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Research Article

Biphasic Electrosynthesis of 2-Isoxazol(in)e-3-carboxylates: Reaction Optimization from Milligram to Hectogram Scale

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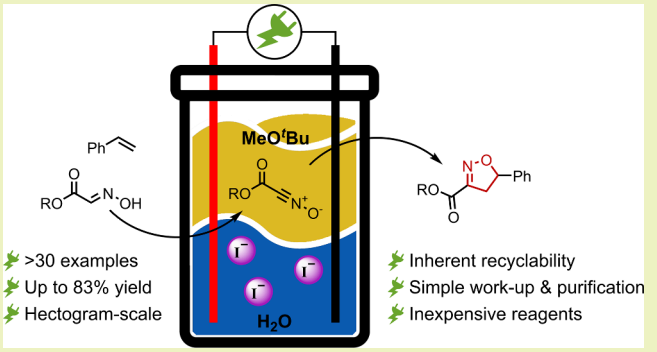
ABSTRACT: An electrochemical synthesis of isoxazol(in)e-3-carboxylates in a biphasic system allowing the direct access to technically relevant motifs in good yields has been established. The versatility of this protocol was demonstrated by >30 highly functionalized and diverse examples. Furthermore, a derivative of isoxadifen-ethyl was synthesized in a more sustainable approach, avoiding hazardous reagents and the generation of large amounts of waste. A nitrile oxide as the key intermediate is formed without addition of strong bases or oxidizers and directly undergoes the desired cycloaddition. The technical relevance of the established method was underlined by hectogram-scale synthesis while purifying the crude product by simple silica filtration. By simple distillation, nonconverted styrene was largely recovered, demonstrating the sustainability of this method.

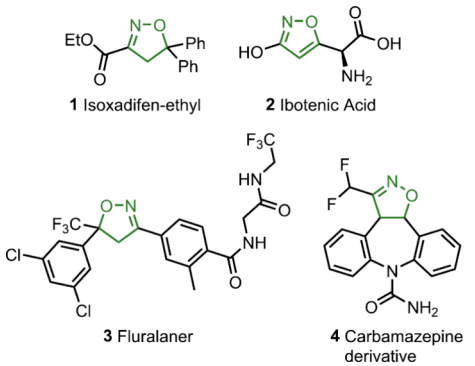


KEYWORDS: *electrosynthesis, dipolar cycloaddition, iodide-mediated, herbicide, scale-up*

1. INTRODUCTION

Isoxazol(in)es represent important structural motifs among biologically potent substances. They are found in various natural compounds, pharmaceuticals, and agrochemicals.[1] Isoxadifen-ethyl (Scheme 1, **1**), for example, is widely used as an herbicide safener to protect crops against several herbicides and thus enhances the efficiency of the treatment.[2−4] Furthermore, ibotenic acid (**2**) and fluralaner (**3**) represent pharmaceutically active isoxazol(in)es. Ibotenic acid (**2**) is a well-known, naturally occurring isoxazole with psychoactive properties found in *Amanita muscaria* (fly agaric).[5,6] Fluralaner (**3**) is a potent commercial antiparasitic drug for the therapy of cats and dogs infested with flea or ticks.[7] In addition, **4** is an isoxazoline derived from the anticonvulsant carbamazepine, demonstrating the application of dipolar cycloadditions in the late-stage functionalization of pharmaceuticals.[8,9]

Scheme 1. Biologically Active Isoxazolines Found as Naturally Occurring Products, Herbicide Safeners, or Pharmaceuticals



Common synthetic routes for accessing isoxazolines and isoxazoles involve the in situ formation of highly reactive nitrile oxides from *N*-hydroximidoyl halides followed by their 1,3-dipolar cycloaddition.[10,11] The major drawback of this synthetic protocol is the necessity for equimolar amounts of oxidants, large quantities of hazardous halogenating agents, and harsh reaction conditions.

