conversion is immediately stopped by turning off the electricity and therefore preventing thermal runaway reactions.[63−68]

RESULTS AND DISCUSSION

Substrate **4a** was chosen as a test substrate for the optimization of the cathodic reduction synthesized in two steps from 2-nitrobenzoic acid in a high yield (see the ESI for a detailed description). Based on the work of Tallec and co-workers,[51] Lund et al.,[50] and Waldvogel,[69−71] the initial electrolytic conditions for the cathodic reduction of nitro arene **4a** were chosen (Table 1, entry 1). A water−ethanol mixture (1:1 (*v*:*v*)) was used as a green solvent. Sulfuric acid plays a dual role as a supporting electrolyte and as a catalyst for the cyclocondensation as well as the selective nitro reduction.[72] Based on previous work, a sulfuric acid concentration of 0.5 M was used initially.[51,69,73] Constant current electrolysis was performed in an undivided cell by applying the theoretical amount of charge (4 *F*) and a current density (4.7 mA cm^{-2}). Electrolysis was performed utilizing carbon-based electrode materials, with glassy carbon (GC) as the anode and boron-doped diamond (BDD) as the cathode. BDD offers a unique reactivity toward electrochemical conversion of a multitude of substrates and fulfills sustainable requirements through its sustainable production using methane as a carbon source.[54,74−76] Applying the described conditions, the desired 1-hydroxyquinonlin-4-one **5a** was obtained in 66% yield (Table 1, entry 1). Molecular structure could be unequivocally confirmed by X-ray analysis (CCDC: 2367756). Systematic variation of the electrolytic conditions was carried out in linear screening experiments.[77] However, several parameters and counter reactions seem to play a crucial role for success.[55,78] First, the influence of the cathode material was investigated with platinum, lead, and leaded bronzes. Platinum as the cathode material resulted in 59% requiring a precious and rare

Table 1. Optimization of the Electrolytic Conditions for the Cathodic Synthesis of 1*H*-1-hydroxy-2-methylquinol-4-one



entry	deviation from standard conditions	yield **5a**[a]
1	none	66%
2	Pt instead of BDD	59%
3	Pb instead of BDD	2% (**6a**: 24%)
4	CuSn5Pb20	20% (**6a**: 9%)
5	DSA (RuO_2@Ta) instead of GC	64%
6	formic acid instead of H_2SO_4	57%
7	acetic acid instead of H_2SO_4	30%
8	acetate buffer instead of H_2SO_4	38%
9	methanol instead of ethanol	95% (92%[b])
10	acetone instead of ethanol	52%
11	acetonitrile instead of ethanol	63%
12	MeOH:H_2O (1:3)	91%
13	$c(H_2SO_4)$ = 1.0 M; MeOH:H_2O	86%
14	$c(H_2SO_4)$ = 0.25 M; MeOH:H_2O	78%
15	j = 3.0 mA cm^{-2}; MeOH:H_2O	76%
16	j = 6.0 mA cm^{-2}; MeOH:H_2O	83%

[a]Yield of **5a** was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield.

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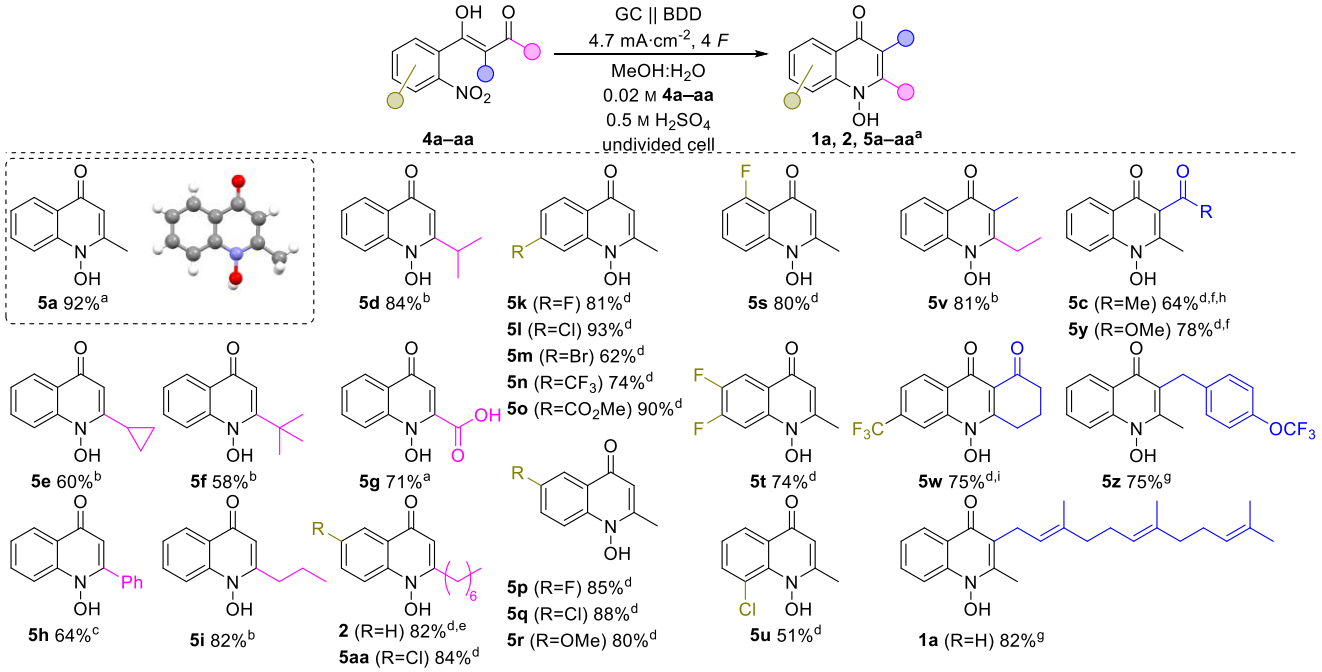
Chart 2. Scope of the Electrosynthesis of 1*H*-1-hydroxyquinol-4-ones with Isolated Yields on a 0.5 mmol Scale in 25 mL Beaker-Type Electrolysis Cells (SynLectro)



