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Article

Dehydrogenative Imination of Low-Valent Sulfur Compounds—Fast and Scalable Synthesis of Sulfilimines, Sulfinamidines, and Sulfinimidate Esters

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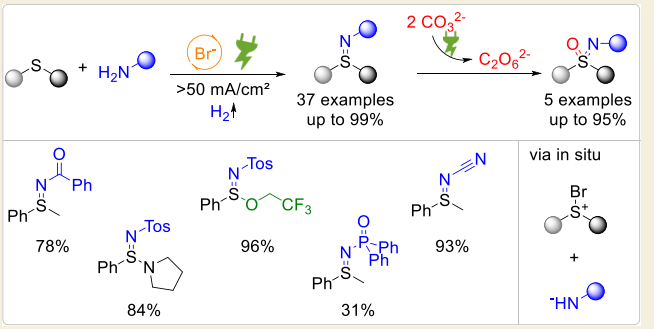
ABSTRACT: Herein, we describe an electrochemical pathway for the synthesis of sulfilimines, sulfoximines, sulfinamidines, and sulfinimidate esters from readily available low-valent sulfur compounds and primary amides or their analogues. The combination of solvents and supporting electrolytes together act both as an electrolyte as well as a mediator, leading to efficient use of reactants. Both can be easily recovered, enabling an atom-efficient and sustainable process. A broad scope of sulfilimines, sulfinamidines, and sulfinimidate esters with *N*-EWGs is accessed in up to excellent yields with broad functional group tolerance. This fast synthesis can be easily scaled up to multigram quantities with high robustness for fluctuation of current densities of up to 3 orders of magnitude. The sulfilimines are converted into the corresponding sulfoximines in an ex-cell process in high to excellent yields using electro-generated peroxodicarbonate as a green oxidizer. Thereby, preparatively valuable NH sulfoximines are accessible.



KEYWORDS: *electrochemistry, sulfoximines, green chemistry, paired electrolysis, cross-dehydrogenative coupling*

INTRODUCTION

In drug discovery, there is a growing interest in the development of new syntheses for the application of sulfur-bearing functional groups.[1−3] The pharmaceutical scenery of trivalent sulfur structures is dominated by sulfoxides.[4] The production of other potentially important trivalent sulfur aza analogues, such as sulfilimines, sulfinimidate esters, and sulfinamidines, is still an under-researched topic. This is due to the limited availability of potential synthesis for these scaffolds. However, sulfilimines find practical use in organic chemistry as nitrene transfer reagents[5,6] and the construction of various heterocycles.[7] In addition to these possibilities in direct application, a very special interest exists in the correlated tetravalent S-species for which the the trivalent S-compounds are important synthons.

Sulfoximines are, therefore, an interesting functional group of increasing importance in both academic and pharmaceutical chemistry.[8] A configurationally stable stereocenter and highly polarized S−N bond gives rise to unique features. Therefore, sulfoximine-containing compounds are readily used as reagents in organic synthesis[9,10] and ligands in organometallic chemistry.[11] Furthermore, these moieties are found in compounds with biological activity.[8,12,13] Namely, the glufosinate inhibitor L-methionine sulfoximine and the modern insecticide sulfoxaflor (Figure 1).[14]

Due to the high interest in this moiety, the development of new synthetic routes is a major target in academia. There are

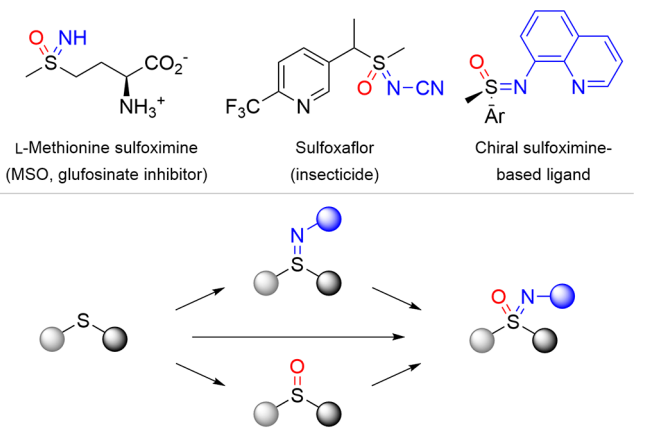


Figure 1. Representative examples of sulfoximine containing structures (above) and oxidative strategies toward sulfoximines (below).

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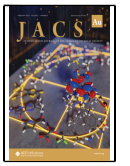