While facing the climate crisis, the demand for more sustainable processes and synthetic protocols represents a main challenge for the modern organic chemist.[12−16] Electrochemistry as a synthetic tool can fulfill many points of green chemistry.[17−23] Electrical current as an inherently safe

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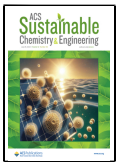
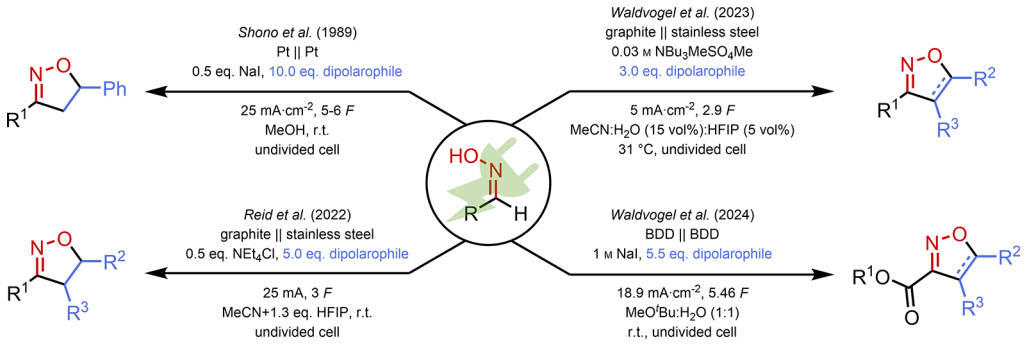
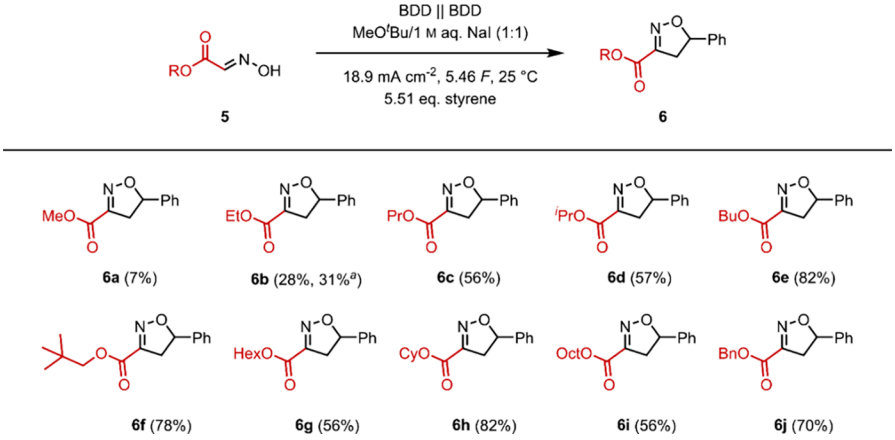


Scheme 2. Electrochemical Access to Isoxazolines and Isoxazoles



Scheme 3. Variation of the Ester Chain for the Electrochemical Synthesis of Isoxazolines[a]



[a]Isolated yields, 3.44 mmol scale. Superscript *a* in scheme: 4.27 mmol, 4.41 equiv of styrene, graphite||graphite, EtOAc/1 M aq. NaI (1:4), 18 mA cm^{-2}, 4.14 *F*, 25 °C.

surrogate for equimolar quantities of oxidants and recyclable solvents can be employed, avoiding large amounts of waste.[24−27] Additionally, the downstream processing of chemical reactions plays a crucial role, which should be considered in the design of industrial processes.[22]

The electrochemical synthesis of isoxazolines and isoxazoles is of great interest to the electro-organic community. Several methods have been reported based on halide-mediated electrochemical oxidation (Scheme 2). The earliest by Shono et al. used sodium iodide in methanol to gain access to several 3,5-disubstituted isoxazolines by trapping the intermediately formed nitrile oxide with a large excess of styrene.[28] Reid et al. presented a chloride-mediated homogeneous method.[29] The mechanism was further investigated, and the efficacy was shown on a larger scope. A mediator-free protocol was provided by Waldvogel et al. in a simple galvanostatic setup by direct anodic oxidation of several aldoximes.[30] The solvent system used in that method could be easily recycled by a simple distillation, minimizing fluorinated waste products.

