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In-Situ Electrolyte for Electrosynthesis: Scalable Anodically-Enabled One-Pot Sequence from Aldehyde to Isoxazol(in)es

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Electrochemical transformations are considered a green alternative to classical redox chemistry as it eliminates the necessity for toxic and waste producing redox reagents. Typical electrochemical reactions require the addition of a supporting electrolyte – an ionic compound to facilitate reaction medium conductivity. However, this is often accompanied by an increase in the amount of produced waste. Here, we report an "*in-situ electrolyte*" concept for facile, transition-metal-free, additive-free one-pot electrochemical preparation of isoxazol(in)es, important scaffolds for biologically active natural and synthetic molecules, from the respective aldehydes. The protocol utilizes no halogenated solvents and no external oxidants, while salt side-products provide the ionic conductivity necessary for the electrosynthesis. The electrolysis is performed in an undivided cell, using the state-of-the-art electrodes for the chlor-alkali industry dimensionally stable and scalable mixed metal oxide anode and platinized titanium cathode of high durability. The cascade transformation comprises the condensation of aldehyde to oxime followed by its anodic oxidation and subsequent intra- and/or intermolecular [3+2] cycloadditions with an appropriate dipolarophile. Chemical yields up to 97%, and good Faradaic efficiency, scalability, and stability are observed for most substrates in a broad scope.

Introduction

Modern retrosynthetic analysis for organic transformations must consider not only synthetic versatility but also the overall environmental impact, prioritizing those utilizing renewable energy and feedstock sources and producing less waste.[1] Electrosynthesis of organic compounds fits the green agenda exceptionally well, as it utilizes polarized electrode surfaces as terminal and "traceless" oxidants and reductants, enabling direct use of electricity from non-fossil-based resources.[2] Despite great success over the last decade, most organic electrochemical protocols still require considerable amounts of supporting electrolytes (ionic compounds) to ensure the reaction medium conductivity.[3] This fact might pose an issue for scalability, as downstream purification and recovery are energy- and labor-demanding processes. Although protocols requiring no supporting electrolytes are known, they are not generally applicable, limited mostly to polar or ionic reactants or when low-production microfluidic flow cells are employed.[4]

Yet, ionic reagents or side-products (acids, bases, or salts) are commonly present in the media of a large number of various organic reactions. For instance, ammonium-to-amine neutralization or transformations with organometallic reagents (magnesium or lithium) produce inorganic residue, often considered waste and discarded. Instead, they can be kept in the reaction mixture and utilized as "*in-situ electrolytes*",[5a–c] requiring the addition of no external supporting electrolyte.[5d,e] Thus, the applicability of such an intriguing approach requires further conceptualization over a broad range of electrosynthetic protocols as a strategy to gain even greater sustainability of organic electrosynthesis.

1,2-oxazoles and their 4,5-dihydro-derivatives, often named isoxazol(in)es, are important for medicine and crop-science R&D structural scaffolds found in natural products and synthetic compounds with psychoactive, anti-inflammatory, or antibiotic, as well as herbicidal, fungicidal, and insecticidal activities (Figure 1A).[6] Their synthesis is typically done by a [3+2]-cycloaddition ([3+2]-CA), a straightforward and atom-efficient protocol, utilizing readily available alkenes or alkynes and nitrile oxides.[7] However, the latter is unstable and thus commercially unavailable, resulting in the need to be prepared before utilization.[8] Justified by the availability of forgoing aldehydes, dehydrogenation of aldoximes is so far the most used approach, employing inorganic (CrO_2, MnO_2, $NaBrO_2$, NaClO, Oxone®)[9] or organic (m-CPBA, peroxides, t-BuOCl(I), $ArI(OAc)_2$, $PhICl_2$, NXS, Chloramine-T)[10] oxidants.