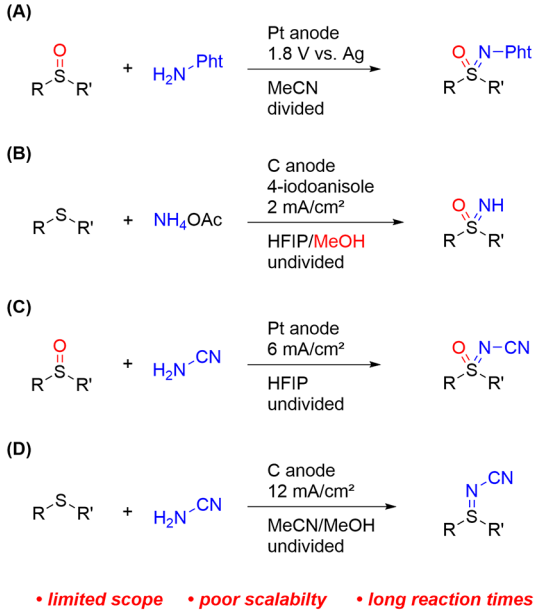
three conventional methodologies starting from a sulfide: imination followed by oxygenation, oxygenation then imination, or simultaneous oxygenation and imination.[15] However, the imination step is the most synthetically challenging.[16] Imination can be carried out via oxidation of sulfur and a subsequent nucleophilic attack by nitrogen. This combines the use of halogen-based oxidizers and strong bases like *t*BuOCl/deprotonated amides,[17] *N*-bromo succinimide/KO*t*Bu,[18] or 1,3-dibromo-5,5-dimethylhydantoin/NaH.[19] Alternatively, imination can be carried out via electrophilic nitrenoid precursors. These can be generated using NaN_3 in oleum,[10] *O*-mesitylenesulfonylhydroxylamine,[20] photolytic,[21] or catalyzed elimination in the presence of a metal catalyst for stabilization.[22]

Further examples of imination processes use iodine(III) reagents to enable simultaneous N,O transfer resulting in NH sulfoximines,[23] which can then be further functionalized in a wide variety of processes.[15,24,25] For the oxygenation, numerous literature precedents using strong oxidizers are available, such as H_2O_2/MeCN,[26] *m*-CPBA,[27] $NaIO_4$/RuO_2,[21,28] or $KMnO_4$.[29]

Such conventional methods require harmful terminal oxidants, strong bases, and complex pre-functionalization of starting materials and/or transition-metal catalysts; this lowers the atom efficiency and results in high amounts of reagent waste and safety issues when performed on a larger scale. A powerful tool in organic synthesis to ensure more economically and ecologically reasonable processes is electro-organic chemistry.[30−39] It is often seen as a 21st century technique to overcome stoichiometric amounts of hazardous reagents, which in turn decreases waste generation and ensures safe processing, as reactive intermediates are formed exclusively in situ.

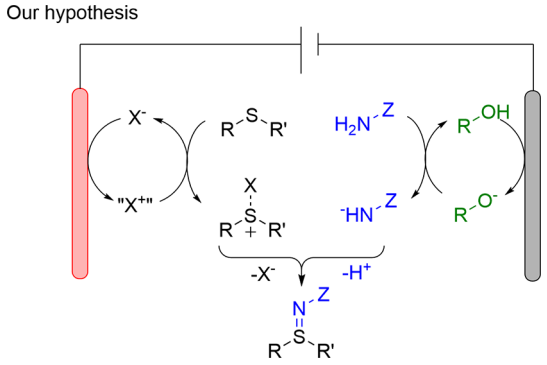
Recent examples of electrochemical imination reactions can be found in Scheme 1. Yudin and Siu described a method for the imination of sulfoxides with *N*-aminophthalimide in a divided cell under potentiostatic conditions. The *N*-phthalimidoyl sulfoximines were converted into more synthetically useful NH-sulfoximines by reduction at a Pt cathode (Scheme 1A).[40,41] In 2021, the Xu group described a method for the synthesis of NH-sulfoximines using *p*-iodoanisole as a redox mediator in fluorinated solvents, forming iminoiodine(III) at the Pt anode (Scheme 1B).[42] Wirth and Amri performed an imination of sulfoxides with cyanamide in poor to moderate yields (Scheme 1C),[43] whereas our group established a method for the imination of sulfides with cyanamide to form *N*-cyanosulfilimines in excellent yields (Scheme 1D).[44] These electrochemical methods have advantages over conventional synthesis; however, they are limited to specific substituents on the nitrogen. So, we challenged ourselves to develop a general method to enable the imination of several low-valent sulfur compounds to form stable sulfilimines.

Scheme 1. Electrochemical Methods for the Imination of Sulfides or Sulfoxides[40−44]



Based on the work of Swern,[17] we formed the following hypothesis (Scheme 2): a mediated oxidation of sulfur paired with the simultaneous electrochemical generation of a base will lead to a selectively controlled preparation of electrophile and nucleophile in situ, which will undergo dehydrogenative coupling. Therefore, sulfilimines can be simply oxygenated to sulfoximines using mild and green oxidizers, such as electrogenerated peroxodicarbonate.

Scheme 2. Concept for the Imination of Low-Valent Sulfur Compounds and Amides Using Mediated Oxidation and Electrogenerated Base[a]



[a]Z: Electron-withdrawing substituent.

RESULTS AND DISCUSSION

Electrolyte

The initial screening of suitable electrolysis conditions for imination was carried out in a commercially available undivided cell for electrosynthetic screening under constant current conditions (see the Supporting Information). Thioanisole (**1a**) and *p*-toluenesulfonamide (**2a**) were chosen as test substrates for the imination reaction, as the stability of sulfilimines is enhanced by electron-withdrawing groups attached to nitrogen (*N*-EWGs). First, a suitable electrolyte/electrode system was identified. It was found that the selection of (oxidation-mediating) supporting electrolytes had the most crucial impact on the outcome of the reaction. In all cases, sulfoxide **4a** was detected as a major byproduct. Inert supporting electrolytes such as BF_4^- or acetates only led to trace amounts of product **3aa** (Table 1, entry 1). When using a chloride containing electrolyte, the product formation was less selective and mono-chlorinated byproducts, as well as sulfones, were observed by HPLC/MS and NMR analysis of the crude

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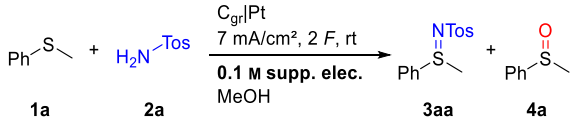
JACS Au 2023, 3, 575−583

Table 1. Impact of Supporting Electrolytes on the Yield of 3aa[a]



entry	supporting electrolyte	3aa [%]	4a [%][a]
1	NEt_4BF_4	4	70
2	NEt_4Cl	5	71
3	**NEt_4Br**	**28**	**41**
4	NEt_4I	0	traces
5	KBr	23	47
6	no supporting electrolyte	n.d.	n.d.