Electrolysis in biphasic systems offers unique reactivity for the selective and efficient synthesis of various structural motifs like pyrazolines, oligosaccharides, and sophisticated cyclic hydrocarbons.[23,31−34] For large-scale processes, the recycling of both layers could be achieved by an easy separation and recovery and reuse of the organic solvent.

Here, we report an iodide-mediated approach for the synthesis of isoxazolines and isoxazoles in a biphasic system of methyl *tert*-butyl ether and water. Simple galvanostatic electrolytic conditions in an undivided setup and sustainable, carbon-based boron-doped diamond (BDD) electrodes[35−37] were used. Inexpensive and readily available sodium iodide as a supporting electrolyte was used, and the recyclability of styrene was demonstrated, underlining the green nature of this approach. To highlight the technical relevance of the established method, the scalability of the reaction was demonstrated by decagram- and hectogram-scale electrolysis.

2. RESULTS AND DISCUSSION

2.1. Optimization of the Electrolytic Conditions. The envisioned setup was based on methods for the electro-organic synthesis of pyrazolines and pyrazoles published by Waldvogel et al.[33,38,39] Starting from the reported conditions for the pyrazoline synthesis from glyoxylate hydrazones, a transfer on the conversion of ethyl 2-(hydroxyimino)acetate (Scheme 3, **5b**) and the reaction of the corresponding nitrile oxide with styrene was attempted. The appropriate supporting electrolyte, electrode material, and solvent were tested first (see Table S4). A biphasic system of ethyl acetate and a 1 M aqueous sodium iodide solution with isostatic graphite electrodes turned out to be the most feasible. In the following, further optimization of the amount of applied charge (Q), current density (j), and the equivalents of dipolarophile by Design of Experiment (DoE)[40−44] was performed. A 2^{3-1} fractional factorial design with a center point and rotatable axial points was chosen. The center point was acquired in triplicate. Additionally, ambient temperature and vigorous stirring turned out to be the most favorable conditions. However, the optimum conditions received from this optimization resulted only in an

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unsatisfactory yield of 31% for the corresponding isoxazoline **6b**.

Leakage of the highly polar nitrile oxide into the aqueous layer was accounted for the resulting low yields in the conversion of **5b**. Therefore, the test substrate was changed to butyl 2-(hydroxyimino)acetate (**5e**), which readily improved the yield to 51%, and the process was re-evaluated for the conversion of **5e**. Again, solvent, halide source, electrode material, and the ratio between organic and aqueous layers were tested first. This led to a 1:1 (v/v) system of methyl *tert*-butyl ether and 1 M aqueous sodium iodide with BDD as the anode and cathode. Further optimization was done in two DoE steps: first, the amount of applied charge, the current density, the equivalents of styrene, and the temperature were tested in a 2^{4-1} fractional factorial design (with a center point and rotatable axial points, every data point in triplicate). This revealed an optimal current density of 18.9 mA cm^{-2} independent from the other parameters. For *Q*, *T*, and the equivalents of styrene, the optimal settings were determined as their respective extreme settings. Thus, a second DoE included *Q*, *j*, and *T* with an adjusted range (2^{3-1} fractional factorial design with a center point and rotatable axial points, every data point in duplicate). The optimum conditions from both optimization steps were tested and revealed an optimal isolated yield of 82% at 18.9 mA cm^{-2}, 5.46 *F*, 25 °C, and 5.51 equiv of dipolarophile. Investigations on the substrate concentration finally revealed the initially chosen oxime concentration of 40 g/L (0.28 M) with respect to the organic layer as the optimum.