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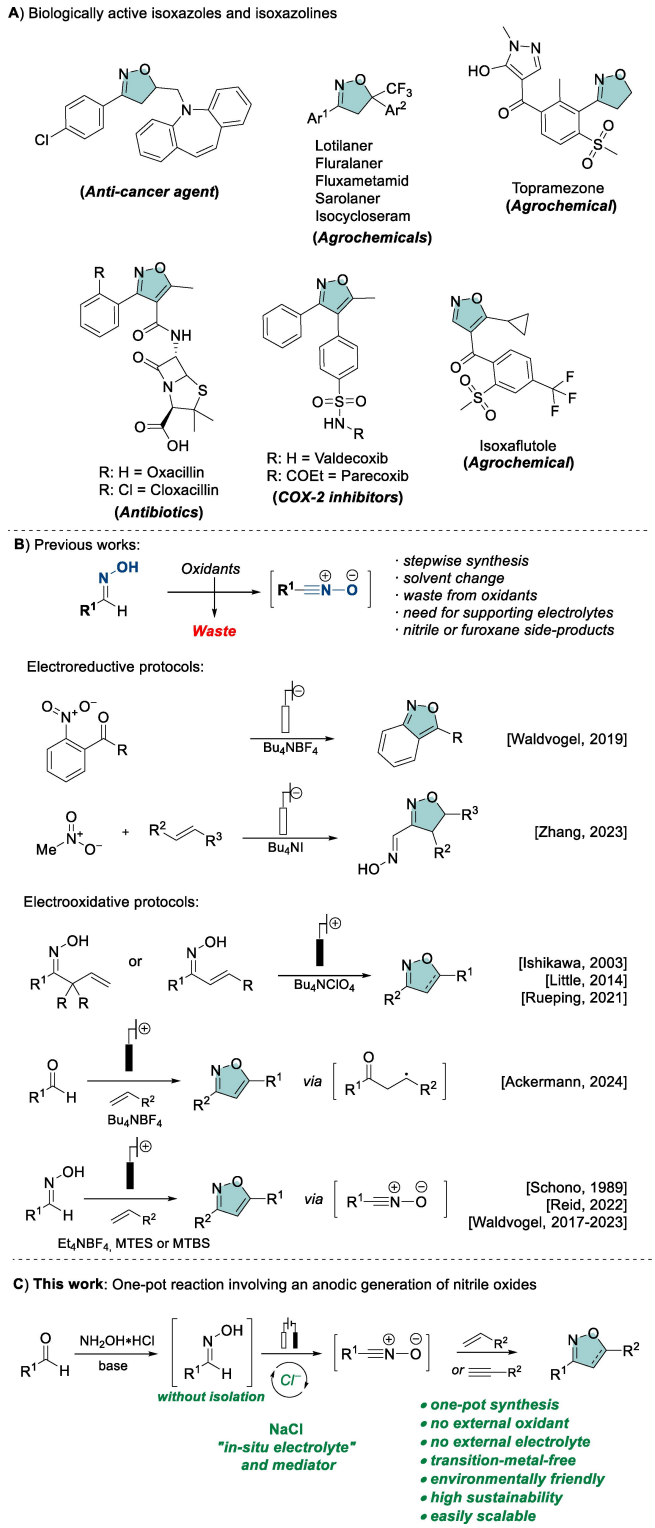


Figure 1. Biologically active isoxazol(in)e derivatives (**A**); known electrochemical synthetic strategies toward isoxazol(in)es (**B**); and a one-pot approach toward isoxazol(in)es, involving the anodic generation of nitrile oxides, developed in this work (**C**).

Besides the need for oxidants, a series of solvent exchange steps is also a common requirement for such protocols, compromising the sustainability of the otherwise atom-efficient [3 + 2]-CA and posing safety risks when scaled up.

As a "green" alternative, the electrochemical preparation of isoxazolines has recently received increased attention. It outperforms its chemical analogs, requiring no terminal oxidants or solvent exchange. Due to the exceptional tunability of electrochemical conditions,[11] many labile functional groups can be tolerated under mild reaction conditions.

As such, pioneered by Shono et al.,[12] generation of nitrile oxides upon aldoximes oxidation, anodic oxidation of the approach was further developed by teams of Waldvogel[13] and Reid.[14] At the same time, Ishikawa and Rueping have reported oxidative intramolecular cyclization of vinyl- and allyl-substituted ketoximes.[15] Very recently, Ackermann et al. have reported a multicomponent electrochemical transformation toward isoxazoles, comprising the formation of β-C-centered radical species.[16] Additionally, protocols toward isoxazol(in)es upon electroreductive transformation of a nitro-group have been developed.[17]

Yet, tetraalkylammonium salts as supporting electrolytes and hexafluoroisopropanol (HFIP) as a co-solvent remain a prerequisite, substantially limiting the scalability and versatility of the reported protocols. The attempt toward solvent and electrolyte recycling further confirms the existing issue. Owing to the increased interest, we envisioned and presented an "*in-situ electrolyte*" protocol for the transformation mentioned above. The hydroxylammonium chloride neutralization step is shown to provide solution conductivity along with possible chloride mediation, which is known to form hypochlorite under cathodically generated basic conditions.[18] Targeted [3 + 2]-CA is successfully performed under one-pot procedure in an undivided cell, furnishing the desired isoxazol(in)e products (Figure 1C).