[a]MeOH:H_2O (1:1 (*v*:*v*)), 0.04 M **4a**, 1 mmol. [b]MeOH:H_2O (2:1 (*v*:*v*)). [c]MeOH:acetone:H_2O (40:9:1 (*v*:*v*:*v*)). [d]MeOH:H_2O (3:1 (*v*:*v*)). [e]4.5 *F*. [f]2.4 mA cm^{-2}. [g]MeOH:H_2O (5:1 (*v*:*v*)). [h]Side product: **5a** 25%. [i]From Nitisinone.

metal (Table 1, entry 2). To our delight, utilizing a lead cathode led to a shutdown of product formation **5a**, whereas the full reduction of the nitro group was observed resulting in the formation of 1*H*-2-methylquinol-4-one (**6a**) (Table 1, entry 3). Leaded bronzes are robust alternatives to pure lead electrodes, as they are more mechanically and chemically stable. However, by using a leaded bronze cathode, the product was only formed in 20% yield (Table 1, entry 4).[52,79]

To investigate the influence of the counter reaction, a dimensionally stable anode (DSA) with low overpotential for oxygen evolution reaction was used, resulting in a similar yield of 64% (Table 1, entry 5). Therefore, no advantage is gained for using an expensive transition-metal-based electrode material instead of glassy carbon. The influence of weaker organic acids was investigated by using formic acid and acetic acid instead of sulfuric acid, resulting in lower yields (57 and 30%) (Table 1, entries 6 and 7). Especially, acetic acid led in a high cell voltage (>32 V), so an acetic buffer was used. However, desired **5a** was obtained only in 38% yield (Table 1, entry 8). To our delight, the yield of **5a** was dramatically increased by using methanol (95%) and could be isolated in 92% yield (Table 1, entry 9). In comparison, aprotic solvents generally led to lower yields, e.g., acetone with 52% and acetonitrile with 63% (Table 1, entry 10 and 11). Lowering the MeOH content to the solubility limit of the starting material (water:methanol (1:3 (*v*:*v*))) resulted in a slightly decreased yield of 91% (Table 1, entry 12). Lower and higher sulfuric acid concentrations (0.25 and 1 M) resulted in a decreased yield of **5a** (86 and 78%), underlining the significant influence of the acid concentration on the outcome of the reaction (Table 1, entries 13 and 14). The increase (6.0 mA cm^{-2}) and decrease (3.0 mA cm^{-2}) in current density also led to lower yields (76 and 83%) (Table 1, entries 15 and 16). Full conversion of the starting material was observed by applying the theoretical amount of charge, which require no further optimization of this parameter.

The optimized electrolytic conditions were applied to a broad and diverse range of substrates (Chart 2). However, due to the lower solubility in the electrolyte of the substituted starting materials **4c–y**, the methanol content needed to be increased, and the substrate concentration needed to be lowered to 0.02 M. The influence of primary, secondary, and tertiary alkyl substitutions was investigated in the synthesis of heterocycles **5d–f**, resulting in decreasing yield in accordance with increasing steric bulk (58–84%). Here, *tert*-butyl derivative **5f** gave the lowest yield. Interestingly, 2-cyclopropylquinol-4-one **5e** was obtained in a moderate yield of 60% compared to its corresponding isopropyl derivative **5d** with 84%. Furthermore, 1*H*-1-hydroxy-2-propylquinol-4-one (**5i**) as well as HQNO (**2**) with increasing hydrophobic side chains were obtained both in a good yield of 82%. The carboxylic acid **5g** was obtained in 71% yield by conversion of 2,4-dioxobutanoic acid. Phenyl substituted **5h** was isolated in 64% yield. However, an adapted solvent mixture of methanol, water, and acetone was required due to the low solubility of the starting material. The 2-amino and 2-oxo derivatives could not be obtained possibly due to the decreased reactivity of the corresponding nitrile and ethyl ester starting material in cyclocondensation reactions.

After the influence of the 2-substitution was investigated, the impact of the modification of the nitro arene core (**5k–u**) was explored. Fluoro compounds **5k**, **5p**, **5s**, and **5t** were obtained in good yields of 85%, whereby no influence of the substitution pattern on the yield was determined. The chloro compounds **5l** and **5q** were obtained in very good yields of 93% and 88% respectively. The moderate yield (51%) of chloro compound **5u** should be attributed to the steric and electronic influence. Bromo compound **5m** was obtained in a good yield of 62%.