[a]^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as the internal standard. n.d.: none detected.

mixture (Table 1, entry 2). Bromide as supporting electrolytes gave the highest yields for the desired imination product **3aa** and selectivity **3aa**/**4a** (Table 1, entry 3 + 5). Interestingly, use of the iodide as an electrolyte showed only trace amounts of **4a** and almost no conversion of starting materials (Table 1, entry 4). It was found that changing the cation of the bromide electrolyte had little impact on product formation (Table 1, entry 5). Therefore, NEt_4Br was chosen for further investigations as the solubility in organic media is superior compared to KBr. As expected, without the supporting electrolyte, there was no electrical conductivity (Table 1, entry 6). In attempt to pregenerate, the amide base NaOMe (1.5 equiv) was added. This did not lead to satisfactory yields (5%). Using MeOH, a polar protic solvent, led to good results as the electrogenerated base (methanolate) promoted crucial deprotonation steps. Full survey of all supporting electrolytes and solvents is listed in Table S1.

Alternative acidic alcohols EtOH and *i*PrOH were also investigated as potential solvents. Although these led to higher yields of sulfilimine **3aa** (65 and 35%, respectively), the overall mass balance when using these alternative alcohols was lower than MeOH systems (60−83%). This is likely due to the higher cell voltage observed when using longer alkyl chain alcohols (Table S1). Fluorinated alcohols lead to the formation of large amounts of **4a** (47−59%, Table S1). When aprotic solvents like MeCN were used, only traces of sulfoxide **4a** were detected and **3aa** was formed in high yields (74%). However, the potential for the deprotonation of amide (as it is now performed directly at the cathode and not via the electrogenerated base) is quite negative. So, amides less acidic than **2a**, for example, benzamide (**5a**) did not undergo conversion. The electrolysis in MeOH/NEt_4Br was further investigated and the influence of other reaction parameters on the reaction outcome was examined.

Optimization Studies

The anode material was found to have a low impact on the yield. Using graphite as the anode gave 10% lower yields of sulfilimine **3aa** compared to anodes with inert surfaces, for example, glassy carbon or boron-doped diamond (BDD). It has been noted that metallic cathode materials with a low overpotential for hydrogen evolution is beneficial.[45] Pt gave the best yields for **3aa** (38%), but similar results were obtained with stainless steel (32%); therefore, the latter was chosen as a more sustainable and less expensive cathode material (Table S2). The reaction parameters of the imination process were investigated to assess their individual importance and then optimized using modern screening technologies.[46] An optimization strategy based on a design of experiments (DoE) approach was used (Figure 2).

It was found that the concentration of NEt_4Br had the most significant impact on the yield of **3aa**. By increasing the concentration of NEt_4Br from 0.10 to 0.15 M an up to 1.6-fold increase of **3aa** was observed. Increasing the current density from 5 to 10 mA/cm^2 also increased the yield of **3aa** (33% → 39%). An increased amount of charge had to be applied to ensure full conversion of **1a**. The equivalents of **2a** and *c*(**1a**) had a negligible impact on the yield within the investigated area. Accordingly, the concentration of **1a** was kept at 0.1 M and 1 equiv of **2a** was chosen. The current density, charge, and concentration of the supporting electrolyte were further optimized (Tables S3−S6).

The following reaction conditions were identified by optimization studies: 0.40 M NEt_4Br in MeOH, 2.8 *F* total charge, and a current density of 50 mA/cm^2. Utilizing the aforementioned conditions, **3aa** was produced with an NMR yield of 95% and could be isolated in 91% yield by recrystallization. A comprehensive description of all screening experiments and their results are listed in the Supporting Information. Implementation of the optimized reaction conditions with other N-sources was then trialed; benzamide (**5a**) was successfully converted into the corresponding acyl sulfilimine **6aa** in 32% yield. A somewhat lower yield than for sulfonamide **2a** was observed alongside an increased amount of sulfoxide **4a**. In an additional study, we figured out that the combination of MeCN as a solvent with MeOH as a co-solvent for base generation was the key to successfully suppressing sulfoxide formation (Figure 3). By decreasing the quantity of MeOH, the amount of **4a** also decreased almost linearly. However, if less MeOH is used, the conversion of **1a** is less successful. It was also shown that the formation of the carbamate, as well as cathodic reduction of *N*-acylsulfilimine **6aa**, also occurs under these conditions. This issue can be

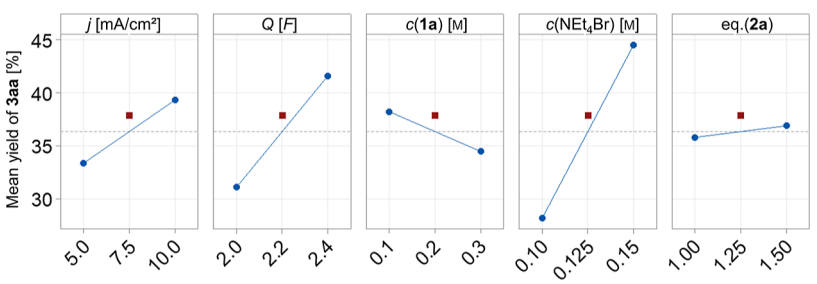


Figure 2. Mean yield of **3aa** by a single parameter impact.