Results and Discussion

At the outset, a condensation of benzaldehyde with hydroxylammonium chloride was examined in solvents suitable for the following electrolysis based on dielectric permittivity.[19] Most of the media tested successfully provided oximes with good chemical yield within a short reaction time under ambient conditions. Adding water facilitates an oximation reaction, increasing the solubility of inorganic residue and the overall conductivity of the reaction mixture. High water content, however, is found detrimental due to phase separation and poor solubility of aldehydes in water. The successful compositions were next tested upon quick electrolysis with graphite anode and stainless steel cathode under excess ethyl acrylate. At this stage, acetonitrile was found to be a solvent of choice for further optimization of reaction parameters. Using an undivided cell, the highest yield of the desired isoxazol(in)es can be obtained when following criteria are fulfilled: *a*) the oxidation of an oxime is the only anodic process; *b*) water reduction (hydrogen evolution reaction, HER) is an exclusive cathodic reaction; at the same time, *c*) a rate for nitrile oxide production is in accordance within kinetic of the following

cycloaddition, and *d*) the reaction medium remains neutral due to cathodically generated base (OH^-). Acidic conditions were detrimental to the overall nitrile oxide generation, while strong bases affect ester functionalities, e.g., in ethyl acrylate. In this regard, sodium bicarbonate is beneficial for buffering effect. Nitrogen-containing bases (e.g., pyridine or Et_3N) were strongly detrimental to the overall transformation, delivering no desired product.

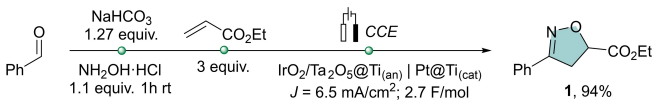
Adding other halide mediators which demand less anodic potentials, such as Br or I, decelerates the conversion under undivided cell conditions, most probably because of the slow chemical oxidation of oxime and reduction of $\{Hal^+\}$ species at the available cathode surface. Performing oxidation under different atmosphere compositions (argon or air) and visible light irradiation does not affect the reaction outcome. The stirring rate variations, however, change the reaction performance only to a small extent, indicating a rate determining step to be off-electrode rather than a mass transport limited. Notable, the reaction tolerates current densities, ***j***, in the range of 5 to 10 mA cm^{-2}, whereas the amount of consumed charge, **Q**, is not exceeding 3 F/mol. Increasing the amount of charge did not enhance the reaction outcomes, but rather led to the formation of unidentified side-products (Table 1).

Finally, electrochemical oxime oxidation was performed in a thermostated reaction mixture at 20 °C, which featured better reproducibility. Examination of the presence of water content in acetonitrile revealed that 5% of the latter was optimal, making the cell voltage between 4–6 V_{DC}. However, the latter strictly depends on the interelectrode distance, which has to be as short as possible. At the same time, allocating two flat foil electrodes in a batch cell very close to each other limits convection. To mitigate such an issue, one or both electrodes shall be in a mesh or grid shape, while a thin and porous dielectric spacer avoids an electric shortcut.

Having established graphite as the anode, further cathode materials were examined. Thus, metals substantially outperform carbon-based cathodes, which is in accordance with previous reports. Besides the material, the reaction outcome benefits from slightly higher cathodic current density than those at the anode, set by the cathode-to-anode surface ratio of $S_{C/A} = 0.8$. The expanded meshes, introduced before due to fewer restrictions in convection, fulfill the setting flawlessly. Among other meshes, pure titanium is not suited; stainless steel could be used, whereas platinized titanium (Pt@Ti) is the best performer. Only traces of benzonitrile were observed with such a cathode, confirming HER as the major cathodic process.

However, other side-products, such as benzaldehyde, furoxane, and its N-oxide, were detected by GC-MS, known to originate from nitrile oxide dimerization.[20] We hypothesize their formation through an inner sphere electron transfer mechanism facilitated by the aldehyde adsorption on the graphite surface. The first hint is seen during linear sweep voltammetry (LSV) of the reaction mixture, during which a shoulder with the on-set at +0.25 V vs. $E_{Fc/Fc+}$ is detected before a main current increase after the applied potential has become more positive than +0.75 V vs. $E_{Fc/Fc+}$. The latter matches the only on-set potential for sodium chloride-saturated wet acetonitrile (SI, Fig. S-3). Additionally, the interactions between graphite and aldehyde or aldoxime are expected to correlate with the graphite surface properties, which can be observed upon OCV drifts right after adding the latter to a blank electrolyte. The smallest amounts of furoxane were

Table 1. Electrochemical cascade [3 + 2]-CA toward isoxazol(in)es: optimization of reaction conditions.[a]



Entry	Variations from the standard conditions[a]	Yield **1**,[b]
1	MeOH, EtOH, or ^{i}PrOH instead of CH_3CN[c]	10–35%
2	DMSO, DMF, DCM, THF instead of CH_3CN[c]	n.d.[d]
3	1,4-dioxane/H_2O (2 : 1), NaOH, 10 mA/cm^2 [c]	30%
4	"N"-bases[e] instead of $NaHCO_3$[c]	n.d.
5	M_2CO_3[f]-bases instead of $NaHCO_3$[c]	25–60%
6	MOH[f]-bases instead of $NaHCO_3$[c]	18–55%
7	[Benzaldehyde] > 0.15 M[c]	< 70%
8	[Ethyl acrylate] < 0.45 M[c]	< 55%
9	J > 7 mA/cm^2 or < 6 mA/cm^2 [c]	< 76%
10	Q > 2.7 F/mol or < 2.3 F/mol[c]	< 54%
11	Carbon-based cathodes	< 33%
12	Graphite anode instead of MMO DSA	82%
13	t > 30 °C or < 10 °C	< 60%
14	RuO_2/TiO_2 or $IrO_2/RuO_2/TiO_2$ MMO@Ti	96%

