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Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline *N*-oxides by Cathodic Reduction of Nitro Arenes

Johannes Winter,[a] Tobias Prenzel,[a] Tom Wirtanen,[a] Dieter Schollmeyer,[a] and Siegfried R. Waldvogel*[a, b]

Abstract: The use of electric current in synthetic organic chemistry offers a sustainable tool for the selective reductive synthesis of quinoline *N*-oxides starting from easily accessible nitro compounds. The reported method employs mild and reagent-free conditions, a simple undivided cell, and constant current electrolysis set-up which provides conversion with a high atom economy. The synthesis of 30 differently substituted quinoline *N*-oxides was successfully performed in up to 90% yield. Using CV studies, the mechanism of the selective formation of the quinoline *N*-oxides was elucidated. The technical relevance of the described reaction could be shown in a 50-fold scale-up reaction.

Introduction

Nitrogen- and oxygen-containing heterocyclic compounds are prevalent in nature and modern organic synthesis.[1] Quinoline *N*-oxides should be emphasized because of their unique chemical features of the N–O motif. They can be used as intermediates in organic synthesis for C2 functionalization of quinoline[2] or as ligands in asymmetric synthesis, like 3,3-dimethyl-2,2′-biquinoline *N,N′*-dioxides (**1**) (Figure 1, left).[3] In addition, 8-alkylated quinoline *N*-oxides (**2**) (Figure 1, center) have been applied as mild oxidizers in the formation of α-oxo gold carbenes which are used as safer surrogates for α-diazo carbonyl compounds.[4]

The structural motif of quinoline *N*-oxides is found in biomolecules such as Aurachin A (**3**) (Figure 1, right), an antimicrobial agent found in *Stigmatella aurantiaca*, a member of an emerging class of new antibiotics found in nature.[5] Novel antibiotics are needed to combat a growing number of drug-resistant bacteria.[6] Substances containing an N–O motif could potentially be a class of novel drugs.[7] The conventional synthesis of quinoline *N*-oxides can be approached by

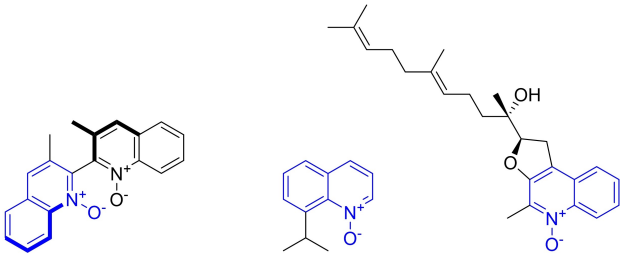

Figure 1. Ligand **1**, oxidizer **2**, and a biologically active quinoline *N*-oxide **3** bearing quinoline *N*-oxide motif.

Friedländer's quinoline synthesis starting from the corresponding 2-aminobenzaldehydes followed by their subsequent oxidation resulting in the desired quinoline *N*-oxide.[8] However, this process requires stoichiometric quantities of oxidizing agents, harsh reaction conditions, and generates large amounts of waste. A modern, biochemical approach involves bakers' yeast in the direct transformation of 2-nitrocinnamaldehydes under alkaline conditions to their respective quinoline *N*-oxides.[9] Despite the simple set-up, this reaction was only performed on a narrow scope with a low selectivity for the desired quinoline *N*-oxide. A direct metal-free approach by cyclization utilizes carcinogenic and highly toxic hydrazine under basic reaction conditions and therefore, does not represent a suitable alternative (Scheme 1).[10]

A potent tool in the preparation of various nitrogen-containing heterocycles is electro-organic synthesis.[11] The application of electric current as an inexpensive and traceless activator replaces the stoichiometric quantities of hazardous reagents.[12] Therefore, the amount of waste generated can be tremendously decreased and harmful reagents can be avoided.[13] For these reasons organic electrochemistry can be considered a green and modern synthetic tool.[14] Initial investigations into the electrochemical synthesis of quinoline *N*-oxides were conducted by *Lund* and *Feoktistov* in polarographic

[a] *J. Winter, T. Prenzel, Dr. T. Wirtanen, Dr. D. Schollmeyer, Prof. Dr. S. R. Waldvogel*
Department of Chemistry
Johannes Gutenberg University Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: waldvogel@uni-mainz.de