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JACS Au 2023, 3, 575−583

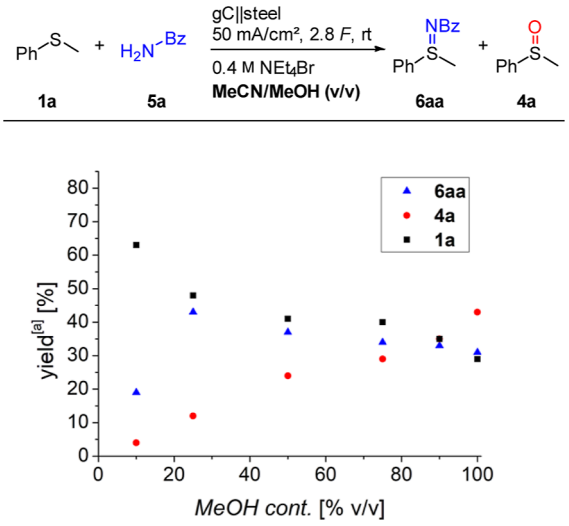

Figure 3. Impact of the MeOH content onto yield of **6aa**. (a) ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.

circumvented with the use of 1.2 equiv of amide and a Pt cathode. With this, the yield of **6aa** increased from 41 to 84% (Table S7).

Versatility and Scope

To highlight the broad applicability and versatility of the protocol, the optimized reaction conditions were used to synthesize a library of different compounds using the method applied for **6aa** as higher yields were observed at a platinum cathode (Scheme 3). Herein, we demonstrate the application onto different primary N-sources as well as low-valent sulfur compounds. As the stability of the sulfilimines is dependent on N-electron-withdrawing groups, several examples were investigated.

It was found that anodic imination is also applicable for carbamates **7**, ureas **8**, sulfamides **9**, phosphinamides **10**, and cyanamides **11** to form the corresponding sulfilimines in good to excellent yields (31−94%). Primary anilines with electron-withdrawing groups (e.g., $-NO_2$, −CN) in the para position and 5-amino-1*H*-tetrazole did not yield sulfilimines (a full list of unsuccessful substrates is given in the Supporting Information). When the imination method was applied to different low-valent S-compounds, sulfenamides and sulfenic esters resulted in the corresponding sulfinamidine **12** (84%) or sulfinimidate ester **13a** (43%), which are typically difficult to access motifs.[47−51] Surprisingly, **12** is accessible by this method, as these structures tend to form sulfinimidate ester when synthesized in alcoholic solutions. The formation of sulfinimidate ester is also observed when disulfides are used. These undergo nucleophilic substitution with an alkoxide during product formation. As the cleaved thiolates are prone to undergo fast disulfide formation under electrochemical conditions,[52] the starting material is reformed and both sulfur units can undergo product formation. Hence, only a half equivalent of disulfide was added compared to **2a**, and enhanced charge (3.1−3.4 *F*) was applied to achieve full conversion. This effective transformation of both thio motifs has not been previously reported in the literature. Sulfinimidate ester **13b** was synthesized in good yields (63%). When the methanol portion of the solvent was changed to 1,1,1-trifluoroethanol, the corresponding sulfinimidate ester **13c** also becomes accessible in excellent yields (96%). Interestingly, the intramolecular coupling of sulfonamides gave 1,3,2-benzodithiazol-3,3-dioxide **14** in an excellent yield of 95%. The conversion of 2-methylthio benzamide only led to the formation of the corresponding sulfoxide.

The reaction of thioanisoles and sulfonamides did not require a Pt cathode and mixed solvent. Comparable yields of **3aa** were observed using a less expensive stainless-steel cathode (91% instead of 94%). Hence, the formation of *N*-sulfonyl-*S*-monoarylated sulfilimines (**3aa**−**3ha** and **3ab**−**3ag**) was carried out at this cathode. A plethora of different substituted thioanisoles were successfully converted into the corresponding sulfilimines **3ba**−**fa**. Overall, electron-withdrawing groups in the *ortho* or *para* positions to the sulfide gave lower yields (**3da** + **ea**, 39, 55%) compared to electron-donating groups at those positions (**3ba** + **fa**, 81, 73%). Strongly electron-deficient phenyl 1,1,1-trifluoromethyl sulfide gave no conversion. The conversion of thioanisole bearing the oxidation-sensitive benzylic alcohol (**3ga**) was successful in yields of 83% without the need of a protecting group. A heteroaromatic and sterically demanding sulfilimine **3ha** was synthesized in moderate yields (47%). Next, several sulfonamides were investigated in synthesis with stainless-steel cathodes. Arylsulfonamides with different substitution patterns **3ab**−**ad** as well alkylsulfonamides **3af** + **ag** were converted successfully in good yields (61−86%). This process was also effective for bulky substrate **3ae** (85%).