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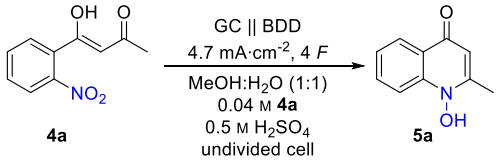
The derivative bearing a trifluoromethyl group **5n** was obtained in a good yield of 74%. Derivatives with an electron-withdrawing group and an electron-donating group were obtained in very good yields. In particular, 6-methoxyquinol-4-one **5r** was obtained in 80% yield and the methyl ester **5o** in 90%. Resulting *N*-hydroxyquinolones (**5a–u**) could serve as novel precursors for biocatalytic prenylation, resulting in novel Aurachin C-based antibiotics.[35]

In addition, 2,3-disubstituted quinol-4-ones (**1a**, **5c**, and **5v–z**) were obtained in moderate to good yields. In particular, 2-ethyl-3-methylquinol-4-one **5v** bearing two alkyl substitutions was isolated in 81% yield. The tolerance of electrolytic conditions for 3-prenyl derivatives was demonstrated by the synthesis of a 3-farnesyl *N*-hydroxyquinolone (**1a**) in 82% yield, emphasized by the synthesis of the natural antibiotic Aurachin C (**1a**). **5w** was obtained in a good yield of 75% from Nitisinone, a medication to treat hereditary tyrosinemia type 1.[80] **5c** and **5y** containing a carbonyl moiety in 3-position were obtained in 64 and 78% yields, respectively. However, the synthesis of **5c** leads to an additional yield of **5a** (25%) by decarboxylation of the starting material **4c** under electrolytic conditions. **5z**, a novel drug candidate for tuberculosis therapy as a cytochrome oxidase inhibitor, was obtained in 75% yield.[81−83] With **5aa**, a chloro-functionalized derivative of the natural antibiotic **2** was obtained in 84% yield, demonstrating the potential for the synthesis of novel drug candidates.

Considering preparative aspects, glassy carbon was tested as an alternative cathode material for BDD in the synthesis of **5a**, which led to slightly decreased selectivity and a yield of 87%. Furthermore, we focused on the multigram synthesis of the Aurachin C precursor **5a** (Table 2). Initially, a 4-fold scale-up

Table 2. Scale-Up of the Electrochemical Synthesis of 1*H*-1-hydroxy-2-methylquinol-4-on (5a)



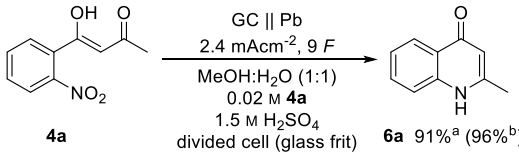
cell volume[a]	scale	yield **5a**
25 mL	1.0 mmol	161 mg (92%)
25 mL	1.0 mmol[b]	152 mg (87%)
100 mL	4.0 mmol	643 mg (92%)
300 mL	12 mmol	1.871 g (89%)
300 mL	24 mmol[c]	3.651 g (87%)

[a]Commercially available electrochemical cell (SynLectro). [b]GC instead of BDD. [c]0.08 M **4a** in MeOH:H_2O (1:1).

was performed on a 4.0 mmol scale in a batch-type electrolysis using a 100 mL glass cell, resulting in a constant yield of 92% of **5a** accordingly, 643 mg. Importantly, gram-scale electrolysis was performed on a 12-fold scale (12.0 mmol) in a 300 mL glass cell, affording 1.871 g (89%) of the desired **5a**. Multigram electrolysis was conducted with a doubled substrate concentration, resulting in a slightly decreased yield of 87%, accordingly 3.651 g. The trend of decreased yield at higher concentrations coincides with previous work.[69,73]

Based on the observation of selective deoxygenation of nitro arenes to their anilines by using lead or leaded bronzes, we investigated in addition in a proof-of-concept study the electrochemical synthesis of 1*H*-2-methylquinol-4-one **6a**. In contrast, reduction to **6a** on BDD cathodes could not be carried out in good yields. The linear optimization of the electrolytic conditions (see Tables S6–S13) resulted in deviated electrolytic conditions. Crucial for the full reduction of the nitro group proved to be stronger cathodic conditions by utilizing a lead cathode. As reported, a higher sulfuric acid concentration proved to be favorable for the nitro reduction to the aniline.[84] A divided setup as well as lower current densities had a positive influence on the yield by preventing side reactions. In addition to the direct nitro reduction, a telescoped approach resulting from deoxygenation of **5a** into the desired product **6a** was possible. Full conversion was observed with 9 *F*, resulting in an isolated yield of 91% (Scheme 2).

