How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 23197–23201
International Edition: doi.org/10.1002/anie.202109033
German Edition: doi.org/10.1002/ange.202109033

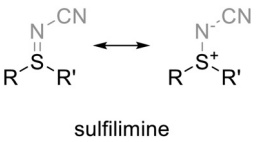
Electroorganic Synthesis

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

*Martin Klein and Siegfried R. Waldvogel**

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 of 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]



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

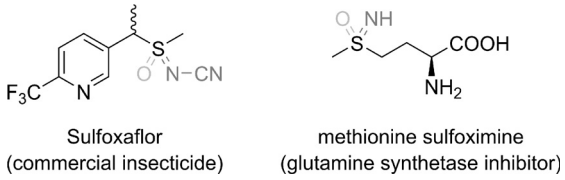
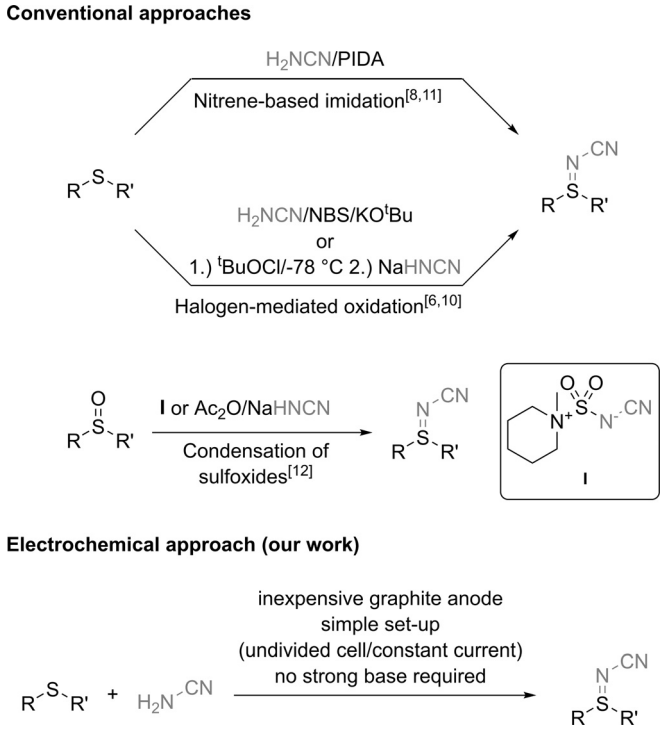


Figure 1. Examples of biologically active sulfoximines.

Therefore, *N*-cyano-substituted sulfilimines exhibit unique features. They can be used as stable entities,[5] as easily cleavable precursor in the synthesis of NH-sulfoximines,[6] or the later conversion of the cyano group to, for example, heterocycles.[8,9]

The commonly used synthetic approaches leading to *N*-cyanosulfilimines (Scheme 2) can be carried out by either



Scheme 2. Synthetic strategies leading to *N*-cyanosulfilimines.

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Supporting information (experimental methods) and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.202109033.

halogen-mediated oxidation of the sulfide followed by a subsequent nucloephilic displacement by cyanamide,[6,10] the in situ synthesis of a *N*-cyano-based nitrene,[8,11] or condensation of sulfoxides with cyanamide.[12] 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 electrosynthesis, 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,[22] there is previous work on the electrochemical synthesis of sulfoximines. First progress was made in 2002 by Yudin and co-workers,[23] who found a way for the imination of sulfoxides using *N*-aminophtalimide under potentiostatic conditions in a divided cell at a Pt anode. Very recently a synthesis of *N*-cyanosulfoximes 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 sulfilimines were not accessible by their synthesis.

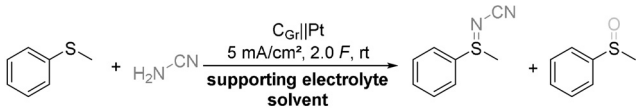
Based on the experience of our lab in the dehydrogenative coupling of (thio-)amides[25] and the use of cyanamide as a potent building block in electroorganic conversions,[26] we designed a novel and very simple to perform protocol for the synthesis of several *N*-cyanosulfilimines in good to excellent 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 electrosynthesis.

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 sulfoximine, 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 NMe_4OAc 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]

Table 1: Initial investigations of the electrolyte system.