Dialkylsulfides were converted in moderate to good yields of 35% to 58% to the corresponding sulfilimines **3ia**−**la**. If these were prepared on a stainless-steel cathode, lower yields were observed (31% instead of 59% for **3ja**). Consequently, all *S*,*S* dialkylated sulfilimines were also produced on Pt. The oxidation-prone benzylic $-CH_2$ adjacent to sulfur in **3la** remained untouched during oxidation. When 1,3-dithiane was used, monoiminated sulfilimine **3ma** was obtained in moderate yields of 34%. It was further shown that aliphatic **6ab** and synthetically valuable *N*-trifluoroacetylsulfilimine **6ac** were converted successfully into their corresponding sulfilimines. The imination procedure is less suitable for diaryl sulfides (**3na**) as this only led to poor conversion of starting materials. This is likely to be due to the intermediate's stabilization and subsequent reduction prior to imination, regardless of the type of the cathode selected. Sulfonamides bearing an easy reducible functional group such as the electron-poor iodoarene (**3ah**) undergo the reduction of the group, as evidenced by the observed deiodination. Because a broad variety of simple molecules were converted successfully, the reaction was applied to the late-stage functionalization of natural products and biologically active structures. The selected examples, *N*-acetylmethyl-L-methionate **3oa**, D-methyl biotinate **3pa**, and sulfanilamide **3ai**, were converted into their corresponding sulfilimines in moderate to excellent yields (39−99%).

Robustness and Preparative Scale

For standard conditions, it could be assumed that the traces of sulfoxide formed is predominantly due to moisture or oxygen reduction. However, when the reaction was carried out under anhydrous conditions, sulfoxide **4a** was still observed, as well as a decreased conversion of **1a** (Table 2, entry 2). Hence, it was assumed that MeOH could also serve as an oxygen source after demethylation. Neither using a Pt cathode, the method applied for less stabilized sulfilimines, nor cooling the reaction to stabilize the halo-sulfonium intermediate (Table 2, entries 3−

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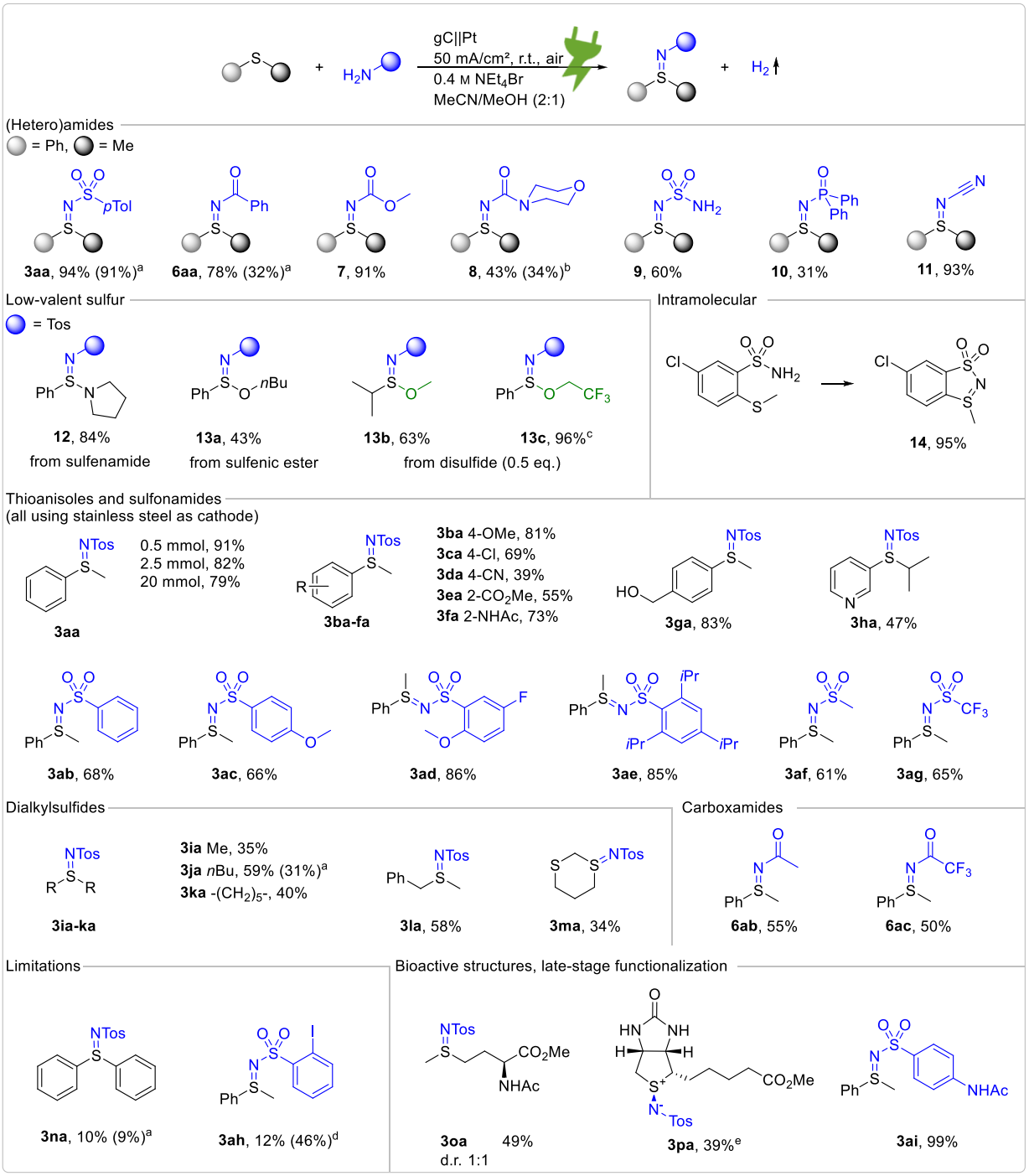
Scheme 3. Selected Scope for the Imination of Low Valent Sulfur Compounds with Various (Hetero)Amides[a]