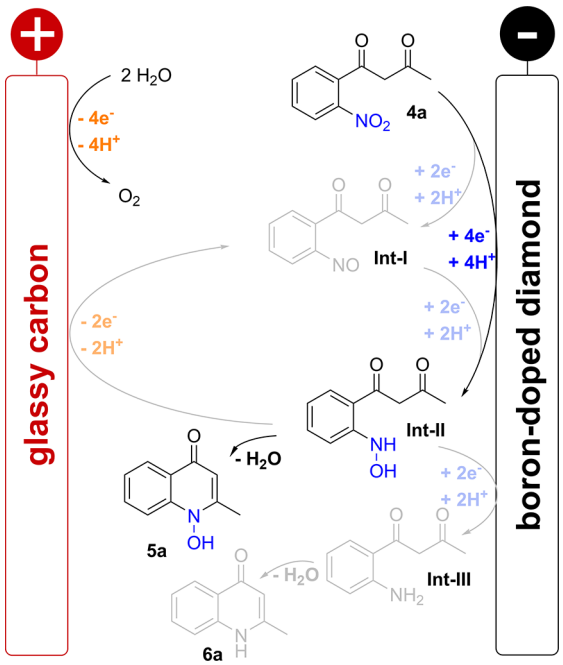
Scheme 2. Optimized Conditions of the Electrochemical Synthesis of 1*H*-2-methylquinol-4-one (6a)



[a]Isolated yield. [b]Yield determined by LC-MS using 8-hydroxyquinoline as an internal standard.

Mechanistic considerations were performed based on reported data for the reduction of nitro arene **4a** and our previously reported studies on nitro reductions in *N*-hydroxy and *N*-oxy heterocycles synthesis as well as cyclic voltammetry measurements, resulting in a postulated mechanism (Scheme 3). The reduction of the nitro arene **4a** in two two-electron reduction steps at BDD electrodes results in the corresponding hydroxylamine **Int-II** via the nitroso intermediate **Int-I**. Two-electron steps in protic solvents have been occupied in multiple

Scheme 3. Proposed Mechanism for the Electrosynthesis of 1*H*-1-hydroxyquinol-4-ones 5a and Over-Reduction to 6a



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studies.[42,50−52,69,84] However, the cyclic voltammogram (Figure S5) shows only a single broad reduction wave at −0.91 V, which accounts for the high selectivity to the hydroxylamine **Int-II**. A subsequent reduction of the product does not take place at the BDD. In contrast, a direct and selective reduction to the amine **Int-III** is observed at lead cathodes. This heavy metal electrode material possesses a high selectivity toward deoxygenation reactions and possesses a high overpotential for hydrogen evolution reaction.[54] Subsequently, cyclo-condensation is accomplished in the desired product (**5a** or **6a**).

CONCLUSIONS

In summary, the established electrochemical method provides simple, direct, and sustainable access to *N*-hydroxyquinol-4-ones **5** by selective cathodic nitro reduction and subsequent cyclo-condensation. In addition to the previous reports on the simple electrochemical synthesis of N,O heterocycles by reduction of nitro arenes, the protocol described adds up to these as a sustainable tool for the modern organic chemist in heterocycle chemistry highlighted by utilizing broadly available and sustainable carbon-based electrodes as well as an environmentally benign solvent. Sulfuric acid serves in a multiple role as a supporting electrolyte, a selectivity criterion for the nitro reduction, and an acidic catalyst for the subsequent cyclo-condensation. Applying a simple and commercially available electrochemical setup ensured high reproducibility. The broad applicability of the reported electrochemical protocol was demonstrated by diverse 26 examples in up to 93% isolated yield. The electrolytic conditions tolerate various functional groups, including sterically demanding, redox-labile substituents, as well as electron-withdrawing and -donating groups. The natural antibiotics Aurachin C (**1a**) and HQNO (**2**) with multiple potential pharmaceutical applications were isolated both in 82% yield. In proof-of-concept studies, electrochemical synthesis of 2-methylquinol-4-one **6a** was obtained in 91% by full nitro reduction. In mechanistic considerations, selective nitro reduction to the hydroxylamine at the BDD cathode was confirmed by cyclic voltammetry measurements as a key step. Robust scalability of this electrochemical protocol was demonstrated by multigram electrolysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.4c00337.

General information, optimization data, electrochemical setup, experimental procedures, cyclic voltammetry data, compound characterization, and crystal structure data (PDF)

Molecular structure 5a (CIF)

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Author Contributions

T.P. and S.R.W. conceived the project. T.P., N.S., J.H., F.K, S.P., J.W., and M.d.J.G.-V. conducted the experiments and analyzed the results. D.S. performed the X-ray analysis and structural elucidation of the synthesized compound. T.P., J.W., and S.R.W. wrote and reviewed the manuscript. S.R.W. supervised the project. All authors discussed the results and agreed to the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

BDD, boron-doped diamond; CCDC, Cambridge Crystallographic Data Center; DSA, dimensionally stable anode; GC, glassy carbon; HQNO, 1*H*-2-heptyl-1-hydroxyquinol-4-one; NADH, nicotinamide adenine dinucleotide phosphate; *m*CPBA, *meta*-chloroperoxybenzoic acid

REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257−10274.

(2) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25* (8), 1909.

(3) Millanao, A. R.; Mora, A. Y.; Villagra, N. A.; Bucarey, S. A.; Hidalgo, A. A. Biological Effects of Quinolones: A Family of Broad-Spectrum Antimicrobial Agents. *Molecules* **2021**, *26* (23), 7153.