[b] *Prof. Dr. S. R. Waldvogel*
Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS-FMS)
Hermann-von-Helmholtz-Platz 1
76344 Eggenstein-Leopoldshafen (Germany)

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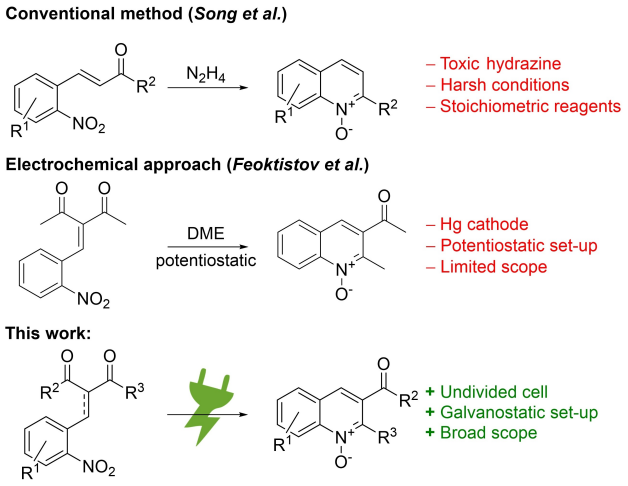


Scheme 1. Conventional and electrochemical approaches to quinoline *N*-oxides.

studies and gave the desired *N*-oxide. However, toxic mercury electrodes were applied in a sophisticated potentiostatic reaction set-up which only provided three derivatives on a very small scale.[15] The method described herein allows for the synthesis of a broad scope of quinoline *N*-oxides in high yields using a simple constant current set-up.

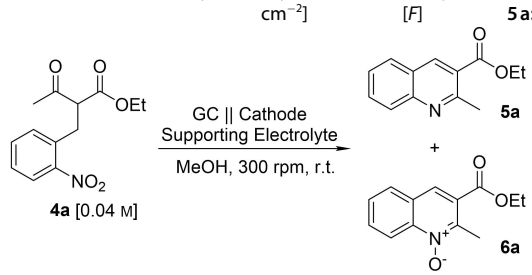
Results and Discussion

Nitro group containing compounds are easily accessible and inexpensive to obtain.[16] Based on previously reported results by the *Waldvogel* group the reduction of nitro groups provides a powerful tool for the direct synthesis of nitrogen containing heterocycles.[17] The direct electrochemical synthesis of N-heterocycles was demonstrated on different motifs in the past.[18] The retrosynthetic analysis of the quinoline *N*-oxide scaffold created the idea of partial reduction of the nitro group followed by a condensation reaction, resulting in the desired *N*-oxide motif. Initially, compound **4a** was chosen as a test substrate, which was easily synthesized in a single step by alkylation of the readily available ethyl acetoacetate with 2-nitrobenzyl bromide.[19] Based on conventional chemical considerations, sulfuric acid was chosen as an additive to promote cyclization after the reduction of the nitro group. The remaining electrolytic conditions were based on previously reported reductive reactions.[17,20] The screening of the electrosynthetic reaction was focused on all relevant parameters.[21–23] The yield of products **5a** and **6a** as well as the conversion of the substrate **4a** was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. Under the initially chosen electrolytic conditions (Table 1, Entry 1) quinoline **5a** was formed as the major product in 69% yield and only 19% of the quinoline *N*-oxide **6a** was observed. The molecular structure of **6a** was confirmed by X-ray analysis (CCDC: 2207689).

From these preliminary results, variation of different reaction parameters was conducted to further improve the selectivity of the reaction towards quinoline *N*-oxide **6a** and to increase its yield. Detailed information of each experiment is provided in the Supporting Information. To suppress a possible re-oxidation of the product a divided set-up was compared to the initially used undivided set-up (Table 1, Entry 2). The yield and selectivity decreased significantly in a divided cell, thus highlighting the importance of the counter reaction.[23]

Based on this, further experiments were carried out in undivided 5 mL Teflon® cells. As the supporting electrolyte can greatly influence the overall reaction, different electrolyte systems were tested.[22] A variation of the concentrations of sulfuric acid showed no improvement of selectivity, higher concentrations of sulfuric acid proved detrimental resulting in decomposition of the starting material (Supporting Information, Table S3). The selectivity was improved by using an acetate buffer (Table 1, Entry 3), suggesting weak acids were superior for the formation of the desired quinoline *N*-oxide **6a**. By using

Table 1. Initial screening of reaction conditions using dihydrocinnamate **4a**.