[a] If not otherwise stated, the reactions were performed at the 0.45 mmol scale in 3 mL (0.15 M) of wet CH_3CN[5% H_2O] at r.t., isolated yield; [b] Yields are determined by GC-FID; [c] Graphite anode | | SS316 cathode; [d] n.d. – not detected; [e] Pyridine, picoline, triethylamine, imidazole; [f] M: Li^+, Na^+, K^+, Cs^+.

detected during bulk electrolysis only when a freshly sanded, acetone-sonicated, and paper-polished graphite was used. The repetitive use of the same electrode with only acetone washings in between dramatically increased side product formation. Conclusively, despite the low material price, using graphite as an anode might compromise the scalability due to high operational and cleaning expenses and poor long-term stability.

Inspired by the transition in the multi-ton-scale chlor-alkali industry from graphite to dimensionally stable mixed metal oxide anodes (DSA-MMO)[21] and the hypothesized chloride mediation of the oxime anodic oxidation,[14] we have tested commercially available iridium or ruthenium oxide coated titanium plates. Notably, RuO_2-coated titanium has been recently reported as both anode and cathode materials for the electrochemical preparation of hetero-aromatic sulfoxides and sulfones.[22] Interestingly, the performance of all tested materials for the generation of nitrile oxide was excellent. Nevertheless, we decided to use IrO_2/Ta_2O_5 coating as the most stable composition, also used in electrochemical soil remediation from organic pollutants.[23] A set of LSVs, including the blank $NaCl_{sat}$ in acetonitrile, shows no of the pre-onset shoulder previously seen for graphite. The oxidation of oxime under given conditions is faster than the oxidation of ethyl acrylate, providing a basis for one-pot cycloaddition. Hydroxylamine oxidation under such conditions is also fast; thus, its slight excess from the initial stage of the one-pot procedure shall cause no problems.

With the optimized one-pot reaction conditions, we next studied the protocol's applicability toward various combinations of aldehydes and dipolarophiles (Table 2).

First, benzaldehyde oxime was fixed as a repetitive fragment to test substituted olefins (products **1**–**13**, **42**, **43**) or acetylenes (products **14**–**18**, **44**) as dipolarophiles. As such, ethyl acrylate, acrylonitrile, α-trifluoromethyl-styrene, and substituted maleimides provide corresponding isoxazolines **1**, **2**, **3**, **9**, and **10** in excellent yields. Products **4** and **8** were successfully derived from a trifluoromethylated allyl alcohol and allyl benzoate, although in moderate yields. In contrast, para-methoxyphenyl (PMP) allyl sulfone is more active under optimized conditions, providing isoxazoline **12** in a good 87% yield. α,β-unsaturated ketones were also successfully converted to the corresponding isoxazolines **5** and **11**. Interestingly, no trans-oximation was observed, while diminished yield for cyclopentanone is explained by sluggish cycloaddition kinetics. Direct preparation of aminomethyl-isoxazolines is confirmed (**6**, **7**) only for sulfonyl N-protected ones and in low yield.

The application of arylacetylenes is found to be problematic, as can be seen for oxazoles **14** and **44**. Nevertheless, more synthetically versatile derivatives from ethyl propiolate, propargyl benzoate, and trimethylsilylacetylene (**15**–**17**) were obtained in good yields. Luckily, propargyl bromide also provides the desired bromomethylated product **18**.

Utilizing ethyl acrylate for various aldehydes under the presented cascade conditions provides isoxazolines **19**–**30** in consistently good yields. Only para-iodo-substituted benzaldehyde is rather problematic, showing low conversion due to partial proto-deiodination cathodic reaction. Released, in such a case, iodide-anion lowers the Faradaic efficiency of the process, resulting in only a 10% yield of the desired product after consumption of 2.7 F/mol of charge. An intramolecular version of the 3 + 2 cycloaddition is exemplified on O-allyl-derivatives from salicylic aldehydes (isoxazolines **31** and **32**). No excess of the dipolarophile is possible in such a case, yet the desired annulated heterocycles were obtained in good yields.

In contrast to aromatic aldoximes, the alkyl-substituted analogs form during the oximation reaction as a mixture of E/Z isomers in an almost 1:1 ratio. Interestingly, electrochemical oxidation of E-isomer has been found to be kinetically more favorable. Therefore, to prepare the butanal-derived products **34** and **35**, the dipolarophile was taken as a limiting reagent, while the oxime was in excess. Nevertheless, these were obtained in almost doubled yield compared to benzaldehyde-derived aminomethyl isoxazoline **6**.

