Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride

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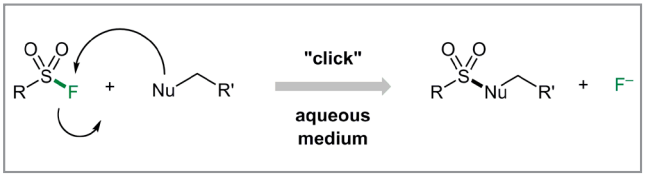
Sulfonyl fluorides are emerging as important reagents in chemical biology, owing to their capacity to undergo 'click'-type reactions – i.e. Sulfur(VI) Fluoride Exchange (SuFEx) (Scheme 1) – with nucleophilic functions of biopolymers, such as peptides and proteins, in water or aqueous media.[1]



Scheme 1 The Sulfur(VI) Fluoride Exchange (SuFEx) reaction

The group of Dr. Timothy Noël at the Eindhoven University of Technology (The Netherlands) was carrying out investigations towards the development of an electrochemical synthesis of sulfonamides[2] and found that, using an electrolyte with BF_4 counterion, traces of the sulfonyl fluoride product were observed in the GC-MS (Scheme 2). One of the two first authors, Gabriele Laudadio, remarked: "This observation gave us the confidence that by tweaking the sulfonamide reaction conditions, we probably could steer product formation selectively to sulfonyl fluoride."

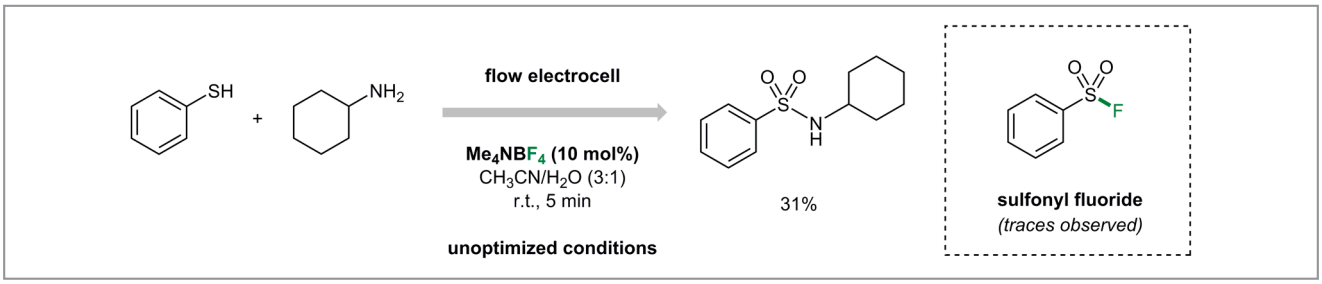
Dr. Noël, who was obviously aware of the importance of sulfonyl fluorides, especially within the realm of SuFEx click chemistry – the use of which is curbed by the fact that most methods for their preparation are rather cumbersome[1] – said: "As soon as Gabriele told me about the formation of the sulfonyl fluoride as a trace byproduct, I became really excited. In view of how important sulfonyl fluorides are for SuFEx click chemistry and the need for a simple way to prepare them, we decided that this project was a priority in our group." At that point, Aloisio de Andrade Bartolomeu, a visiting PhD student from the de Oliveira group at the Universidade Federal de São Carlos (Brazil), joined the group for a year and Dr. Noël decided he should join the sulfonyl fluoride team.

Aloisio, who is co-first author of the published paper, recalled: "When Tim asked me to join the sulfonyl fluoride team I was both excited and cautious, as I had no experience with electrochemistry. But upon seeing the interesting proof-of-concept results, I did not hesitate a single moment and I grabbed this opportunity with both hands."

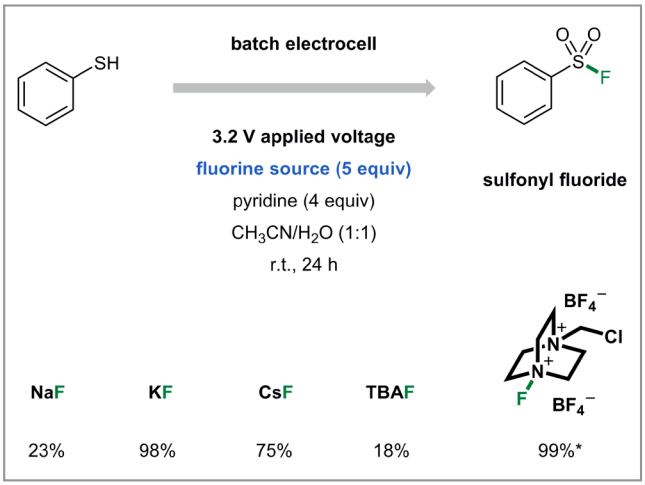
Aloisio set to work with Gabriele and the pair rapidly found that potassium fluoride was the most convenient 'F' source (Scheme 3). Gabriele remarked: "This was an important finding as KF is an inexpensive, abundantly available and safe fluoride source. We found that we had to add about 5 equivalents of KF to obtain optimal results. Most of the fluoride was, however, used as a cheap supporting electrolyte."