(4) Chu, X.-M.; Wang, C.; Liu, W.; Liang, L.-L.; Gong, K.-K.; Zhao, C.-Y.; Sun, K.-L. Quinoline and quinolone dimers and their biological activities: An overview. *Eur. J. Med. Chem.* **2019**, *161*, 101−117.
(5) Dine, I.; Mulugeta, E.; Melaku, Y.; Belete, M. Recent advances in the synthesis of pharmaceutically active 4-quinolone and its analogues: a review. *RSC Adv.* **2023**, *13* (13), 8657−8682.
(6) Dube, P. S.; Legoabe, L. J.; Beteck, R. M. Quinolone: a versatile therapeutic compound class. *Mol. Divers.* **2023**, *27* (3), 1501−1526.
(7) Lightbrown, J. W.; Jackson, F. L. Inhibition of cytochrome systems of heart muscle and certain bacteria by the antagonists of dihydrostreptomycin: 2-alkyl-4-hydroxyquinoline N-oxides. *Biochem. J.* **1956**, *63* (1), 130−137.
(8) Kunze, B.; Höfle, G.; Reichenbach, H. The aurachins, new quinoline antibiotics from myxobacteria: production, physico-chemical and biological properties. *J. Antibiot.* **1987**, *40* (3), 258−265.
(9) Höfle, G.; Bööhlendorf, B.; Fecker, T.; Sasse, F.; Kunze, B. Semisynthesis and antiplasmodial activity of the quinoline alkaloid aurachin E. *J. Nat. Prod.* **2008**, *71* (11), 1967−1969.
(10) Katsuyama, Y.; Harmrolfs, K.; Pistorius, D.; Li, Y.; Müller, R. A semipinacol rearrangement directed by an enzymatic system featuring dual-function FAD-dependent monooxygenase. *Angew. Chem., Int. Ed.* **2012**, *51* (37), 9437−9440.
(11) Saalim, M.; Villegas-Moreno, J.; Clark, B. R. Bacterial Alkyl-4-quinolones: Discovery, Structural Diversity and Biological Properties. *Molecules* **2020**, *25* (23), 5689.
(12) Tatsuta, K.; Tamura, T. Novel synthesis and structural elucidation of quinolone antibiotics PC-3 (SF2420B) and YM-30059. *J. Antibiot.* **2000**, *53* (4), 418−421.
(13) Jünemann, S.; Wrigglesworth, J. M.; Rich, P. R. Effects of decyl-aurachin D and reversed electron transfer in cytochrome bd. *Biochemistry* **1997**, *36* (31), 9323−9331.
(14) Debnath, J.; Siricilla, S.; Wan, B.; Crick, D. C.; Lenaerts, A. J.; Franzblau, S. G.; Kurosu, M. Discovery of selective menaquinone biosynthesis inhibitors against Mycobacterium tuberculosis. *J. Med. Chem.* **2012**, *55* (8), 3739−3755.
(15) Li, X.-W.; Herrmann, J.; Zang, Y.; Grellier, P.; Prado, S.; Müller, R.; Nay, B. Synthesis and biological activities of the respiratory chain inhibitor aurachin D and new ring versus chain analogues. *Beilstein J. Org. Chem.* **2013**, *9*, 1551−1558.
(16) Nachtigall, J.; Schneider, K.; Nicholson, G.; Goodfellow, M.; Zinecker, H.; Imhoff, J. F.; Süssmuth, R. D.; Fiedler, H.-P. Two new aurachins from Rhodococcus sp. Acta 2259. *J. Antibiot.* **2010**, *63* (9), 567−569.
(17) Kitagawa, W.; Tamura, T. A quinoline antibiotic from Rhodococcus erythropolis JCM 6824. *J. Antibiot.* **2008**, *61* (11), 680−682.
(18) Zhang, M.; Yang, C. L.; Xiao, Y. S.; Zhang, B.; Deng, X. Z.; Yang, L.; Shi, J.; Wang, Y. S.; Li, W.; Jiao, R. H.; Tan, R. X.; Ge, H. M. Aurachin SS, a new antibiotic from Streptomyces sp. NA04227. *J. Antibiot.* **2017**, *70* (7), 853−855.
(19) Sandmann, A.; Dickschat, J.; Jenke-Kodama, H.; Kunze, B.; Dittmann, E.; Müller, R. A Type II polyketide synthase from the gram-negative Bacterium Stigmatella aurantiaca is involved in Aurachin alkaloid biosynthesis. *Angew. Chem., Int. Ed.* **2007**, *46* (15), 2712−2716.
(20) Höfle, G.; Irschik, H. Isolation and biosynthesis of aurachin P and 5-nitroresorcinol from Stigmatella erecta. *J. Nat. Prod.* **2008**, *71* (11), 1946−1948.
(21) Kamigiri, K.; Tokunaga, T.; Shibazaki, M.; Setiawan, B.; Rantiatmodjo, R. M.; Morioka, M.; Suzuki, K. YM-30059, a novel quinolone antibiotic produced by Arthrobacter sp. *J. Antibiot.* **1996**, *49* (8), 823−825.
(22) Szamosvári, D.; Prothiwa, M.; Dieterich, C. L.; Böttcher, T. Profiling structural diversity and activity of 2-alkyl-4(1H)-quinolone N-oxides of Pseudomonas and Burkholderia. *Chem. Commun.* **2020**, *56* (47), 6328−6331.