[a]Reaction conditions: sulfur compound (0.5 mmol, 1 equiv), amide (1, or 1.2 equiv for carboxamides), Et_4NBr (4 equiv, 0.4 M), MeCN/MeOH (2:1, 5 mL) at r.t. under air. Glassy carbon anode, platinum cathode (stainless steel for thioanisoles and sulfonamides **3aa**−**ha** and **3aa**−**3ag**) at 50 mA/cm^2 for 2.6−4.0 *F*. 1 *F* corresponds to a reaction time of 10 min. Isolated yields unless otherwise noted. a. Isolated yield of sulfilimine if stainless steel was used as the cathode. b. ^{1}H NMR yield, isolated yield of sulfoximine is given in parentheses. c. 1,1,1-Trifluoroethanol instead of MeOH. d. The amount of deiodinated sulfilimine **3ab** is given in parentheses. e. Electrolysis performed at 40 °C.

5) increased the yield of **3aa** further. Excellent yields of **3aa** (96%) were achieved using a ElectraSyn 2.0, a widely used setup for preparative electrosynthesis (Table 2, entry 6). As previously stated, when no current was applied, no formation of **3aa** or **4a** was observed (Table 2, entry 7).

If bromine is used as an oxidizer instead of electricity, the yield of **3aa**, as well as the selectivity of the reaction, decreased remarkably (56%, Table 2, entry 8). The reaction of **4a** with **2a** under electrolysis conditions revealed that the reaction proceeds by oxidative imination of the sulfide, and no condensation of sulfoxide into sulfilimine is observed (Table 2, entry 9).

As only low amounts of sulfone and low starting material consumption was detected, it is conceivable that an excess of

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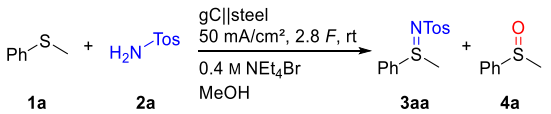
JACS Au 2023, 3, 575−583

Table 2. Additional Experiments



entry	deviation from standard conditions	3aa [%][a]	4a [%][a]
1	none	95	4
2	anhydrous conditions, inert atmosphere	84[b]	3
3	Pt as cathode	93	6
4	T = 0°C	95	5
5	MeCN/MeOH and Pt	98	trace
6	ElectraSyn, MeCN/MeOH and Pt as cathode	96	trace
7	no current	0	0
8	Br_2/NaOMe instead of electricity	56	41
9	**4a** as starting material	n.d.	94

[a]^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [b]No other side products observed, decreased conversion of **1a**. n.d.: none detected.

mediator activated in the electrolysis is reduced at the cathode. Therefore, only low concentrations of reactive species are present at all times. As indicated by screening experiments, the current density had only a low impact on the yield; this was investigated further for potential technical applications: how high can it be increased to ensure very fast reaction times (Figure 4). To enhance the temperature control, external

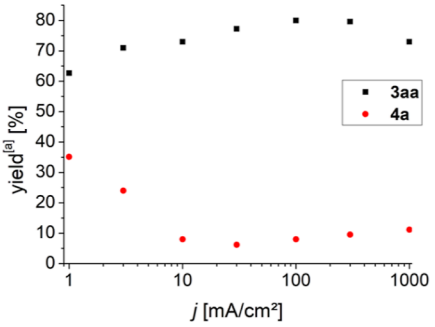


Figure 4. Impact of the current density on the yield of sulfilimine **3aa** (black) and sulfoxide **4a** (red). Electrolysis conditions: 2.5 mmol of **1a**, **2a** (1 equiv), gC||steel, 2.8 *F*, 0.4 M NEt_4Br, MeOH (25 mL). (a) ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.

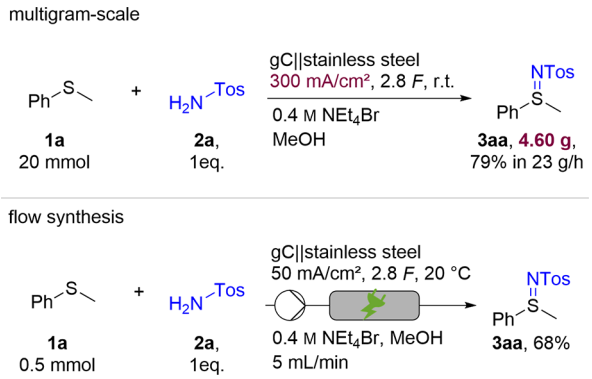
cooling of the reaction vessel was carried out on a 2.5 mmol scale in a beaker-type cell with a cooling jacket. Amazingly, **3aa** can also be synthesized at very high current densities up to 1000 mA/cm^2 and in good yields (72%).