2.2. Scope. After optimization, the scope of the reaction was explored. First, the influence of the ester moiety was investigated. While only 7% of methyl ester **6a** could be isolated, the yield already increased to 28% (or 31% applying the conditions from the first optimization) for ethyl ester **6b**. Interestingly, propyl **6c** and *iso*-propyl ester **6d** were isolated in similar yields of 56 and 57%, respectively. The isoxazoline yield reached a maximum for butyl ester **6e** (82%), *neo*-pentyl ester **6f** (78%), and cyclohexyl ester **6h** (82%). For longer linear alkyl chains, the yield decreased again (**6g**, 56%; **6i** 56%). The observed trend very well corresponds to the log *P* values[45] of the corresponding alcohols with an optimum log *P* of ca. 1 (Figure 1). Merely the benzyl ester **6j** (70%) slightly deviates from this trend. The observed behavior indicates a well-balanced lipophilicity of the substrates **5** as a key factor for a successful conversion. A very hydrophilic oxime leads to the leakage of the oxime or the formed nitrile oxide into the aqueous layer, thus escaping the intended reaction. A very lipophilic oxime, on the other hand, does not accumulate in sufficient concentrations at the interphase where the oxidation takes place, or its surfactant-like properties may interfere with a smooth conversion.

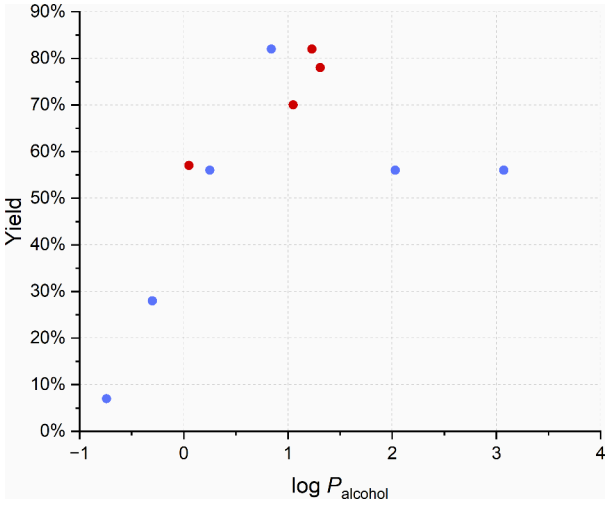

Figure 1. Correlation between the yields of isoxazolines with varying ester chains and the log *P* values[45] of the corresponding alcohols. Blue circle: linear esters; red circle: branched esters.

Second, the dipolarophile was varied (Scheme 4). A broad variety of isoxazolines bearing different functional groups was accessible in moderate to very good yields. In particular, for 5-aryl-substituted isoxazolines, appealing results were achieved (**6k**−**6z**). Among these, the 5-mesityl-substituted isoxazoline **6k** (81%) and the 5-(4-*tert*-butyl)phenyl-substituted isoxazoline **6l** (82%) gave the best results. Differently methoxylated styrenes were converted into the corresponding isoxazolines **6o**−**6q** in yields up to 63%. Furthermore, various halophenyl-substituted isoxazolines **6s**−**6y**, especially the 5-(chlorophenyl)isoxazolines **6s**−**6v**, were successfully obtained in up to 73% yield. The direct synthesis of diverse halo-substituted isoxazolines allows access to a broad variety of novel isoxazoline pesticides, as the halo substituents play a crucial role in the development of new pesticides.[46] 5,5-Disubstituted isoxazolines were accessible in moderate to good yields (**6n**, 69%; **6r**, 54%), emphasizing the influence of an increased steric demand on the cycloaddition. **6r** represents the butyl analogue of isoxadifen-ethyl, a commercial herbicide safener,[4,47] demonstrating the application potential of the established method.