(23) Hays, E. E.; Wells, I. C.; Katzman, P. A.; Cain, C. K.; Jacobs, F. A.; Thayer, S. A.; Doisy, E. A.; Gaby, W. L.; Roberts, E. C.; Muir, R. D.; Carroll, C. J.; Jones, L. R.; Wade, N. J. Antibiotic substances produced by pseudomonas aeruginoas. *J. Biol. Chem.* **1945**, *159* (3), 725−750.
(24) Kitamura, S.; Hashizume, K.; Iida, T.; Miyashita, E.; Shirahata, K.; Kase, H. Studies on lipoxygenase inhibitors. II. KF8940 (2-n-heptyl-4-hydroxyquinoline-N-oxide), a potent and selective inhibitor of 5-lipoxygenase, produced by Pseudomonas methanica. *J. Antibiot.* **1986**, *39* (8), 1160−1166.
(25) Cornforth, J. W.; James, A. T. Structure of a naturally occurring antagonist of dihydrostreptomycin. *Biochem. J.* **1956**, *63* (1), 124−130.
(26) Ames, D. E.; Franklin, C. S.; Grey, T. F. N-Oxides of some hydroxy- and amino-quinolines. *J. Chem. Soc.* **1956**, 3079.
(27) Inaba, T.; Oura, H.; Morinaga, K.; Toyofuku, M.; Nomura, N. The Pseudomonas Quinolone Signal Inhibits Biofilm Development of Streptococcus mutans. *Microbes Environ.* **2015**, *30* (2), 189−191.
(28) Lightbrown, J. W. An antagonist of streptomycin and dihydrostreptomycin produced by Pseudomonas aeruginosa. *J. Gen. Microbiol.* **1954**, *11* (3), 477−492.
(29) Szamosvári, D.; Böttcher, T. An Unsaturated Quinolone N-Oxide of Pseudomonas aeruginosa Modulates Growth and Virulence of Staphylococcus aureus. *Angew. Chem., Int. Ed.* **2017**, *56* (25), 7271−7275.
(30) Supong, K.; Thawai, C.; Supothina, S.; Auncharoen, P.; Pittayakhajonwut, P. Antimicrobial and anti-oxidant activities of quinoline alkaloids from Pseudomonas aeruginosa BCC76810. *Phytochem. Lett.* **2016**, *17*, 100−106.
(31) Höfle, G.; Kunze, B. Biosynthesis of aurachins A-L in Stigmatella aurantiaca: a feeding study. *J. Nat. Prod.* **2008**, *71* (11), 1843−1849.
(32) Pistorius, D.; Li, Y.; Sandmann, A.; Müller, R. Completing the puzzle of aurachin biosynthesis in Stigmatella aurantiaca Sg a15. *Mol. BioSyst.* **2011**, *7* (12), 3308−3315.
(33) Li, Y.; Müller, R. Non-modular polyketide synthases in myxobacteria. *Phytochemistry* **2009**, *70* (15−16), 1850−1857.
(34) Kruth, S.; Schibajew, L.; Nett, M. Biocatalytic production of the antibiotic aurachin D in Escherichia coli. *AMB Express* **2022**, *12* (1), 138.
(35) Kruth, S.; Zimmermann, C. J.-M.; Kuhr, K.; Hiller, W.; Lütz, S.; Pietruszka, J.; Kaiser, M.; Nett, M. Generation of Aurachin Derivatives by Whole-Cell Biotransformation and Evaluation of Their Anti-protozoal Properties. *Molecules* **2023**, *28* (3), 1066.
(36) Woschek, A.; Mahout, M.; Mereiter, K.; Hammerschmidt, F. Synthesis of 2-Heptyl-1-hydroxy-4(1 H)-quinolone - Unexpected Rearrangement of 4-(Alkoxycarbonyloxy)quinoline N -Oxides to 1-(Alkoxycarbonyloxy)-4(1 H)-quinolones. *Synthesis* **2007**, *2007* (10), 1517−1522.
(37) Zou, D.; Wang, W.; Hu, Y.; Jia, T. Nitroarenes and nitroalkenes as potential amino sources for the synthesis of N-heterocycles. *Org. Biomol. Chem.* **2023**, *21* (11), 2254−2271.
(38) 2.7 Reduction of Nitro Compounds to Amines, Azo Compounds, Hydroxylamines, and Oximes, and Reduction of N-Oxides to Amines. In *Catalytic reduction in organic synthesis*; De Vries, J. G., Ed.; Science of synthesis; Thieme Chemistry, 2018.
(39) Waldvogel, S. R.; Streb, C. Redox mediators facilitate selective electrocatalytic nitroarene-to-aniline reduction. *Chem.* **2022**, *8* (8), 2071−2073.
(40) Swaminathan, K.; Anantharaman, P. N.; Subramanian, G. S.; Udupa, H. V. K. Preliminary studies on the electrolytic reduction of nitrobenzene to aniline. *J. Appl. Electrochem.* **1972**, *2* (3), 169−173.
(41) Winter, J.; Prenzel, T.; Wirtanen, T.; Schollmeyer, D.; Waldvogel, S. R. Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline N-oxides by Cathodic Reduction of Nitro Arenes. *Chem.—Eur. J.* **2023**, *29* (12), No. e202203319.
(42) Wirtanen, T.; Rodrigo, E.; Waldvogel, S. R. Recent Advances in the Electrochemical Reduction of Substrates Involving N−O Bonds. *Adv. Synth. Catal.* **2020**, *362* (11), 2088−2101.
(43) McCluskey, K. L. Some new derivatives of quinaldine. *J. Am. Chem. Soc.* **1922**, *44* (7), 1573−1577.

