

# Dehydrogenative Imination of Low-Valent Sulfur Compounds – Fast and Scalable Synthesis of Sulfilimines, Sulfinamidines, and Sulfinimide Esters

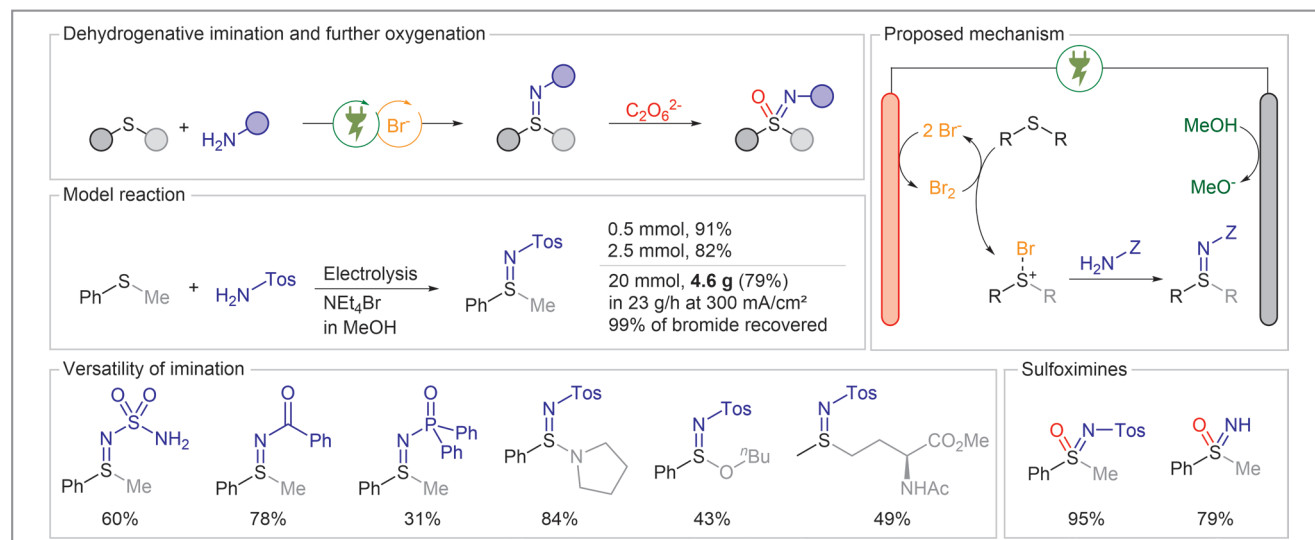
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Sulfur-containing functional groups are of utmost importance in medicinal chemistry. This is due to their structural diversity as well as their frequent natural occurrence. The pharmaceutical landscape of trivalent sulfur species is dominated by sulfoxides, sulfinates, and sulfinamides. The use of other potential candidates in drug discovery, such as sulfilimines, sulfinimide esters, and sulfinamidines, is an underexplored topic. This is mainly due to the lack of protocols for the preparation of these classes of compounds, which are often converted into their corresponding tetravalent siblings – such as sulfoximines – which are of high value for medicinal chemistry applications.

The Waldvogel research group at the Johannes Gutenberg University Mainz (Germany) has extensive expertise in electro-organic transformations. Professor Waldvogel explained: “This technique is often regarded as one of the most promising 21<sup>st</sup> century methods for avoiding the use of hazardous and waste-producing oxidants or reducing agents. Consequently, it is experiencing a renaissance in academic and technical synthesis. The use of low-cost electric power is a sustainable force to gently drive redox reactions.” He continued: “The importance of specialized sulfur-based functional

groups, together with the expertise in electro-organic transformations, led us to investigate new methods for preparing these valuable compounds.”