Entry	Cathode	Supporting electrolyte	Current Density [mA cm^{-2}]	Applied charge [*F*]	Yield[a] [%] **5a:6a**
1[b]	BDD	0.5 M H_2SO_4	4.1	6	69:19
2[c]	BDD	0.5 M H_2SO_4	4.1	6	24:3
3[b]	BDD	5 M AcOH 0.45 M NaOAc	4.1	6	4:20
4[b]	BDD	5 M HCOOH 0.27 M NaHCOO	4.1	6	3:27
5[b]	**Pb**	**5 M HCOOH 0.27 M NaHCOO**	**4.1**	**5**	**0:38**
6[b]	CuSn7Pb15	5 M HCOOH 0.27 M NaHCOO	4.1	5	0:14
7[b]	Pb	5 M HCOOH 0.27 M NaHCOO	2.4	5	0:35
8[b]	Pb	5 M HCOOH 0.27 M NaHCOO	4.1	4	0:37

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Undivided 5 mL Teflon® cell; [c] Divided reaction set up, separator: glass frit; GC = glassy carbon, BDD = boron doped diamond.

a formate buffer as supporting electrolyte (Table 1, Entry 4) the yield of **6a** was increased to 27%.

By applying lead as cathode material, which showed excellent results in previous studies for selective deoxygenation and has a high overpotential for hydrogen evolution, the yield increased up to 38% (Table 1, Entry 5).[24] Leaded bronze as a novel cathode material and a substitute for lead decreased the yield significantly (Table 1, Entry 6), which is why lead was used as cathode material in future experiments.[25] To reduce possible degradation of both the starting material and the product a lower current density was investigated (Table 1, Entry 7). Since no significant change in yield was observed this suggests the current density has a marginal influence on the overall reaction. As a total amount of applied charge of 4 *F* (Table 1, Entry 8) resulted in 92% conversion of the starting material, 5 *F* were used in further experiments resulting in 100% conversion of **4a**.

Considering the keto-enol tautomerism of the test substrate **4a** may have a significant influence on the overall reaction, a cinnamate test substrate **8a** was compared to the previously obtained results. Theoretically, a 1,3-diketo compound is more reactive compared to a β-ketoester as the opportunity for condensation is doubled with 2 keto groups.

The cinnamyl methyl ketone **8a** as conjugated test substrate was obtained by *Knoevenagel* condensation of 2-nitro benzaldehyde with acetylacetone.[26] By utilizing the previously optimized reaction conditions the corresponding quinoline *N*-oxide **10a** was obtained in 80% yield (Table 2, Entry 3) revealing a significant influence of the keto-enol tautomerism and the more reactive 1,3-diketo substitution pattern of substrate **8a**. BDD as cathode material did not seem to be beneficial in neither the optimized formate buffer as electrolyte nor the sulfuric acid (Table 2, Entries 1 and 2). Finally, other carbon-based cathode materials were tested, resulting in a remarkable decrease in both yield and selectivity (Table 2, Entries 4 and 5). For scientific control, no electric current was applied, resulting in no conversion of the starting material **8a**.