https://doi.org/10.1021/acs.oprd.4c00337
Org. Process Res. Dev. 2024, 28, 3922−3928

(44) Gabriel, S.; Gerhard, W. Derivate einiger o -Nitro-Ketone. *Ber. Dtsch. Chem. Ges.* **1921**, *54* (5), 1067−1078.
(45) Enomoto, M.; Kitagawa, W.; Yasutake, Y.; Shimizu, H. Total synthesis of aurachins C, D, and L, and a structurally simplified analog of aurachin C. *Biosci., Biotechnol., Biochem.* **2014**, *78* (8), 1324−1327.
(46) Walker, H. G.; Hauser, C. R. The Acetylation of o-, m- and p-Nitroacetophenones by the Boron Trifluoride Method 1. *J. Am. Chem. Soc.* **1946**, *68* (12), 2742−2743.
(47) Jung, J.-C.; Jung, Y.-J.; Park, O.-S. Synthesis of 4-hydroxyquinolin-2(1 H)-one analogues and 2-substituted quinolone derivatives. *J. Heterocycl. Chem.* **2001**, *38* (1), 61−67.
(48) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. Synthesis of quinolines, 2-quinolones, phenanthridines, and 6(5h)-phenanthridinones via palladium0-mediated Ullmann cross-coupling of 1-bromo-2-nitroarenes with beta-halo-enals, -enones, or -esters. *Org. Lett.* **2004**, *6* (16), 2741−2744.
(49) Sano, T.; Toda, J.; Saitoh, T. Synthesis of 2-Aroylmethylquinolin-4-ones via the Addition Reaction of ortho-Nitrobenzoylketene to 1-Aryl-1-trimethylsilyloxyethylenes. *Heterocycles* **1997**, *45* (10), 1937.
(50) Lund, H.; Feoktistov, L. G.; Nielsen, P. H. Electroorganic Preparations. XXVIII. Preparation of Some Heteroaromatic N-Oxides by Ring Closure. *Acta Chem. Scand.* **1969**, *23*, 3482−3492.
(51) Hazard, R.; Jubault, M.; Mouats, C.; Tallec, A. Electrochemical synthesis of quinoline derivatives—III. Electroreduction of difunctionalized o-nitrobenzoyl compounds. *Electrochim. Acta* **1988**, *33* (10), 1335−1341.
(52) Wirtanen, T.; Prenzel, T.; Tessonnier, J.-P.; Waldvogel, S. R. Cathodic Corrosion of Metal Electrodes-How to Prevent It in Electroorganic Synthesis. *Chem. Rev.* **2021**, *121* (17), 10241−10270.
(53) Gütz, C.; Klöckner, B.; Waldvogel, S. R. Electrochemical Screening for Electroorganic Synthesis. *Org. Process Res. Dev.* **2016**, *20* (1), 26−32.
(54) Heard, D. M.; Lennox, A. J. J. Electrode Materials in Modern Organic Electrochemistry. *Angew. Chem., Int. Ed.* **2020**, *59* (43), 18866−18884.
(55) Beil, S. B.; Pollok, D.; Waldvogel, S. R. Reproducibility in Electroorganic Synthesis-Myths and Misunderstandings. *Angew. Chem., Int. Ed.* **2021**, *60* (27), 14750−14759.
(56) Devi, S.; Jyoti; Kiran; Wadhwa, D.; Sindhu, J. Electro-organic synthesis: an environmentally benign alternative for heterocycle synthesis. *Org. Biomol. Chem.* **2022**, *20* (26), 5163−5229.
(57) Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem., Int. Ed.* **2018**, *57* (21), 6018−6041.
(58) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R. Electrifying Organic Synthesis. *Angew. Chem., Int. Ed.* **2018**, *57* (20), 5594−5619.
(59) Waldvogel, S. R.; Janza, B. Renaissance of electrosynthetic methods for the construction of complex molecules. *Angew. Chem., Int. Ed.* **2014**, *53* (28), 7122−7123.
(60) Pollok, D.; Waldvogel, S. R. Electro-organic synthesis - a 21st century technique. *Chem. Sci.* **2020**, *11* (46), 12386−12400.
(61) Seidler, J.; Strugatchi, J.; Gärtner, T.; Waldvogel, S. R. Does electrifying organic synthesis pay off? The energy efficiency of electro-organic conversions. *MRS Energy & Sustainability* **2020**, *7* (1), 42.
(62) Meyer, T. H.; Choi, I.; Tian, C.; Ackermann, L. Powering the Future: How Can Electrochemistry Make a Difference in Organic Synthesis? *Chem.* **2020**, *6* (10), 2484−2496.
(63) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117* (21), 13230−13319.
(64) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chem.* **2010**, *26* (12), 2099.
(65) Kärkäs, M. D. Electrochemical strategies for C-H functionalization and C-N bond formation. *Chem. Soc. Rev.* **2018**, *47* (15), 5786−5865.