Aliphatic alkenes were sufficiently tolerated. The butyl-substituted isoxazoline **6aa**, hexyl-substituted isoxazoline **6ab**, and the octyl-substituted isoxazoline **6ac** were accessed in moderate yields of 51−53% with almost no impact of the dipolarophile's periphery. Additionally, the trimethylsilyl-substituted isoxazoline **6ad** was obtained in 49% yield, allowing late-stage modifications by Hiyama cross-coupling reactions.[48] The cyclohexene-derived isoxazoline **6ae** and cyclooctene-derived isoxazoline **6af** were obtained in 51 and 73% yields, respectively. This is easily explained by the *cis*-configuration enforced by the cycloaddition reaction. For the cyclohexane ring of **6ae**, this results in a boat conformation introducing high ring strain. The cyclooctane ring of **6af**, on the other hand, can bypass this strain to a certain extent due to its higher degrees of freedom. Finally, the phthalimide-modified isoxazoline **6ag** was isolated in a good yield of 72%, enabling access to aminomethyl isoxazolines. In contrast, the Boc-protected isoxazole **6ah** was obtained in only 35% yield. The decreased yield is a result of the less reactive alkyne used as a dipolarophile.

Finally, the conversion of a nonglyoxylate-based oxime and the reaction of **5e** with phenylacetylene as dipolarophile were investigated. It was found that the herein presented method very well complements the recently described protocol[30] as it allows easy access to isoxazolines in an in-cell process. Isoxazoline **6ai** was thus obtained in an improved yield of 73% (instead of 66%, Scheme 5i). In contrast, isoxazoles were better accessible by the previously reported protocol (**6aj**/**ak**, Scheme 5ii). However, isoxazol(in)e-3-carboxylates remained scarcely available by electrochemical means. For the isoxazolines, this was readily circumvented by this new protocol.

2.3. Mechanistic Considerations. Based on the described findings and in accordance to previous reports,[28,33,39,49] the

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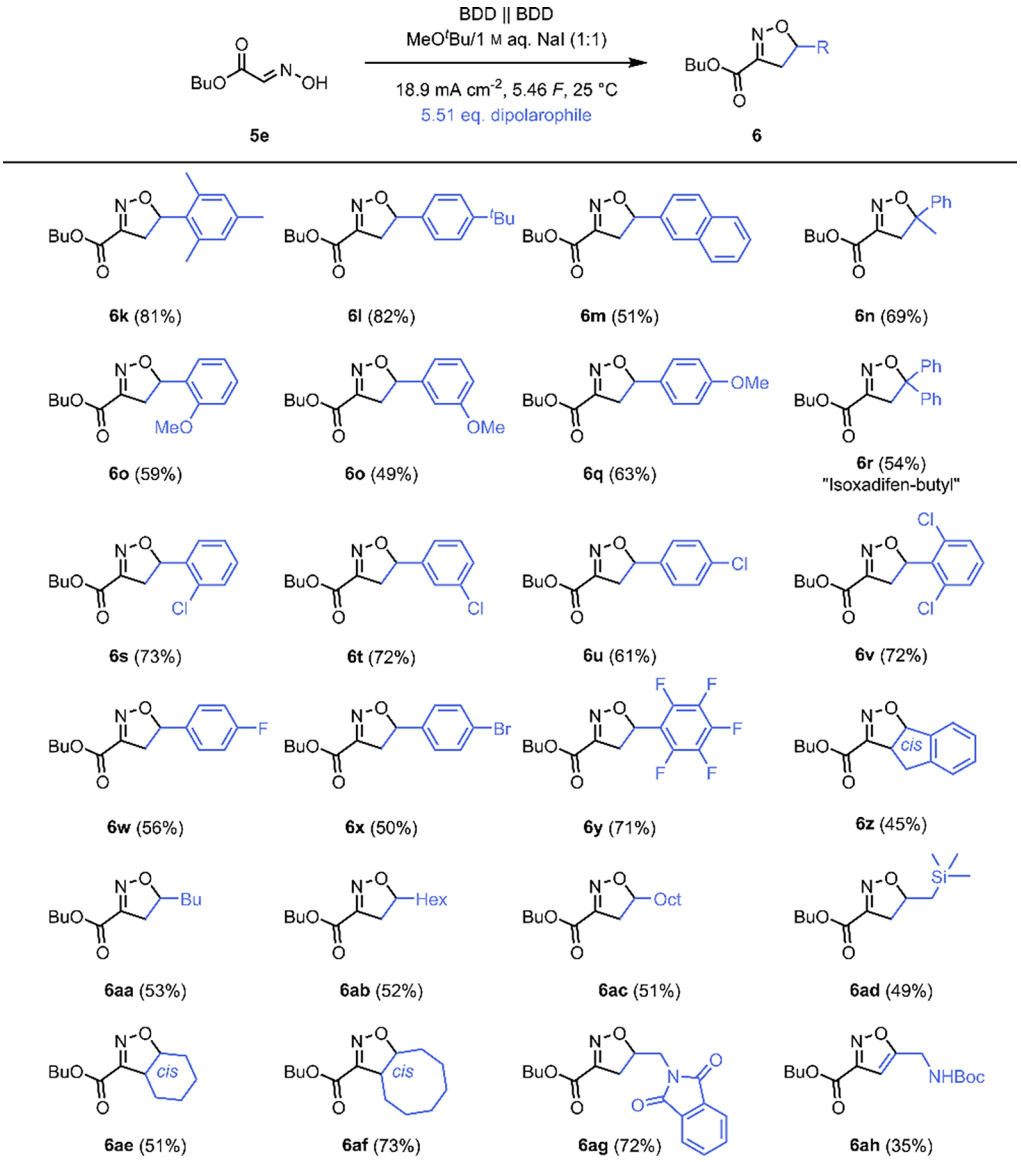
Scheme 4. Variation of the Dipolarophile in the Electrochemical Synthesis of Isoxazolines[a]