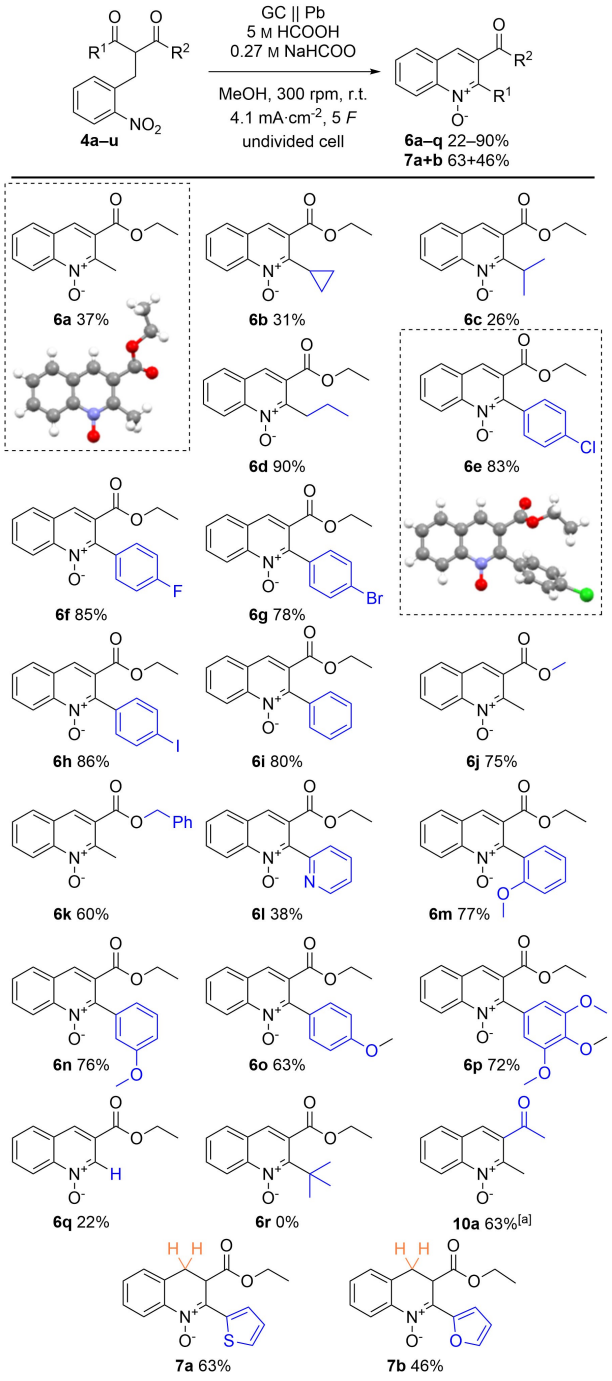
After optimizing the reaction conditions the scope of the reaction was explored. Initially the scope of different 2-nitrobenzyl β-ketoesters was investigated (Scheme 2). Variation of the aliphatic substituent at position 2 revealed the effect of increasing steric demand of the substituent. Comparing **6b** to

Table 2. Screening of reaction conditions using cinnamyl ketone **8a**.

Entry	Cathode	Supporting electrolyte	Applied charge [*F*]	Yield[a] [%] **9a**:**10a**
1	BDD	0.5 M H_2SO_4	6	1:11
2	BDD	5 M HCOOH 0.27 M NaHCOO	5	5:49
3	Pb	5 M HCOOH 0.27 M NaHCOO	5	0:80(77[b])
4	GC	5 M HCOOH 0.27 M NaHCOO	5	19:38
5	RVC	5 M HCOOH 0.27 M NaHCOO	5	1:67
6[c]	Pb	5 M HCOOH 0.27 M NaHCOO	5	0:0

8a [0.04 M] → GC || Cathode, Supporting Electrolyte, MeOH, 300 rpm, r.t., 4.1 mA·cm^{-2} → **9a** + **10a**

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] isolated yield; [c] No electricity was applied; GC = glassy carbon, BDD = boron doped diamond; RVC = reticulated vitreous carbon.



Scheme 2. Reaction scope of the 2-nitrobenzyl β ketoesters **4a–u**. [a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