(66) Little, R. D.; Moeller, K. D. Introduction: Electrochemistry: Technology, Synthesis, Energy, and Materials. *Chem. Rev.* **2018**, *118* (9), 4483−4484.
(67) Röckl, J. L.; Pollok, D.; Franke, R.; Waldvogel, S. R. A Decade of Electrochemical Dehydrogenative C C-Coupling of Aryls. Acc. *Chem. Res.* **2020**, *53* (1), 45−61.
(68) Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. Electrochemical Arylation Reaction. *Chem. Rev.* **2018**, *118* (14), 6706−6765.
(69) Koleda, O.; Prenzel, T.; Winter, J.; Hirohata, T.; Jesús Gálvez-Vázquez, M. de; Schollmeyer, D.; Inagi, S.; Suna, E.; Waldvogel, S. R. Simple and scalable electrosynthesis of 1H-1-hydroxy-quinazolin-4-ones. *Chem. Sci.* **2023**, *14* (10), 2669−2675.
(70) Rodrigo, E.; Baunis, H.; Suna, E.; Waldvogel, S. R. Simple and scalable electrochemical synthesis of 2,1-benzisoxazoles and quinoline N-oxides. *Chem. Commun.* **2019**, *55* (81), 12255−12258.
(71) Rodrigo, E.; Waldvogel, S. R. A very simple one-pot electrosynthesis of nitrones starting from nitro and aldehyde components. *Green Chem.* **2018**, *20* (9), 2013−2017.
(72) Gombos, L. G.; Nikl, J.; Waldvogel, S. R. Dual Roles of Supporting Electrolytes in Organic Electrosynthesis. *ChemElectroChem* **2024**, *11* (8), No. e202300730.
(73) Winter, J.; Prenzel, T.; Wirtanen, T.; de Jesús Gálvez-Vázquez, M.; Hofman, K.; Schollmeyer, D.; Waldvogel, S. R. Highly selective scalable electrosynthesis of 4-hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxides. *Cell Rep. Phys. Sci.* **2024**, *5* (5), No. 101927.
(74) Einaga, Y. Boron-Doped Diamond Electrodes: Fundamentals for Electrochemical Applications. *Acc. Chem. Res.* **2022**, *55* (24), 3605−3615.
(75) Waldvogel, S. R.; Mentizi, S.; Kirste, A. Boron-doped diamond electrodes for electroorganic chemistry. *Top. Curr. Chem.* **2011**, *320*, 1−31.
(76) Lips, S.; Waldvogel, S. R. Use of Boron-Doped Diamond Electrodes in Electro-Organic Synthesis. *ChemElectroChem.* **2019**, *6* (6), 1649−1660.
(77) Dörr, M.; Hielscher, M. M.; Proppe, J.; Waldvogel, S. R. Electrosynthetic Screening and Modern Optimization Strategies for Electrosynthesis of Highly Value-added Products. *ChemElectroChem.* **2021**, *8* (14), 2621−2629.
(78) Klein, M.; Waldvogel, S. R. Counter Electrode Reactions-Important Stumbling Blocks on the Way to a Working Electro-organic Synthesis. *Angew. Chem., Int. Ed.* **2022**, *61* (47), No. e202204140.
(79) Gütz, C.; Grimaudo, V.; Holtkamp, M.; Hartmer, M.; Werra, J.; Frensemeier, L.; Kehl, A.; Karst, U.; Broekmann, P.; Waldvogel, S. R. Leaded Bronze: An Innovative Lead Substitute for Cathodic Electrosynthesis. *ChemElectroChem.* **2018**, *5* (2), 247−252.
(80) McKiernan, P. J. Nitisinone in the treatment of hereditary tyrosinaemia type 1. *Drugs* **2006**, *66* (6), 743−750.
(81) Harikishore, A.; Mathiyazakan, V.; Pethe, K.; Grüber, G. Novel targets and inhibitors of the Mycobacterium tuberculosis cytochrome bd oxidase to foster anti-tuberculosis drug discovery. *Expert Opin. Drug Discovery* **2023**, *18* (8), 917−927.
(82) Zhou, Y.; Shao, M.; Wang, W.; Cheung, C.-Y.; Wu, Y.; Yu, H.; Hu, X.; Cook, G. M.; Gong, H.; Lu, X. Discovery of 1-hydroxy-2-methylquinolin-4(1H)-one derivatives as new cytochrome bd oxidase inhibitors for tuberculosis therapy. *Eur. J. Med. Chem.* **2023**, *245* (1), No. 114896.
(83) Saha, P.; Das, S.; Indurthi, H. K.; Kumar, R.; Roy, A.; Kalia, N. P.; Sharma, D. K. Cytochrome bd oxidase: an emerging anti-tubercular drug target. *RSC Med. Chem.* **2024**, *15* (3), 769−787.
(84) Hammerich, O. *Reduction of Nitro Compounds and Related Substrates. In Organic Electrochemistry*, 5th ed.; Hammerich, O.; Speiser, B., Eds.; CRC Press, 2015; pp 1149−1200.

https://doi.org/10.1021/acs.oprd.4c00337
Org. Process Res. Dev. 2024, 28, 3922−3928