This strongly underlines the high robustness of the imination reaction, as it is able to perform well across a broad spectrum of current density. Such conversions are of particular interest for the use of intermittent use of electricity.[53]

The product **3aa** was synthesized in an excellent yield of 80% within 7.5 g/h at 300 mA/cm^2. Current densities above 1000 mA/cm^2 were not investigated, as from that point on very high current combined with H_2 evolution led to safety issues within this simple setup.

In further scale-up to 20 mmol, in two separate experiments a yield of 4.6 g (79%) was obtained with current densities of both 50 and 300 mA/cm^2 without external cooling (Scheme 4, top). A time yield of up to 23.0 g/h was achieved in this very

Scheme 4. Synthesis of 3aa at Multigram Scale and under Flow Electrolysis Conditions

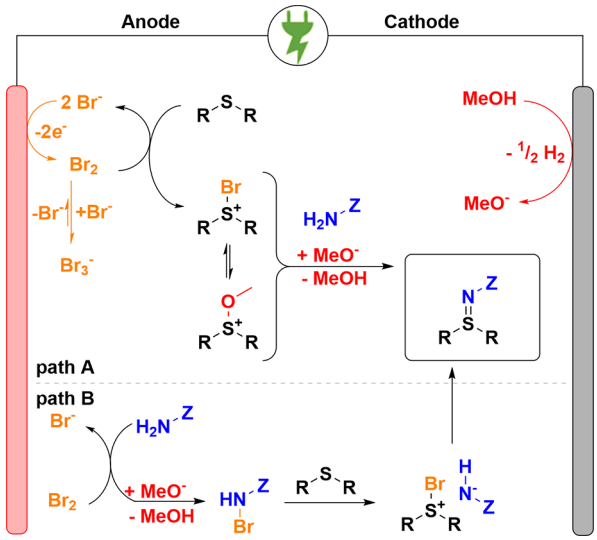


simple setup. Because of the superstoichiometric amounts of mediator used, we investigated whether or not the mediator can be recovered quantitatively. Indeed, after evaporation of the solvent an aqueous extraction of the supporting electrolyte showed quantitative recovery of NEt_4Br, which could be used in further reactions without additional purification. Thereby no significant decrease in yield or selectivity was observed. The reaction conditions have also been successfully transferred from batch to flow electrolysis cells (Scheme 4, bottom). With the narrow gap flow cell, the Ohmic resistance of the electrolyte decreased, while the surface-to-volume ratio of the electrode surface to electrolyte increased. Both led to beneficial increases in energy efficiency, also enabling scalability of process.[54,55]

Mechanistic Studies

Further investigations of the mechanism were performed, a proposed mechanism is given in Scheme 5. Cyclic voltammetry

Scheme 5. Key Aspects of the Proposed Mechanism for the Imination of Sulfides



studies show that the oxidation potentials of Br^- and **1a** are 0.8 and 1.2 V vs. ferrocene/ferrocenium, respectively. So, it was confirmed that bromide is oxidized at a lower potential than the thioanisole (**1a**). No-oxidation of amides **2a** or **5a** was observed. When 1 equiv of sulfuric acid was added, the formation of **3aa** was suppressed as the crucial deprotonation

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JACS Au 2023, 3, 575−583

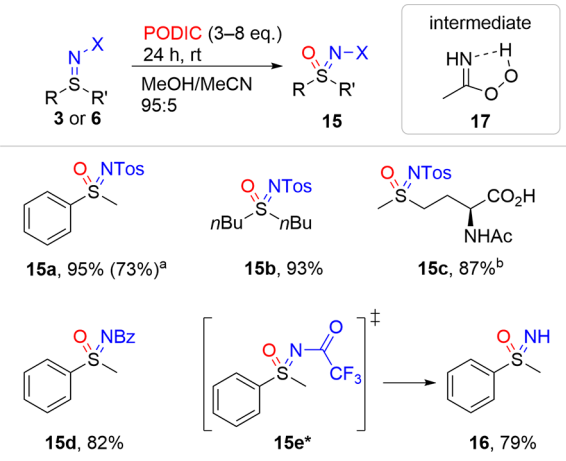
step was not possible. After initial oxidation of bromide into bromine, it is widely reported to form the tribromide anion (Br_3^-), and high concentrations of bromide favor this equilibrium.

As no orange color is observed in the course of electrolysis, it is possible that Br_3^- plays a role in the process.[56] The next step could be the bromination of the amide (path B) or the sulfide (path A). Both reaction pathways can lead to the desired product. As both the carbamate and the sulfoxide were observed as byproducts in the synthesis using carboxamides, it is likely that both paths occur as competing reactions. A more detailed mechanistic scheme is given in the Supporting Information.