Once the optimal reaction conditions had been obtained, Gabriele and Aloisio set out to explore the scope of the method with various aromatic and aliphatic thiols (Scheme 4). Aloisio said: "Mostly, we obtained good to high yields. Some volatile sulfonyl fluorides were more challenging to isolate but we converted those immediately into the corresponding and heavier sulfonate through reaction with phenol."

Dr. Noël remarked: "During the substrate scope activities, we carried out several mechanistic experiments in parallel.



Scheme 2 Traces of sulfonyl fluoride observed in the electrochemical synthesis of sulfonamide

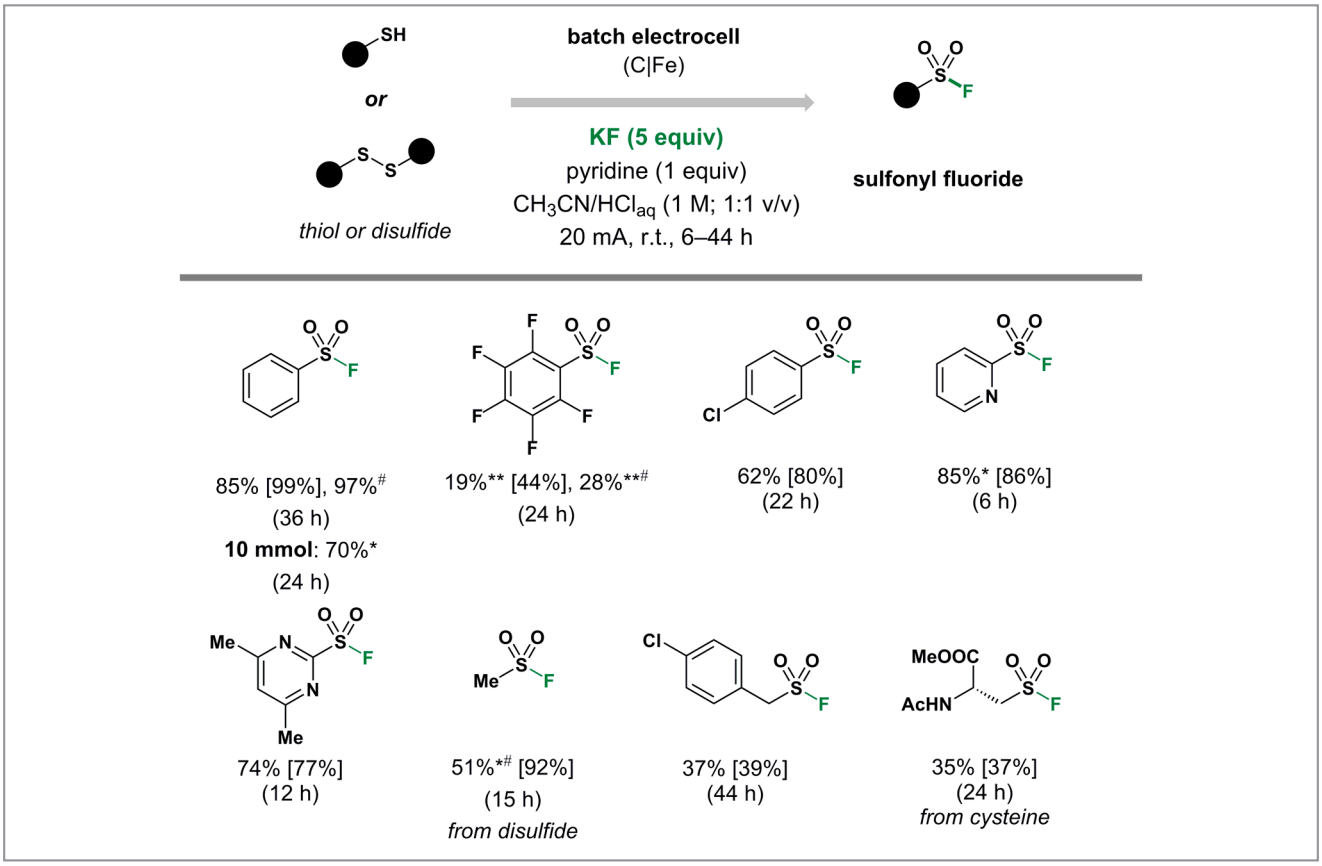


Scheme 3 Different fluorine sources tested in the electrochemical methodology. * 1.5 equiv of Selectfluor.

Kinetic experiments revealed that the thiol is quite rapidly converted into the corresponding disulfide. This observation opens up opportunities to use disulfides directly as less-smelly substrates."

