**Electroorganic Synthesis**

**Anodic Dehydrogenative Cyanamidation of Thioethers: Simple and Sustainable Synthesis of N-Cyanosulfilimines**

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**Abstract:** A novel and very simple to perform electrochemical approach for the synthesis of several N-cyanosulfilimines in good to excellent yields was established. This method provides access to biologically relevant sulfoximines by consecutive oxidation using electro-generated periodate. This route can be easily scaled-up to gram quantities. The S,N coupling is carried out at an inexpensive carbon anode by direct oxidation of sulfide. Therefore, the designed process is atom economic and represents a new “green route” for the synthesis of sulfilimines and sulfoximines.

Sulfilimines exhibit a strongly polarized sulfur–nitrogen moiety. Although they are often drawn with a S,N double bond, the double bond character is negligible and should be rather regarded as sulfur–nitrogen ylides (Scheme 1).[1] Due to this very specific feature, sulfilimines find practical applications, for example, as nitrene transfer agents,[2] as reagents for epoxidation or aziridination,[3] and as building blocks in the synthesis of biologically active sulfoximines.[4–6] Both sulfilimines and sulfoximines are structurally related to corresponding sulfoxides and sulfones. The substitution of oxygen by nitrogen is used to modify the binding affinity to several receptors, also generating a new bond for substitution.[5,6] Prominent examples for widely used sulfoximines are the insecticide Sulfoxaflor and the glutamine synthetase inhibitor methionine sulfoximine (Figure 1). The pronounced basicity of the nitrogen can lead to a decrease in stability of the S,N bond. Consequently, sulfilimines with N-electron withdrawing groups are of synthetic interest.[7]

Therefore, N-cyano-substituted sulfilimines exhibit unique features. They can be used as stable entities,[8] as easily cleavable precursor in the synthesis of NH-sulfoximines,[6] or the later conversion of the cyano group to, for example, heterocycles.[6,9] The commonly used synthetic approaches leading to N-cyanosulfilimines (Scheme 2) can be carried out by either

**Scheme 1.** General structure of N-cyanosulfilimines and their polarization.

**Figure 1.** Examples of biologically active sulfoximines.

**Scheme 2.** Synthetic strategies leading to N-cyanosulfilimines.
halogen-mediated oxidation of the sulfide followed by a subsequent nucleophilic displacement by cyanamide,[6,10] the in situ synthesis of a N-cyano-based nitrene,[8,11] or condensation of sulfoxides with cyanamide.[32] Although these approaches provide the target compounds in good yield, all of these conventional transformations require an external oxidant, a strong base, or dehydrating agent, generating reagent waste which lowers the atom efficiency.

In the design of economically and ecologically more reasonable processes and the avoidance of waste, electroorganic synthesis experiences a renaissance in both academic and technical synthesis.[13,14–17] The use of electrons as redox reagent offers an emerging and powerful field in synthetic organic chemistry. The avoidance of stoichiometric amounts of hazardous oxidants or reducing agents ensures that reactive and toxic intermediates are prepared exclusively in situ, providing an inherently safe reaction.[14–19] Also, due to many variable parameters in electrolysis, such as electrode material, electrolyte, current density, or the use of a mediated or direct process, electroorganic reactions are selective and could lead to products which were otherwise not accessible.[16,18–20,21]

As electroorganic synthesis is a very useful tool in the oxidation of sulfur-containing compounds,[32] there is previous work on the electrochemical synthesis of sulfinoximes. First progress was made in 2002 by Yudin and co-workers,[23] who found a way for the imination of sulfoxides using N-amino- phthalimide under potentiostatic conditions in a divided cell at a Pt anode. Very recently a synthesis of N-cyanosulfinoximes from sulfoxides was published by Wirth.[24] The reaction was carried out in an electrochemical flow set-up without supporting electrolyte. Unfortunately, HFIP as an expensive, halogenated solvent was required, only moderate yields were obtained, and interesting sulfinilimines were not accessible by their synthesis.

Based on the experience of our lab in the dehydrogenative coupling of (thio-)amides[25] and the use of cyanamide as a potent building block in electroorganic conversions,[26] we designed a novel and very simple to perform protocol for the synthesis of several N-cyano sulfinimines in good to excellent yield. Since additional strong bases and halo-based oxidizers represent the source of waste in the conventional synthetic approach we tried to omit them by direct electrolys.

Thioanisole (1a) was chosen as test substrate for the development and optimization of the electrochemical synthesis. The identification of suitable electrolysis conditions was carried out by an electrosynthetic screening technique.[20,27] For the set-up, which is also commercially available, see the Supporting Information.