In the literature, halide-assisted oxidation of thioethers in the presence of strong bases is described as a general approach for this transformation. To avoid the handling of these toxic and corrosive reagents, the group investigated halide-mediated electrochemical oxidation using easy-to-handle and common salts. “This can be combined with the formation of electrochemically generated bases at the cathode,” said Professor Waldvogel. He continued: “We investigated this hypothesis using thioanisole and *p*-toluenesulfonamide as test substrates. Indeed, selective formation of the sulfilimine was observed when bromide was used as the mediator and MeOH as the base. In addition, bromide and MeOH also served as supporting electrolyte and solvent, which allowed for an extremely efficient use of the reactants.” The group used a modern Design of Experiments (DoE)-based optimization strategy to increase the product yield and to study the critical parameters of this transformation. This allowed a rapid evaluation of the process and resulted in a product yield of 91%. “We adapted the method slightly to make it applicable



**Scheme 1** Summary of results for the dehydrogenative imination of low-valent sulfur compounds

to less stabilized sulfilimines, such as the benzamide-derived substrates, which gave only moderate yields with the previous method,” remarked Professor Waldvogel, who went on: “Using these two approaches, we were able to synthesize a variety of different sulfilimines, sulfinamides, and sulfinamidate esters. Numerous amides as well as various low-valent sulfur compounds were converted into the corresponding sulfur-nitrogen compounds. We were able to show that the developed method has a high robustness. It can be operated at many current densities from 1 to 1000 mA/cm<sup>2</sup>. It can be scaled to several grams with very short reaction times, which represents a powerful method for technical development. A transfer of the reaction to a flow cell has also been successful.”

In further studies, the group investigated the reaction mechanism and were able to prove that their hypotheses were correct. The bromide was oxidized at the anode, forming an electrophilic bromonium species that reacts with the starting materials. Depending on the nature of the nucleophile, it reacts with either the sulfur compound or the amide. Both lead to the formation of the desired compound, but with different by-products.

Professor Waldvogel said: “Finally, we wanted to develop a new method to convert the formed sulfilimines into highly pharmaceutically relevant sulfoximines. Since no overoxidation was observed during electrolysis, we focused on the use of electrochemically generated oxidants in this project. The use of peroxodicarbonate, prepared by oxidation of carbonate stock solutions on boron-doped diamond (BDD) electrodes, allowed very selective oxidation with excellent yields. Acetonitrile plays a crucial role in this process for efficient oxygen transfer.”

Professor Waldvogel concluded: “In summary, the group has developed a new protocol for the electrochemical synthesis of several trivalent sulfur-nitrogen compounds such as sulfilimines, sulfinamidines, and sulfinimidate esters. These were converted into highly valuable sulfoximines using a carbonate-mediated system. A modular process for the preparation of such pharmaceutically relevant compounds is described. The mediator for imination can be recovered quantitatively by aqueous extraction. Combined with the high robustness of the method, this leads to a high potential for use as a sustainable technical synthesis. Electrochemistry is becoming an increasingly powerful technique in organic synthesis. Its application, with few exceptions, is limited to small-scale synthesis in academia. General approaches to transfer these methods to large-scale industrial production and to electrify technical organic synthesis need to be explored to unlock the great potential of this sustainable method.”

*Mattias Farnik*

## About the authors



*Dr. M. Klein*

**Martin Klein** studied biomedical chemistry in Mainz, Germany. He received his BSc at the Johannes Gutenberg University (Germany) in 2017 and his MSc in the group of Prof. Waldvogel in 2019, focusing on electrochemical hydrogenations. He did his PhD in the field of electro-organic synthesis until 2023 and is currently working as a postdoc at the Merck group in Darmstadt (Germany) on sustainable synthesis in process development.



*D. Troglauer*

**David Troglauer** received his BSc under the supervision of Prof. Waldvogel at Johannes Gutenberg University (Germany) in 2021 where he focused on the electrochemical synthesis of *N*-sulfilimines. In 2022, he joined the group of Prof. Streb to continue his graduate studies.



*Prof. S. Waldvogel*

**Siegfried R. Waldvogel** studied chemistry in Konstanz (Germany) and received his PhD in 1996 from University of Bochum/Max Planck Institute for Coal Research (Germany) with Prof. M. T. Reetz. After postdoctoral research in La Jolla, CA (USA) with Prof. J. Rebeck, Jr., he started his own research at the Universities of Münster and Bonn (Germany). He became full professor at JGU Mainz (Germany) in 2010.

His research interests are novel electro-organic transformations including bio-based feedstocks. In 2018, he cofounded ESy-Labs GmbH, which provides custom electrosynthesis and contract R&D.