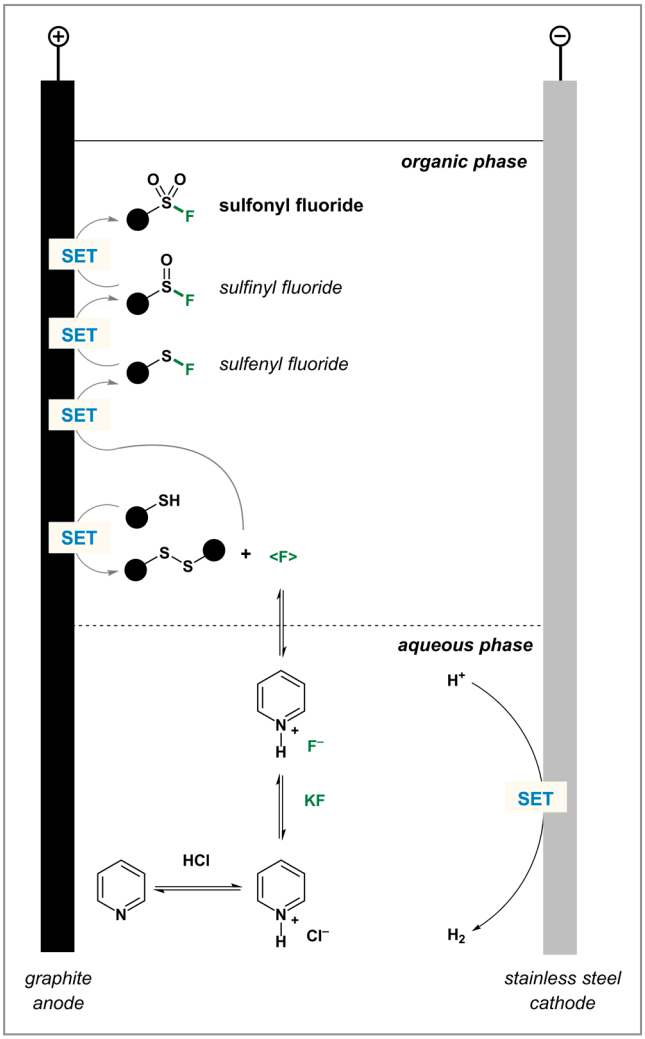
In these kinetic experiments, a pseudo zeroth order was observed for the formation of the sulfonyl fluoride, which indicates the presence of mass-transfer limitations in the batch experiments. Gabriele commented: "Using a continuous-flow reactor with a 250 µm interelectrode gap, we could accelerate the reaction from more than six hours in batch to only five minutes in flow." Aloisio added: "The disulfide is subsequently fluorinated and undergoes a double anodic oxidation towards the corresponding sulfonyl fluoride (Scheme 5)."

Dr. Noël concluded: "The advantage of this method is that it only uses simple starting materials, such as thiols or disulfides and KF, and does not require additional oxidants or catalysts. Meanwhile we are working on some other electrochemical methods, which display some synthetic advantages

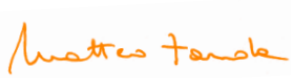


Scheme 4 Selection of sulfonyl fluorides obtained with the electrochemical methodology. Yields between [brackets] are those referring to ^{19}F NMR yields calculated with $PhCF_3$ as internal standard. * 3.2 V applied potential. ** 4.0 V applied potential. # Isolated as phenyl sulfonate derivative through reaction with phenol.

over other established approaches. While there are similarities with photoredox catalysis, we have found in our work that electrochemistry provides unique synthetic opportunities and often uses extremely simple reaction conditions."



Scheme 5 Plausible mechanism



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About the authors

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Gabriele Laudadio was born in 1991 near Pescara, Italy. In 2016 he received his M.Sc. degree in organic chemistry at the University of Pisa (Italy). His Master's thesis was conducted under the supervision of Professor A. Carpita. He is currently a Ph.D. student at Eindhoven University of Technology (The Netherlands) in the group of Dr. Timothy Noël. His research interests focus on novel synthetic methodologies combining continuous-flow microreactor technology with electrochemistry and photochemistry.

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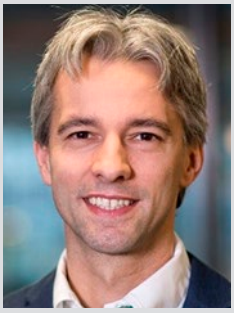
Aloisio de Andrade Bartolomeu, born 1982 in Cabrália Paulista (Brazil), received his B.Sc. degree in chemistry from UNESP (São Paulo State University, Brazil) in 2012. In 2015, he obtained his M.Sc. degree in science and technology of materials from the same university under the supervision of Prof. Luiz Carlos da Silva Filho. Currently, he is a Ph.D. student at UFSCar (Federal University of São Carlos, Brazil), under the supervision of Prof. Kleber Thiago de Oliveira, and is a visiting Ph.D. student with a FAPESP fellowship at the Eindhoven University of Technology (The Netherlands), under the supervision of Associate Professor Timothy Noël. His current research interests are photocatalysis and electrocatalysis.



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Timothy Noël currently holds a position as Associate Professor at Eindhoven University of Technology (The Netherlands). His research interests range from organic chemistry to chemical engineering and encompasses more specifically flow chemistry, organic synthesis and synthetic catalytic methodology development. His work has been recognized with several awards, including most recently the VIDI award (2015), the Thieme Chemistry Journals Award (2016) and the DECHEMA prize (2017).