First, several electrolytes consisting of protic solvents with supporting electrolytes and/or basic additives to promote the deprotonation of cyanamide or potential cationic intermediates were investigated (Table 1). The corresponding sulfoxide 3a was observed as the major by-product in this reaction. Surprisingly, almost no over-oxidation to corresponding sulfinimine, nor sulfone was observed.

Graphite as anode and Pt as cathode were the preferable electrode materials. More cost-efficient cathode materials were investigated. But even those with only slightly higher overpotential for hydrogen evolution (e.g. stainless steel or Ni) gave significantly lower yields (for detailed experimental results, see Supporting Information). A methanolic solution of NaNMe_2OAc led to the best yield of 2a in high selectivity 2a/3a. Hence, the supporting electrolyte had the most important influence on the selectivity and the yield of the target compound 2a: it was assumed that the supporting electrolyte could thus not only be used to achieve an enhanced conductivity of the solution, but that it should have an impact on the reaction by deprotonating or stabilizing intermediates.[28]

When other primary nitrogen sources than cyanamide, for example, amines, anilines, (sulfon-)amides or amidines, were investigated under the these reaction conditions (Table 1, entry 5), the sulfoxide 3a represented the dominating product. Only the sulfonamide gave traces of corresponding sulfinilimine in poor yields.

To further suppress the sulfoxide as by-product, which did mainly occur by electron-rich substrates such as p-methoxythioanisole (1b), we tested methanol as co-solvent in this reaction, since our lab succeeded with this approach in dehydrogenation coupling reactions.[29] Investigations into the more electron-rich 1b demonstrated that MeOH/McCN mixtures gave a good selectivity in the synthesis of sulfinilimine 2b compared to sulfoxide 3b. Thereby, a decrease of conversion of starting material (1b) is observed in higher ratio of McCN (Figure 2). It is noteworthy that the product formation does not happen selectively in pure or in anhydrous McCN.

Based on these facts, the electrolytic conditions were further optimized to increase the yield of 2a (for detailed experiments, see Supporting Information). First, the effects of electrochemical parameters on the outcome of current efficiency were investigated by applying the theoretical amount of charge. It was shown that the amount of MeOH only had a low impact on the yield of 2a. The yield decreased from 57% to 49% using 2 vol.% instead of 25 vol.% MeOH by a decreased conversion of starting material. However, low amounts MeOH were required to depress the amount of sulfoxide 3a, especially on more electron-rich derivatives (e.g. 2b). The yield was increased by a decrease of concentration of supporting electrolyte and an increase in current density. In

| Entry | Solvent | Supporting Electrolyte | 2a [%] | 3a [%] |
|-------|---------|------------------------|--------|--------|
| 1a    | MeOH    | 5% NaOMe               | traces | 20     |
| 2a    | HFIP    | 0.1 M NBu_4PF_6        | 11     | 52     |
| 3     | MeOH    | 0.1 M NBu_4PF_6        | 31     | 55     |
| 4     | MeOH    | 0.1 M LiClO_4          | 18     | 66     |
| 5     | MeOH    | 0.1 M NaNMe_2OAc       | 70     | 5      |
| 6     | MeOH    | 0.1 M NBuBr            | 32     | 25     |

[a] 1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b] Pt as anode.
total, a yield of 2a of 77% was obtained by the application of a theoretical amount of charge. Those optimized conditions were used to accomplish a full conversion of 1a. The maximum yield was achieved by the use of 1.5 equiv cyanamide and a relative charge of 2.8 F referring to 1a. Then an almost complete conversion of starting material was detected by TLC. A NMR yield of 99% was obtained in screening approaches. The product 2a was isolated under these conditions in 99% yield. The optimized reaction conditions were used to synthesize several derivatives (Scheme 3).

Excellent yields were obtained by the oxidation of thioanisole 2a and 4-methoxy derive 2b. The synthesis of para-halogenated sulfilimines 2c and 2d gave good yields by decreased conversion of starting material. Electron-poor substrates for, e.g., 2e and 2f gave only moderate yields. This was attributed to the enhanced oxidation potential of sulfide repressing the electron transfer to sulfide and side-reactions based on cyanamide oxidation getting more dominant. Surprisingly, for the ortho-substituted carboxylic ester 2g a good yield was achieved despite the electron-deficient nature. The carboxy group can potentially interact with thioether via a five-membered ring delivering electrons from oxygen and stabilizing oxidized sulfur species.