Due to the abundance of the quaternary trifluoromethyl-substituted fragment in medicinally relevant compounds,[24] we further expanded the scope for the accordingly substituted isoxazoline **3**. The anisaldehyde, naphthaldehyde, phenylacetaldehyde, and butanal provided corresponding products **36**, **37**, **39**, and **41** in good yields. Whereas, yields of sterically bulkier pentamethylbenzaldehyde- and formyl-adamantane-derived isoxazolines **38** and **40** were even higher. Both electron-deficient pentafluorophenyl and electron-rich 3-furyl provided the expected products **46** and **47** only in poor yields.

Finally, we have tested the scalability of the approach toward selected substrates under 15 and 60 mmol loading conditions (Figure 2). Meanwhile, the yields of isoxazolines **19**, **23**, and **28**, obtained at the gram scale, were comparable with those of the small loadings. The decagram scaling resulted in substantially lowered yields. Analysis of the side product revealed a substantial amount of hydro-dimerized maleimide in the case of **9** and diethyl adipate in the case of **28**. The latter are products of reductive cathodic processes, the preference of which, under given conditions, indicates high hydrogen over-

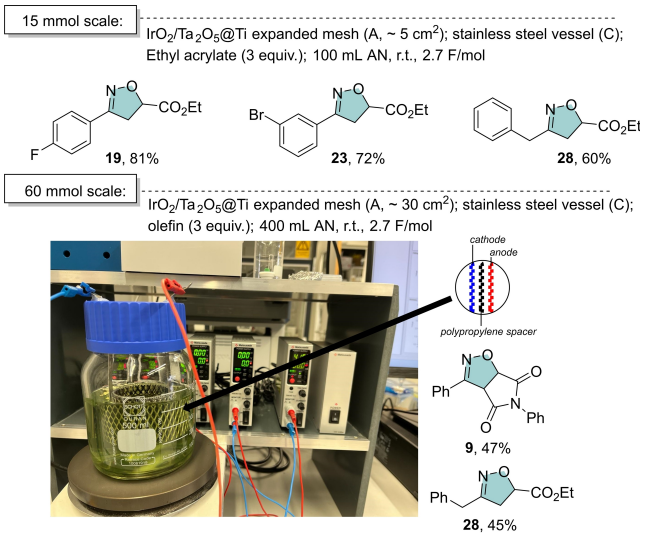
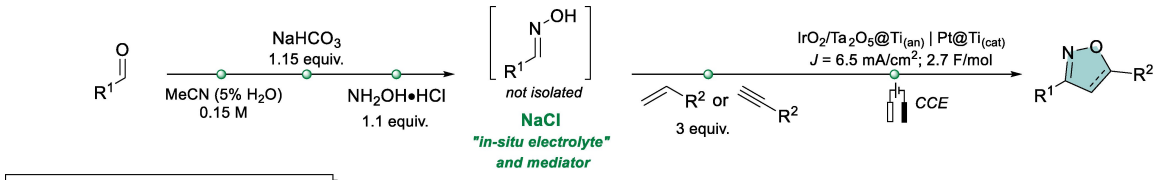
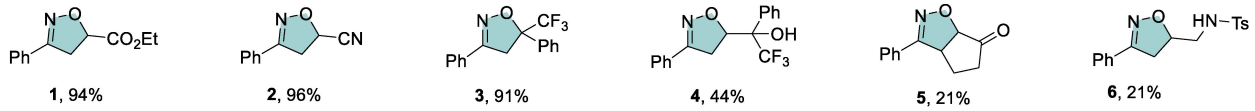


Figure 2. Gram-scale synthesis of the aryl and alkyl-substituted isoxazolines.

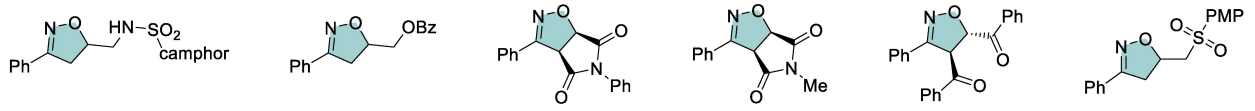
Table 2. The scope and limitations of the one-pot "in situ electrolyte" strategy toward isoxazolines and isoxazoles.[a]



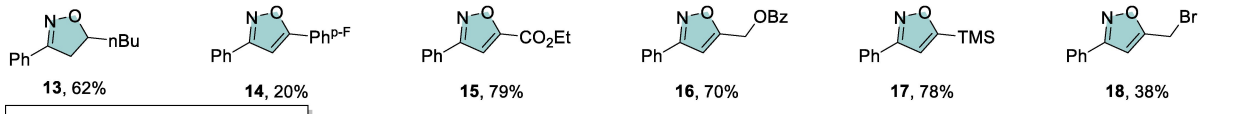
Dipolarophile scope with benzaldehyde:



1, 94% **2**, 96% **3**, 91% **4**, 44% **5**, 21% **6**, 21%

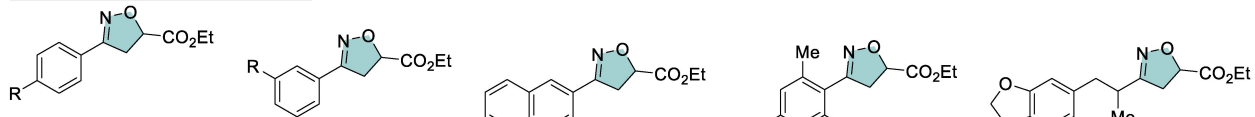


7, 22% **8**, 52% **9**, 97%[b] **10**, 94%[b] **11**, 75%[c] **12**, 87%



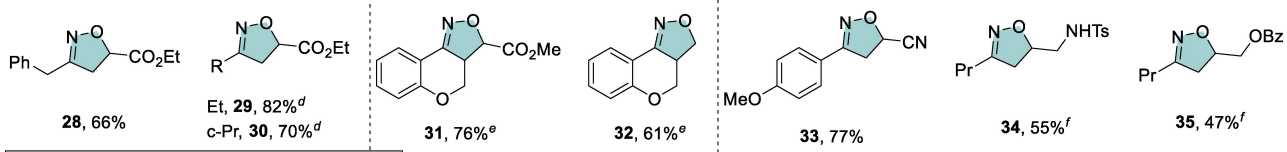
13, 62% **14**, 20% **15**, 79% **16**, 70% **17**, 78% **18**, 38%

Aldehyde scope with Ethyl acrylate:



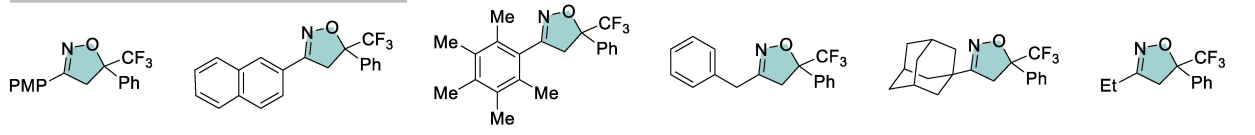
F, **19**, 81%
CF_3, **20**, 85%
Cl, **21**, 78%
OEt, **22**, 75%
Br, **23**, 84%
CO_2Me, **24**, 81%
25, 68% **26**, 85% **27**, 78%

Intramolecular: Other:



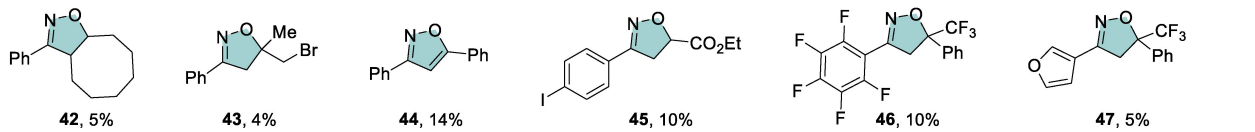
28, 66%
Et, **29**, 82%[d]
c-Pr, **30**, 70%[d]
31, 76%[e] **32**, 61%[e]
33, 77% **34**, 55%[f] **35**, 47%[f]

Aldehyde scope with α-Trifluoromethyl-styrene:



36, 66% **37**, 63% **38**, 91% **39**, 57% **40**, 79% **41**, 63%

Limitations:



42, 5% **43**, 4% **44**, 14% **45**, 10% **46**, 10% **47**, 5%

[a] Reactions were performed under standard reaction conditions at the 0.45 mmol scale. Yields are reported for purified by column chromatography compounds (except 29 and 30); [b] *cis*-diastereomer as a major; [c] *trans*-diastereomer as a major; [d] Yields were obtained by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard; [e] No external dipolarophile was added; [f] Excess of butanal oxime was used, yield is based on the dipolarophile as the limiting reagent. TMS – trimethylsilyl, PMP – *para*-methoxyphenyl.

potential for this particular stainless steel mesh. Notably, the impact on maleimide is higher due to its more electron-deficient nature than ethyl acrylate and, thus, lower reductive overpotential. Further upscaling of the present strategy is currently ongoing in our laboratory.

To get further insights into the electrochemical behavior of benzaldoxime, a set of voltammetric experiments has been carried out. First, cyclic voltammetry on platinum working electrode under water-free reaction conditions revealed two irreversible well-distinguishable one-electron oxidation processes (Figure 3, top, EC path), with $E^1_{pa} = +1.55$ V and $E^2_{pa} = +1.95$ V vs $E_{Fc/Fc+}$, respectively. The oxidation peaks can also be seen by differential pulse voltammetry (DPV) (SI, Fig. S-9). They can be assigned to the sequential electron transfer/deprotonation process, typically depicted as the *ECEC* mechanism.