Oxygenation of Sulfilimines

At the present state of research, the conversion of trivalent sulfur compounds into tetravalent compounds, such as sulfoximines, sulfondiimidamides, or sulfondiimides, is of particular interest.[51,57,58] Because almost no over-oxidation of sulfilimines to the corresponding sulfoximines was observed under these conditions, we focused on designing a novel electrochemical approach for the oxygenation of sulfilimines into valuable sulfoximines. We investigated electrochemically generated ex-cell oxygenation agents. Therefore, electrogenerated PODIC (peroxodicarbonate), a green and mild oxidizer,[59] was able to oxidize the sulfilimines in high to excellent yields with high selectivity (Scheme 6). PODIC can

Scheme 6. Synthesis of Several Sulfoximines From Sulfilimines Using PODIC[a]



[a]Isolated yields, if not stated otherwise. a. ^{1}H NMR yield referring **1a** in the two-step one-pot reaction without isolation of **3aa**. b. **3oa** as the starting material.

be easily prepared from carbonate stock solutions using BDD anodes. The preparation can be performed either in home-made electrolyzers[59] or within commercially available setups, for example, from Condias.[60]

For the oxygenation reaction, polar alcohols like MeOH and EtOH had been shown to work well as cost-efficient and sustainable solvents for this reaction. Interestingly, it was found that using a higher concentration of PODIC solution (800 mM) required less of the solution than the molar equivalent amount of a lower concentration solution (200 mM). Therefore, less of the oxidizer was required when using a more concentrated solution than lower concentration solutions. The addition of low amounts of MeCN was found to be necessary to ensure fast product formation. The formation of peroxyacetimidic acid (**17**) was the anticipated intermediate. This is well known to occur in oxygenation reactions using hydrogen peroxide.[61] It is also noteworthy to mention that under similar conditions the oxidation with hydrogen peroxide worked less efficiently (60% conversion, Table S8). The optimized reaction conditions were used to synthesize a selected scope of sulfoximines **15** from anodically formed sulfilimines (Scheme 6).

Test substrate **3aa** was converted on a 0.25 mmol scale in excellent yields into sulfoximine **15a**. It should be noted that **15a** can also be obtained without purification of **3aa** from the crude product of the electrolysis in a two-step one-pot reaction in good yields (73% ref to **1a**). Here, larger amounts of oxidants were needed to achieve full conversion of **3aa**. However, aqueous extraction of crude is necessary here because bromide ions interfere with the PODIC and prevented the conversion. The oxygenation was applicable to dialkylsulfilimines **15b** and **15c** as well as *N*-acylsulfilimines **15d**. The methylester from **3oa** is cleaved during the reaction, thereby granting access to the free acid. When **6ac** is used, the oxygenation reaction occurs rapidly, building sulfoximine **15e*** as an intermediate, followed by the in situ elimination of the trifluoroacetyl group by methanolysis, leading to very valuable NH-sulfoximine **16** in a single step in excellent yields.

CONCLUSIONS AND OUTLOOK

A simple and novel protocol for the electrochemical synthesis of sulfilimines, sulfoximines, and their analogues is described. The general imination reaction has been shown to be applicable for a very broad range of sulfur-containing moieties and (hetero)amides. Those iminated structures were easily oxygenated using a carbonate-mediated system. For both reactions, the mediators can be recovered by aqueous extraction. The inherent robustness of the reaction ensures that both the imination and the oxygenation meet all prerequisites for technical large-scale applications.

METHODS

General Protocol for Synthesis of Sulfilimines, Sulfinamidines, and Sulfinimidate Esters at Platinum Cathode

The sulfur component (0.5 mmol, 1 equiv) and (hetero-)amide (0.5 mmol, 1 equiv or 0.6 mmol, 1.2 equiv for carboxamides, respectively) were charged into an undivided cell for electrochemical screening (Figure S1). The starting materials were dissolved into 0.4 M solution of NEt_4Br in MeCN/MeOH (2:1 v/v, 5 mL). The electrodes, glassy carbon as the anode and Pt foil as the cathode, were immersed into electrolyte (electrode surface A = 1.6 cm^2) and the electrolysis was performed under constant current conditions.

If not mentioned otherwise (see the Supporting Information), after the electrolysis was finished (2.6−3.0 F), the reaction mixture was transferred into a separation funnel. Water (25 mL) was added and the mixture was extracted three times with CH_2Cl_2 (each 25 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, and crude product was purified by column chromatography.

General Protocol for Synthesis of Sulfilimines 3 at Stainless Steel Cathode

Sulfide **1** (0.5 mmol, 1 equiv) and sulfonamide **2** (0.5 mmol, 1 equiv) were charged into an undivided cell for electrochemical screening (Figure S1). The starting materials were dissolved into 0.4 M solution of NEt_4Br in MeOH (5 mL). The electrodes, glassy carbon as the anode and stainless steel as the cathode, were immersed into the

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JACS Au 2023, 3, 575−583

electrolyte (electrode surface A = 1.6 cm^2) and the electrolysis was performed under constant current conditions.

After the electrolysis was finished (2.8 F), the reaction mixture was transferred into a separation funnel. Water (25 mL) was added and the mixture was extracted three times with CH_2Cl_2 (each 25 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and crude sulfilimine was purified by crystallization or column chromatography.

General Protocol for Synthesis of Sulfoximines

The sulfilimine (0.25 mmol) was dissolved into MeOH (5 mL). MeCN (0.25 mL, 5 vol%) was added. To the stirred mixture, 820−870 mM aq. peroxodicarbonate (3−8 equiv) was added slowly. The mixture was stirred overnight, until full conversion of starting material was confirmed by TLC. Water (25 mL) and EtOAC (25 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, the solvent was removed, and the product was purified by column chromatography.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00663.

General experimental information and protocols, DoE-based optimization studies, cyclic voltammograms, list of unsuccessful substrates, characterization of compounds, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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