The dimethylated thioanisole 2h and sterically hindered sulfides like 2i were converted successfully in excellent yields. The diaryl sulfoxides 2j were all converted in high to excellent yield (2k–n). Acyclic as well as cyclic sulfides can be converted by these reactions. Even bioactive compounds, such as methionine-based sulfilimine 2o and sulfoxaflor precursor 2p, were synthesized in good yield.

The scope was limited (see Supporting Information) by acidic protons next to sulfur or by protons which were that acidic that deprotonation of MeOH at cathode was completely repressed. Also sulfides with a very high oxidation potential failed in this reaction, resulting in no conversion of sulfide.

The reaction could be simply transferred into gram-scale by using beaker-type electrolysis cells (see Supporting Information). The yield was slightly decreased from 99% at 0.5 mmol to 88% at 5-fold increase at 2.5 mmol in 25 mL beaker-type cell, and a yield of 95% was achieved for a 10 mmol scale in 100 mL beaker-type cell, achieving 1.55 g of 2a.

As the N-cyanosulfilimines play a significant role as building blocks in the synthesis of biologically relevant sulfoximines, we focused on the challenge to further oxidize them to sulfoximines. Hence, there are several protocols known in literature in the synthesis of sulfoximines from sulfilimines using oxidizers like KMnO4[30] or NaIO4.[31] We were interested if the oxidation was also applicable with the electro-generated Na3H2IO6 that we had previously reported.[32] This periodate is accessible from simple iodine sources and can be applied in the API synthesis and recovered.[33]

Indeed, initially using classic conditions for oxidation using periodate transferred to paraperiodate showed a selective product formation of sulfoximine 4a, but without complete conversion of starting material.

In a small quantitative study we were able find the optimal conditions for conversion of sulfilimines in high yield, also...
switching the solvent system from dichloromethane/water to a greener system using EtOAc/water (Scheme 4). The conversion was shown on test substrate 2a and on the biologically active substrates 2o and 2p. If the sulfoximine 4 is the compound of synthetic interest, there is not need to purify the sulfilimine after electrolysis. After an aqueous work-up and evaporation of solvent, the crude sulfilimine can be used directly in a telescoped synthesis without significant loss in yield.

For the investigation of the mechanism of sulfilimine synthesis, supportive measurements by cyclovoltammetry (CV) were carried out (see Supporting Information). It was confirmed that the sulfide 1a is oxidized in an irreversible SET (single electron transfer) to the corresponding sulfonium radical cation. The oxidation of cyanamide occurs beneath the oxidation of the sulfide. By oxidizing 1a in presence of cyanamide, the oxidation of sulfide is mainly observed. The oxidation of acetate to an acetoxyl radical is an irreversible oxidation occurring at similar potential as sulfide 1a. More electron-deficient thioanisoles or dialkylsulfides have higher oxidation potentials than the acetate. For those sulfides, the oxidation of acetate can serve as mediator for the generation of sulfonium radicals. These CV studies led to the conclusion that the reaction is carried by a SET from sulfide 1a, followed by nucleophilic addition of cyanamide. A postulated mechanism is given in Scheme 5.

The mechanism is fully in line with the observation that the oxidation can be carried out even with neutral and inert supporting electrolytes (Table 1). The sulfoxide represents also the by-product, which turns into the main product upon addition of an acid to the electrolyte (Table 2, entry 2). Using HNEt3OAc as acetate source remarkably decreased the product formation by low conversion of starting material (Table 2, entry 3). Without cyanamide the sulfoxide 3a is the only observed product in this reaction (Table 2, entry 4) and there is no product formation without the application of current (Table 2, entry 5).

To prove the selectivity of this reaction towards the conversion of sulfides competing with sulfoxides, dimethylsulfoxide-\textsubscript{d6} (3k-\textsubscript{d6}) were converted simultaneously with the cyanamide.

HPLC/MS indicated the formation of the sulfilimine 2k without any formation the deuterated sulfilimine 2k-\textsubscript{d6}. Neither the formation of the non-deuterated sulfoximine 4k nor that of the deuterated sulfoximine 4k-\textsubscript{d6} was detected.

In conclusion, we were able to design a novel and easy protocol for the synthesis of several new and well-known N-cyanosulfilimes. The reaction is carried out by a direct electrochemical oxidation of a readily available sulfide at a carbon electrode. Neither an additional strong base for deprotonation of cyanamide nor any external oxidant is required. As cathodic reaction, hydrogen is generated as a useful and harmless technical by-product. Therefore, this reaction only uses inexpensive reagents by a low waste generation, which makes it a new chemical pathway in the synthesis of a manifold of sulfilimines, and which offers a greener option in synthesis by prevention of reagent waste.
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Conflict of Interest

The authors declare no conflict of interest.

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