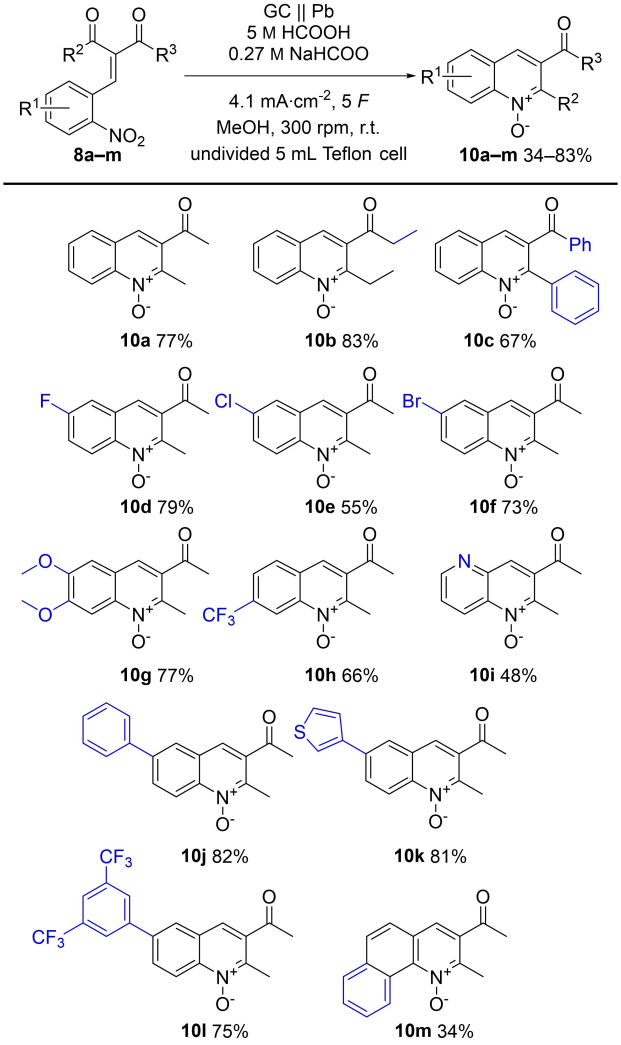
6c, a higher degree of freedom results in a lower yield of 26% for **6c** compared to 31% of **6b**. Following this trend, the *tert*-butyl derivative **6r** could not be isolated due to the complete reduction of the corresponding substrate to its aniline analogue, confirmed by LC–MS. In this case, the hydroxylamine intermediate was further reduced without cyclisation by condensation with the carbonyl group. Interestingly the *n*-butyl derivative **6d** was isolated in excellent yield of 90%. The *p*-halo aryl substituted quinoline *N*-oxides **6e**–**6h** were isolated in up to 86% yield. The high yield of the iodo derivative **6h** is particularly interesting as dehalogenation was suppressed in this electrochemical protocol, which occurred as side reaction in previous studies.[27] These halo derivatives **6e**–**6h** allow for further functionalization, unlocking a variety of novel scaffolds. The molecular structure of the *p*-chlorophenyl substituted derivative **6e** was confirmed by X-ray analysis (CCDC: 2207689). The phenyl substituted derivative **6i** could also be obtained in 80% yield, suggesting that phenyl substrates undergo the cyclization more easily based on the more reactive keto function resulting in better yields. Next, different carboxylic esters were tested. The methyl ester **6j** was obtained in good yield up to 75%. The benzyl ester gave 60% of the desired product **6k**. Next heterocyclic substituents were investigated and **6l** was obtained with 38% yield showing tolerance of additional nitrogen heterocycles which might be oxidized as side reaction.

The electron-rich aryl-substituted derivatives **6m**–**6p** were obtained in up to 77% yield. The non-substituted quinoline *N*-oxide in position 2 **6q** was isolated in 22% yield and opens up the possibility of further modifications in 2-position.

Substrate **4t** and **4u** formed compounds **7a** and **7b** in moderate yields of 63% and 46%, and did not result in the expected quinoline *N*-oxide by missing out the final oxidation revealing interesting insights in the mechanistic considerations.

The β-diketone **4s** gave a 63% yield by ^{1}H NMR of the desired quinoline *N*-oxide **10a** revealing the beneficial effect of the additional, more reactive keto function towards the cyclization compared to test substrate **4a**. Compared to the electroreduction of the cinnamyl methyl ketone **8a** with 77% yield, the effect of conjugation dominated.