1a, 0.5 mmol 1.5 eq. **2a** **3a**

Entry	Solvent	Supporting electrolyte	**2a**[a] [%]	**3a**[a] [%]
1[b]	MeOH	5% NaOMe	traces	20
2[b]	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 NMe_4OAc**	**70**	**5**
6	MeOH	0.1 M NBu_4Br	32	25

[a] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b] Pt as anode.

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 sulfilimine 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/MeCN mixtures gave a good selectivity in the synthesis of sulfilimine **2b** compared to sulfoxide **3b**. Thereby, a decrease of conversion of starting material (**1b**) is observed in higher ratio of MeCN (Figure 2). It is noteworthy that the product formation does not happen selectively in pure or in anhydrous MeCN.

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

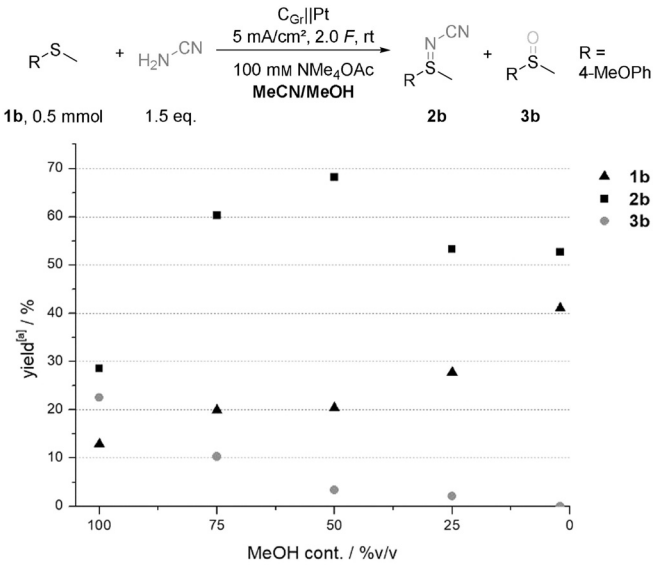


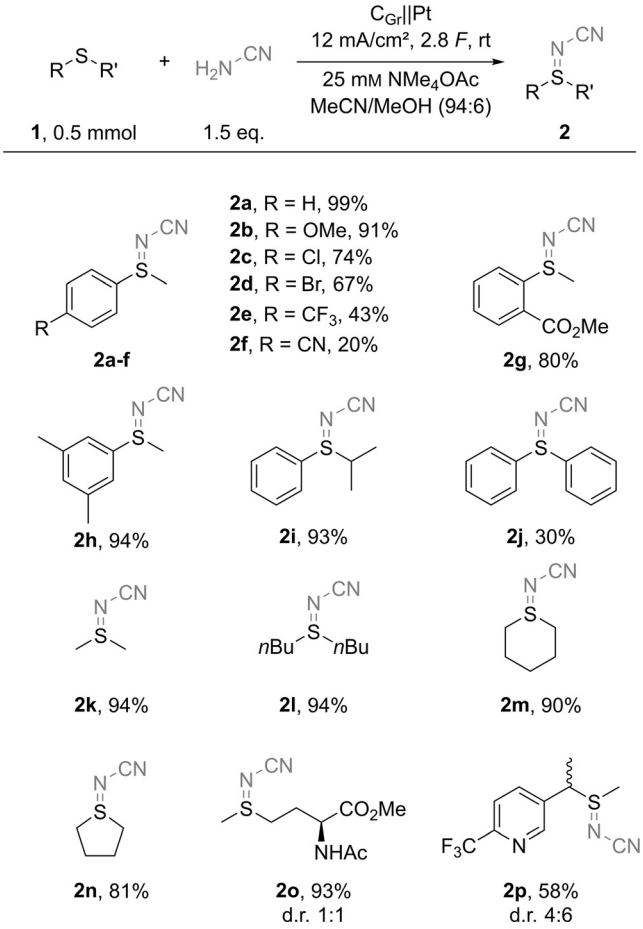
Figure 2. Impact of the MeOH content on the yield of sulfilimine **2b** (square), sulfoxide **3b** (circle), and the conversion of **1b** (triangle). [a] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

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 derivate **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 sucsessfully in excellent yields. The diaryl derivate **2j** gave only low yields of corresponding sulfilimine. The dialkylsulfides 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 MeOH at cathode was completely



Scheme 3. Selected scope for the synthesis of *N*-cyanosulfilimines.

repressed. Also sulfides with a very high oxidation potential failed in this reaction, resulting in no conversion of sulfide.