A cathodic peak at $E = -0.50$ V vs. $E_{Fc/Fc+}$ can also be observed only after the preceding anodic scan, exceeding $+1.00$ V vs $E_{Fc/Fc+}$. This current response is assigned to the electroreduction of anodically generated H^+-species rather than just forming nitrile oxide electroreduction. The latter requires much more negative potentials,[25a] whereas the addition of a strong external base (Bu_4NOH) vanishes the peak at -0.50 V (SI, Fig. S-5). Additionally, the basic medium affects the anodic behavior of the oxime, as oxidation of fully deprotonated benzaldoxime now takes place at $E_D = +0.20$ V vs $E_{Fc/Fc+}$ (Fig. S-6). As such, direct anodic PCET is feasible only under strongly basic conditions or at high electrode potentials.

Notably, the current of all three peaks is linearly scan-rate dependent, indicating diffusion as the major mass transport mode, according to the Randles-Ševčík equation.[25b] The slope of the anodic current increase at $+1.55$ V ($a_{1.55} = 0.101$) is found to be smaller than those at $+1.95$ V ($a_{1.95} = 0.223$), which suggests a shift of oxidation mechanism from two consecutive 1-e^- transfers to the one 2-e^- transfer, over the increase of the applied potential or current density. A slope for cathodic current ($a_{-0.50} = 0.175$) is close to the mean value of anodic slopes, further supporting the abovementioned hypothesis (Fig. S-8).

Although the anodic formation of nitrile oxide can proceed via direct PCET, utilizing chloride as a redox mediator is associated with both thermodynamic and kinetic benefits. Moreover, a halide-free reaction media provides either no or only traces of the desired product. Neither a pre-electrolysis of chloride-containing electrolyte followed by the addition of the benzaldoxime and ethyl acrylate mixture nor slow addition to the same mixture of NaOCl (bleach) solution provides desired isoxazoline **1** in practical yields. As such, we hypothesize the formation of surface-populated hypochlorite species {OCl*},[26] facilitating the formation of oximoyl chloride intermediate, delivering nitrile oxide upon base-assisted Cl^- elimination. Such a notion is also supported by the substantial increase in the current response of the benzaldoxime-containing reaction mixture when compared to the blank (Figure 3, bottom).

Based on the literature,[13,14] the reaction can undergo a radical relay or pericyclic mechanistic pattern, depending on the number of electron transfers. Nevertheless, we believe the presented protocol comprises 2-electron oxidation towards nitrile oxide followed by conventional [3 + 2]-CA, as depicted in Scheme 1. It appeared difficult to obtain direct experimental evidence for the presence of nitrile oxide as an intermediate due to the high reactivity of the latter. Yet, GC-MS analysis of the reaction mixture utilizing mesityl aldehyde as starting material revealed peaks which may correspond to nitrile oxide m/z-ratio, and the intensity correlates with the amount of the final product formed (SI, Table S-17 to S-20). Furthermore, regioselectivity and stereochemistry of the products fits the expectations for pericyclic cycloaddition if it occurs. For instance, maleimide-derived products **9** and **10** were found to have cis-configuration, while **11** and **31** retain trans-configuration from the parental dipolarophiles. In addition, a small

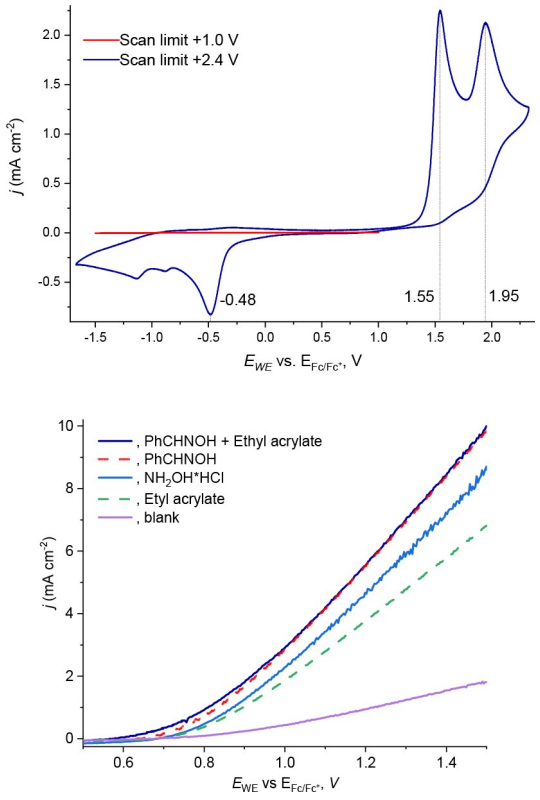
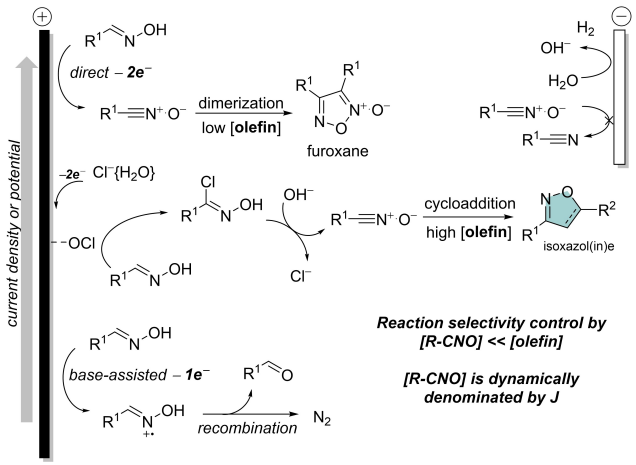


Figure 3. Cyclic voltammetry of benzaldoxime under model neutral and basic conditions on platinum (top) and linear sweep voltammetry of preparative reaction components of IrO_2-based anode (bottom).