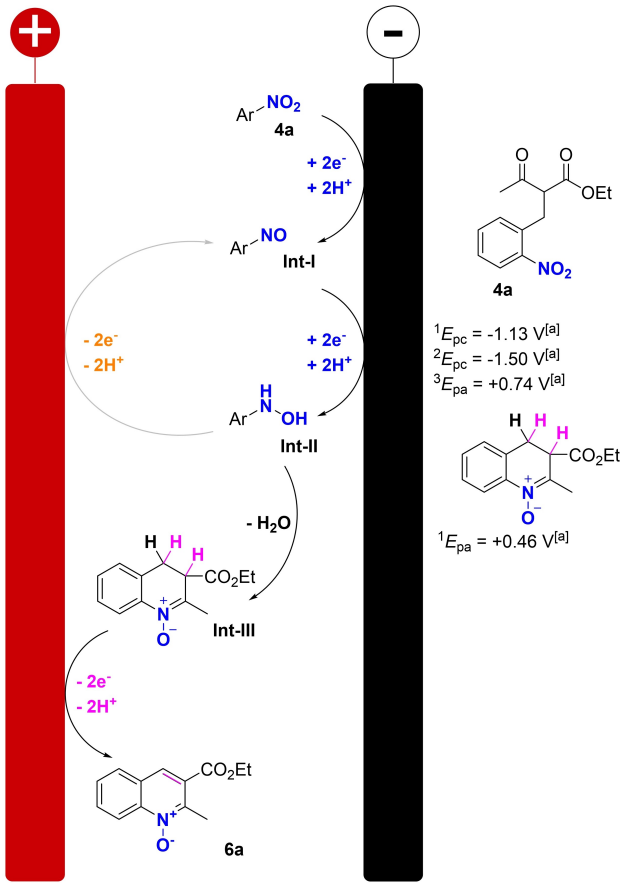
The optimized reaction conditions were then applied to the 2-nitro cinnamyl ketones **8a**–**m** (Scheme 3). Initially, the substituent at positions 2 and 3 were varied. **10b** was isolated in very good yield of 83%. Derivative **10c** gave only 67% yield, possibly due to the high steric demand of both aryl groups. Next, the nitro benzylidene core of each substrate was modified. The halo substituted derivatives **10d**–**10f** were obtained in good yields of up to 79%, enabling further functionalization of the corresponding quinoline *N*-oxides. The trifluoromethyl group, which is considered as important functional group in medicinal chemistry, was tolerated to a moderate yield of 66% of **10h**.[28] The electron deficient derivative **10i** was selectively formed in 48% yield suggesting no secondary oxidation of the additional nitrogen atom occurred as previously observed by substrate **4l**. The electron-rich derivative **10g** was obtained in 77% yield. Substrate **8j** was converted to the resulting quinoline *N*-oxide **10j** in 82% yield



Scheme 3. Reaction scope of 2-nitro cinnamyl ketones and analogues **8a**–**m**.

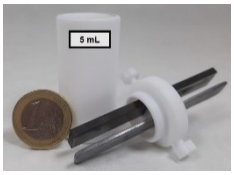
bearing an additional phenyl substituent. The heterocycle containing derivative **10k** was isolated in 81% yield indicating a good tolerance for electron-rich heterocyclic substituents. The electron deficient derivative **10l** could also be obtained in 75% yield. Transformation of substrate **8m** gave the corresponding quinoline *N*-oxide **10m** in 34% yield enabling access to polycyclic aromatic quinoline *N*-oxide derivatives.

Following the investigation of the scope of this electrochemical protocol and based on results of earlier work on the reduction of nitro groups, mechanistic studies were conducted by cyclic voltammetry measurements (Scheme 4).[27] Test substrates **4a** and **8a**, as well as the substrate of the 3,4 dihydroquinoline *N*-oxide **4m**, and the quinoline *N*-oxide **6a** were investigated (for detailed information see Supporting Information: Figures S3–S7). Anodic corrosion of lead in the electrolyte containing formic acid results in the passivation of the electrode surface.[29] Therefore, glassy carbon was used as working electrode in CV studies. By recording substrate **4a** two broad reductive and two oxidative waves were observed, suggesting the mechanistic considerations shown in Scheme 4.



Scheme 4. Proposed mechanism of the electrochemical formation of quinoline *N*-oxides; [a] vs. FcH/FcH^+.

Table 3. Scale-up of the syntheses of **10a** from screening to multigram scale.[b]

Cell	*n*(Substrate) [mmol]	Yield[a] of **10a** [g]
	0.2	0.031 (77%)
	5	0.804 (80%)
	15	2.726 (91%)
	50	8.081 (80%)

[a] Isolated yield; [b] Anode: glassy carbon, cathode: lead, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol; $j = 4.1$ mA cm^{-2}, 5 *F*, 300 rpm, r.t., undivided batch-type cells.

The first wave at −1.13 V corresponds to the reduction of the substrate **4a** to the nitroso intermediate **Int-I** by addition of $2e^-/2H^+$, followed by the subsequent reduction at −1.50 V to hydroxylamine **Int-II** by addition of $2e^-/2H^+$.[27] After condensation of the hydroxylamine **Int-II** resulting in the 1-oxy-3,4-dihydroquinoline **Int-III** the final oxidation at +0.46 V by the loss of $2e^-/2H^+$ was observed resulting in the final quinoline *N*-oxide **6a** matching the suggested mechanistic considerations. A second oxidative wave at +0.74 V relates to the reoxidation of the hydroxylamine **Int-II** to the corresponding nitroso intermediate **Int-I** by the loss of $2e^-/2H^+$. In contrast, the substrate **8a** lacks the characteristic oxidative wave at +0.46 V which corresponds to the final oxidation of the 1-hydroxy-1,4-dihydroquinoline in agreement with the proposed mechanism. Interestingly, this oxidation was not observed in the measurement of substrate **4m** matching the isolated 3,4-dihydroquinoline *N*-oxide products **7a** and **7b**. When measuring **6a** a weak reductive wave at −0.83 V was detected matching the decreased selectivity forming **5a** by subsequent reduction of **6a**.