[a]Isolated yields, 3.44 mmol scale.

following mechanism is proposed (Scheme 6): Similar to the mechanism described by Shono et al.,[28] iodide is, in a first step, anodically oxidized to triiodide in the aqueous layer. At the phase boundary, oxime **5** is then oxidized by triiodide in analogy to the mechanism for the oxidation of oximes with NCS proposed by Togo and Kobayashi.[49] Upon deprotonation of the formed *N*-hydroxy-*N*-iodo iminium ion **5′** by electrogenerated hydroxide and elimination of iodide, nitrile oxide **5″** is released as the key intermediate. The latter then undergoes 1,3-dipolar cycloaddition to yield the desired isoxazol(in)e **6**.[28,49]

In general, the dipolarophile and the product **6** are less polar than the employed oxime **5** and the derived nitrile oxide **5″**. They are therefore located within the nonconductive organic layer (absence of an organo-soluble supporting electrolyte) rather than at the phase boundary. The spatial separation from the electrode reaction and the activated mediator species (triiodide) largely prevents side reactions or overoxidation. This significantly diminishes the required amount of dipolarophile compared to halide-mediated single phase systems. Moreover, a low impurity profile is achieved (see Figures S13−S15) that is advantageous for workup and further downstream processing.

2.4. Scale-up. To demonstrate the applicability of the newly developed method, scale-up to decagram and hectogram scale was envisioned. A first experiment under these conditions in a bipolar setup with 25.0 g (172 mmol) of oxime **5e**, however, revealed a severe drop in yield to only 40% **6e** (qNMR). Therefore, the reaction was reinvestigated on a 25 g scale (Table 1). This included variation of the electrode setup (polarization mode, interelectrode gap, and number of electrodes) and adjustment of the amount of applied charge. As a result, the electrolysis was performed at a sandwich setup of three alternatingly polarized BDD plates (polarization + − + , 10 mm interelectrode gap) with an amount of applied charge of 2.5 *F* (only 125% of the theoretical amount).

By distillation, 71.2 g (3.97 equiv) of styrene was recovered from the crude, indicating an overall dipolarophile con-