Scheme 1. Proposed reaction mechanism and current density dependency of side products formation.

amount of regio-isomer is commonly observed for reactions with ethyl acrylate as a dipolarophile, further supporting the mechanistic hypothesis.

The selectivity toward the desired product matches the kinetic constant between the formation of a nitrile oxide and the cycloaddition reaction.[27] The trends observed during model CV studies were also observed over the preparative one-pot media performance. As such, under low current density, the electrode potential is low for chloride oxidation, and a single proton-coupled electron transfer (PCET) occurs. The latter results in the formation of benzaldoxime radical-cation, the dimerization and recombination of which predominantly results in the formation of parental benzaldehyde (Scheme 1, bottom section). Due to the high polarity of the electrode vicinity solution, only traces of radical relay processes are observed.

On the other hand, under high current density, a direct $2e^-$ PCET is more favorable, directly generating the desired nitrile oxide (Scheme 1, upper section). Under such conditions, in order to obtain the desired isoxazol(in)es, either nitrile oxide has to be stable (aromatic with *ortho*-substitution) or the cycloaddition itself must be fast. Otherwise, the nitrile oxide undergoes dimerization to form a furoxane side product, easily reducible at the cathode to 1,2,5-oxadiazole.

Last, the chloride-mediated process takes place at a moderate current density, resulting in oximoyl chloride, which diffuses from the electrode surface before being converted to nitrile oxide. In such a case, the olefin to nitrile oxide concentrations ratio facilitates the selective formation of desired cycloaddition products through a pseudo-first-order reaction (Scheme 1, middle section).

Finally, at a cathode, the water reduction occurs to generate hydrogen and, beneficial for the overall transformation, hydroxyl-anions. Although simple undivided conditions can be employed, the formation of nitrile or olefin reduction products must be monitored as an indication of inappropriate cathode material or its fouling over the application time.

Conclusions

In summary, we have presented an efficient and green method for one-pot cascade preparation of isoxazol(in)es from readily available aldehydes, alkenes, or alkynes. The multi-component transformation undergoes sequential aldehyde oxime formation, anodic oxidation, and [3 + 2]-cycloaddition; furnishing desired heterocycles in good to excellent yields (up to 97 %) and good selectivity. The protocol features the utilization of neither a stoichiometric oxidant nor an external supporting electrolyte. Neutralizing commercially available hydroxylammonium chloride with sodium bicarbonate provides free-base hydroxylamine for oxime formation, while the resulting salt leftover is utilized as an "in-situ" electrolyte and mediator. The application of dimensionally stable anodes provides a solid basis for the scalability of the decagram-scale synthesis of medicinally and agriculturally relevant building blocks. The obtained results open the direction of further utilization of robust electrode materials from water electrolysis of chlor-alkali industries for efficient organic synthesis. Furthermore, we envision further application of the "*in-situ electrolyte*" concept for efficient electrosynthetic protocols.

Experimental Section

For the preparation of an aldoxime stock solution (0.15 M), the corresponding aldehyde (1.80 mmol, 1.00 equiv.) was dissolved in a mixture of acetonitrile (11.4 mL) and water (0.6 mL). Sodium bicarbonate (2.29 mmol, 1.27 equiv.) and hydroxylammonium chloride (1.98 mmol, 1.10 equiv.) were added, and the reaction mixture was stirred at ambient temperature for 1 h. The remaining solids were filtered, and the obtained aldoxime solution was used further without purification.

3.00 mL of the aldoxime stock solution (0.45 mmol, 1.00 equiv.) were added to an electrochemical cell, followed by the addition of the dipolarophile (1.35 mmol, 3.0 equiv.). The lid, equipped with IrO_2/Ta_2O_5@Ti MMO-anode and a Pt@Ti cathode (1 cm^2 each), was placed over the cell, and the reaction mixture was electrolyzed at r.t. for 5 h at 6.5 mA cm^{-2} (2.7 F mol^{-1}) within vigorous stirring. After the indicated time, the reaction mixture was transferred to a round-bottomed flask to remove the solvent and the unreacted dipolarophile for recycling. The crude product was further purified via column chromatography (EtOAc : hexane).

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Conflict of Interests

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: Isoxazole · One-pot · "*In-situ* electrolyte" · Cycloaddition · Electrosynthesis

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