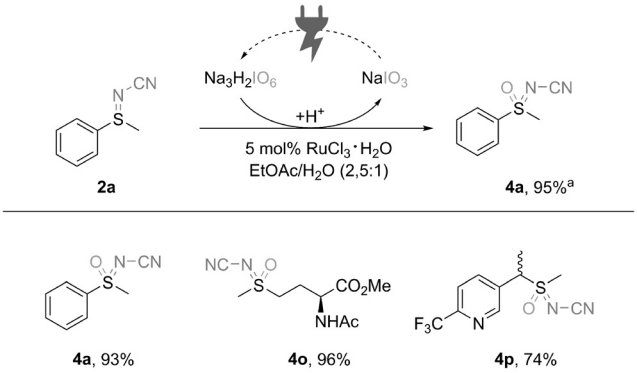
The reaction could be simply transferred into gram-scale by using beaker-type electrolysis cells (see Supporting Information). The yield was slightly decreased from 99% at 0.5 mmol to 88% at 5-fold increase at 2.5 mmol in 25 mL beaker-type cell, and a yield of 95% was achieved for a 10 mmol scale in 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 $KMnO_4$[30] or $NaIO_4$.[31] We were interested if the oxidation was also applicable with the electro-generated $Na_3H_2IO_6$ 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.

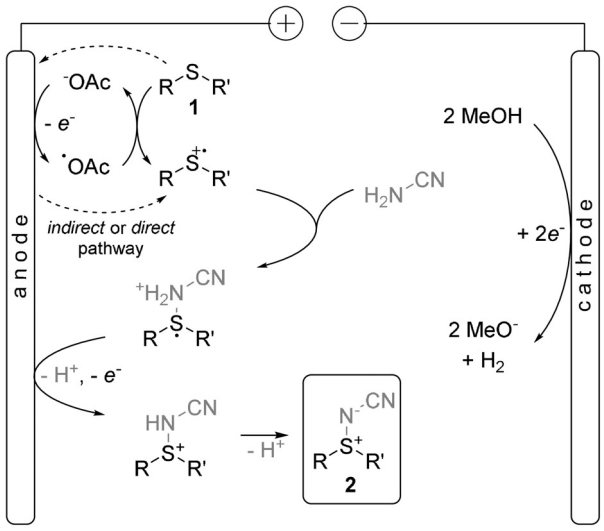


Scheme 4. Oxidation of *N*-cyanosulfilimines to corresponding sulfoximines. [a] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

For the investigation of the mechanism of sulfilimine synthesis, supportive measurements by cyclovoltammography (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.

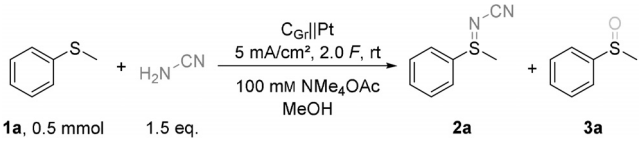
The mechanism is fully in line with the observation that the oxidation can be carried out even with neutral and inert supporting electrolytes (Table 1). The sulfoxide represents also the by-product, which turns into the main product upon addition of an acid to the electrolyte (Table 2, entry 2). Using $HNEt_3OAc$ 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, dimethylsulfide (**1k**) and dimethylsulfoxide-d_6 (**3k**-d_6) were converted simultaneously with the cyanamide.



Scheme 5. Postulated mechanism.

Table 2: Control experiments.



entry	Deviation from standard conditions	**2a**[a] [%]	**3a**[a] [%]
1	None	70	1
2	Add. 0.5% H_2SO_4	0	67
3	100 mM $HNEt_3OAc$	22	3
4	No cyanamide	0	58
5	No current	0	0

[a] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

HPLC/MS indicated the formation of the sulfilimine **2k** without any formation the deuterated sulfilimine **2k**-d_6. Neither the formation of the non-deuterated sulfoximine **4k** nor that of the deuterated sulfoximine **4k**-d_6 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.

Acknowledgements

Financial support by Deutsche Forschungsgemeinschaft (Wa1276/17-2) is highly appreciated. Donation of cyanamide by AlzChem/Trostberg was very helpful. Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: dehydrogenative coupling · electrochemistry · green chemistry · oxidative imidation · sulfilimines

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Manuscript received: July 7, 2021
Revised manuscript received: August 8, 2021
Accepted manuscript online: August 18, 2021
Version of record online: September 22, 2021