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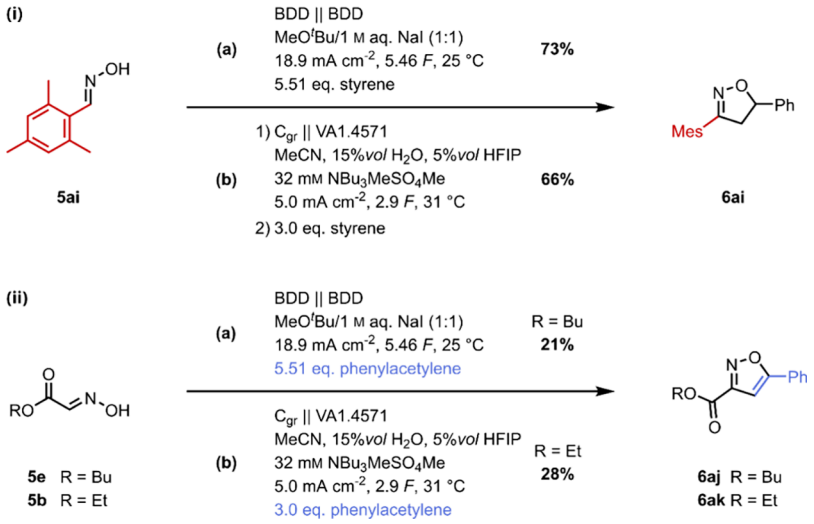
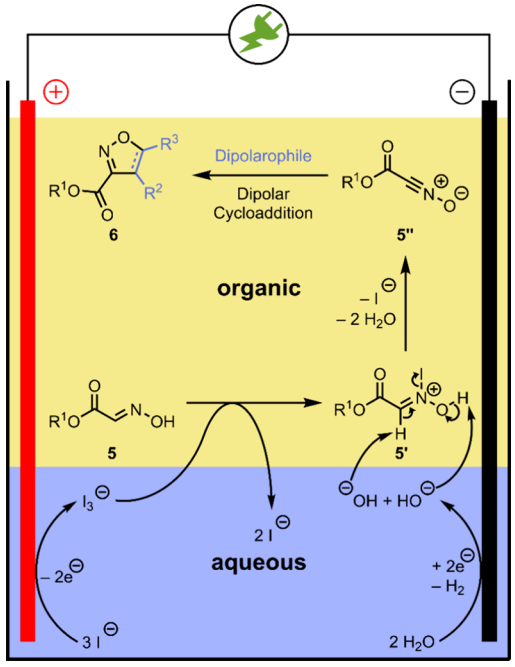
Scheme 5. Comparison between (a) the Newly Developed Method and (b) a Recently Presented[30] Electrochemical Isoxazol(in)e Synthesis for the Respective Test Substrates (i) Mesityl Aldoxime (5ai) and (ii) Alkyl 2-(Hydroxyimino)acetate 5e/b



Scheme 6. Mechanistic Proposal Based on the Observed Reactivity and Findings from Previous Publications[28,33,39,49]



sumption of only 1.54 equiv. Simple silica filtration of the distillation bottoms gave an isolated yield of 82% (35.0 g) of **6e**.

The relation between the interelectrode gap width and the decreased amount of applied charge is easily explained by the mechanism of electron transfer in the biphasic system. While the actual chemical transformation leading to the desired product occurs at the interphase and in the organic layer, the electrode reaction occurs in the aqueous layer. A small interelectrode gap may result in poor mixing in the interelectrode gap and, therefore, a small interphase area, leading to a low reaction rate for the desired conversion. This allows for electrochemical shortcutting of the cell by an iodine/iodide redox shuttle and, therefore, charge dissipation. A larger interelectrode gap facilitates better mixing in the gap and therefore diminishes the described charge dissipation. Similarly, every electrode represents an obstacle and, thus, their number may impact the fluid dynamics within the electrolyte. This in turn influences the size of the interphase area, which is crucial for a minimized charge dissipation and a high reaction rate of the desired conversion and, therefore, the yield.

In the following, the reaction was transferred to a continuously stirred batch tank reactor (CSTR). Without any further alterations, 218 g (1.50 mol) of oxime **5e** was converted, resulting in a yield of 53% (195 g, 0.789 mol) **6e** after silica filtration. On this scale, 3.20 equiv (500.5 g) of styrene could be recovered by distillation of the crude prior to the silica filtration.