The scale-up of the reaction was performed on test substrate **8a** (Table 3). Quinoline *N*-oxide **10a** was isolated in very good yields of up to 80% in a multi-gram scale set-up with a simple work-up procedure by filtration through silica which shows the high potential of the applied reaction conditions for technical purposes.

ICP-OES measurements revealed 0.86 ppm of lead in the crude product and 0.15 ppm in the final product which highlights the safe use of this method. The measured lead content in the electrolyte of 20 ppm is most likely due to the dissolution of the natural lead oxide layer of the electrode upon immersion

into the electrolyte and could be completely removed by the work-up procedure (Table 4).

Conclusion

In summary, the reported method provides a simple tool for the preparation of quinoline *N*-oxides by an electro-organic synthesis, with inexpensive reactants and a broad variety of tolerated functional groups. The optimized reaction conditions utilize a simple undivided reaction set up with inexpensive and easily accessible electrode materials. In addition, a sustainable buffer system was applied as supporting electrolyte keeping the cathode stable. The broad scope of the reaction was demonstrated by 30 examples in yields up to 90%. The diversity of the different substrates reveals the high robustness of the reaction conditions and allows for further functionalization of the different products. The technical relevance of the electrolysis conditions was shown on a multi-gram scale of the reaction. Mechanistic studies utilizing CV measurements revealed the selective reduction of the nitro group to the corresponding hydroxylamine, leading to the selective formation of the desired quinoline *N*-oxides.

Experimental Section

General protocol for the electrochemical synthesis of quinoline *N*-oxides: The electrolyte was prepared by dissolving 0.50 mol formic acid and 0.027 mol sodium formate in 100 mL methanol. The corresponding substrate was dissolved in 5 mL of the electrolyte in a 5 mL undivided Teflon® screening cell equipped with a stirring bar. The electrolysis was performed under constant current conditions (current density of 4.1 mA cm^{-2} for 96.5 C (5 *F*)). After 24 h the reaction mixture was dissolved in dichloromethane and washed once with saturated Na_2CO_3 solution (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3× 10 mL), the combined organic fractions were washed once with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and 0.1 mmol 1,3,5-trimethoxybenzene was added as internal standard for quantification by ^{1}H NMR. Purification was performed using reversed phase flash column chromatography using acetonitrile and water (0.1% v/v formic acid) as eluents.

General protocol for the scale-up of electrochemical synthesis of 10a: The corresponding substrate was dissolved in the electrolyte (5 M formic acid/0.27 M sodium formate in methanol) in the different undivided batch-type cells (50 mL, 100 mL and 250 mL) equipped with a stirring bar. The electrolysis was performed under constant current conditions (current density of 4.1 mA×cm^{-2}, charge applied: 5 *F*). After completion of the electrolysis the reaction mixture was dissolved in dichloromethane and washed once with saturated Na_2CO_3 solution (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed once with brine (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification was performed by filtration through silica using cyclohexane:ethyl acetate 2:1 (v:v) to remove impurities. The product was eluted with ethyl acetate:methanol 95:5 (v:v) and obtained by removing the solvent under reduced pressure.

Deposition Number(s) 2207689 (for 6a), 2207689 (for 6e) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Table 4. ICP-OES measurements of the scale-up electrolysis.

Sample	Work-Up	Pb-contamination
Electrolyte	None	18 ppm
Crude Product	Extraction	0.86 ppm
Product	Filtration through Silica	0.15 ppm

Supporting Information

The Supporting Information (PDF) including detailed optimization studies, experimental procedures, mechanistic studies, crystallographic data and copies of NMR spectra is available in the Supporting materials of this article.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cyclization · electro-organic synthesis · nitrogen heterocycles · *N*-oxides · reduction

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