It is to emphasize that the reaction was easily transferred to the hectogram scale (factor 436 compared to preparative scale) without larger variation of the conditions. On both scale-up stages, the crude product maintained a remarkably low impurity profile (see Figures S13–S15), facilitating a fast, low-effort workup and isolation. The decreased yield in the CSTR may result from a less efficient emulsification compared to the previous setup effecting the overall distribution of the two phases. Furthermore, evaporation of the organic phase was observed, resulting in an inconsistent concentration profile. As the substrate concentration was observed to influence the reaction outcome, this may very well explain the different results for the conventional batch-tank experiment (35.0 g **6e**, 82%) and the CSTR (195 g **6e**, 53%). Nevertheless, this proof-of-concept experiment showed the possibility to generate large quantities of this highly promising isoxazoline while combining well-known reactor concepts with electrolysis in biphasic reaction mixtures. Future developments will require a combination of ultramixing units between CSTR and the electrolyzer as demonstrated previously.[50,51]

3. CONCLUSIONS

A biphasic electrochemical access to 2-isoxazoline-3-carboxylates bearing a broad variety of functional groups via dipolar cycloaddition in up to 83% yield was established. The scope included the successful synthesis of the herbicide safener

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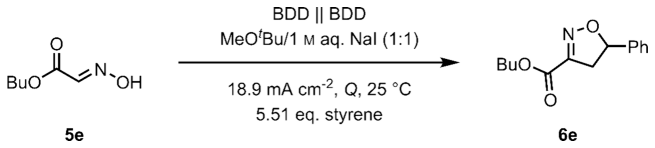
Table 1. Optimization of the Decagram-Scale Synthesis of Butyl 4,5-Dihydro-5-phenylisoxazole-3-carboxylate (6e)



entry	setup	no. of BDD electrodes (polarization)	interelectrode gap/mm	Q/F	post stirring	recovered styrene	yield
1	bipolar	6	5	5.46		n/d	40%[a]
2	bipolar	5	10	3.5		65.1 g (3.63 equiv)	56%[a]
3	bipolar	5	10	2.5		74.1 g (4.13 equiv)	57%[a]
4	bipolar	5	10	2.5	12 h	69.9 g (3.90 equiv)	56%[a]
5	alternatingly polarized	5 (+ − + − +)	10	2.75		74.5 g (4.15 equiv)	63%[a]
6	alternatingly polarized	3 (+ − +)	20	2.5		77.9 g (4.34 equiv)	63%[a]
7	alternatingly polarized	2 (+ −)	10	2.5		72.7 g (4.05 equiv)	83%[a]
8	alternatingly polarized	3 (+ − +)	10	2.5		71.2 g (3.97 equiv)	83%[a] (82%[b])

[a]Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated via silica filtration (0% → 10% EA in CH).

analogue "Isoxadifen-butyl" (**6r**), demonstrating the application potential of the developed method. Furthermore, an interesting impact of the ester chain length on the yield was observed and could be very well correlated to the log *P* values of the corresponding alcohols. The process optimization for butyl 5-phenyl-2-isoxazoline-3-carboxylate (**6e**) over 5 orders of magnitude from screening (10^{-2} g) via decagram to hectogram scale was demonstrated. The excellent and robust scalability of this protocol was shown, resulting in 82% (35.0 g) yield on the decagram scale. Transfer to the hectogram scale demonstrated the large-scale applicability of the presented method, resulting in 53% (195 g) yield and including an easy-to-conduct workup and purification procedure. Therefore, this biphasic approach offers a simple, scalable, and sustainable tool for the electrochemical synthesis of isoxazolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.4c03621.

Experimental details and ^{1}H NMR spectra for all compounds (PDF)

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Author Contributions

⊥Y.N., M.L., and J.W. contributed equally to this work. Y.N., M.L., and S.H. performed the screening for the reaction conditions and analyzed the experimental data. Y.N., M.L., and J.W. synthesized the starting materials. Y.N., M.L., and J.W. conducted the scope and scale-up experiments. Y.N., M.L. J.W., N.S., M.A., and S.R.W. wrote the manuscript. 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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