



Accelerating sulfonyl fluoride synthesis through electrochemical oxidative coupling of thiols and potassium fluoride in flow

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Abstract

Sulfonyl fluorides are valuable synthetic motifs which are currently of high interest due to the popularity of the sulfur (VI) fluoride exchange (SuFEx) click chemistry concept. Herein, we describe a flow chemistry approach to enable their synthesis through an electrochemical oxidative coupling of thiols and potassium fluoride. The reaction can be carried out at room temperature and atmospheric pressure and the yield of the targeted sulfonyl fluoride, by virtue of the short inter-electrode distance between a graphite anode and a stainless-steel cathode, reached up to 92% in only 5 min residence time compared to 6 to 36 h in batch. A diverse set of thiols (7 examples) was subsequently converted in flow. Finally, a fully telescoped process was developed which combines the electrochemical sulfonyl fluoride synthesis with a follow-up SuFEx reaction.

Keywords Electrochemistry · Click chemistry · SuFEx · Sulfonyl fluoride · Flow chemistry

Introduction

Click chemistry is a popular synthetic concept which enables the quick and reliable stitching of two molecular building blocks in high yield and selectivity. The concept has been coined by K.B. Sharpless [1] and has been widely employed in drug discovery [2], chemical biology, and material science as it is amenable to high-throughput experimentation. In general, click chemistry is a collection of synthetic methods that are high yielding, fast, easy to perform and produce little to no byproducts. One of the most popular click reactions is the Cu(I)-catalyzed azide-alkyne cycloaddition which yields triazoles [3]. More recently, a new click reaction was developed by Sharpless and coworkers, i.e. sulfur (VI) fluoride

exchange (SuFEx) which employs sulfonyl fluorides as stable and robust reagents [4].

Key to the success of the click chemistry concept is the access to a broad array of structurally diverse click reagents in large quantities [5]. It is general belief that flow chemistry can be particularly helpful in realizing this objective. As an example, the synthesis of azides has been reported by many research groups and has been successfully coupled with the follow-up Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) [6–10]. The combination of these two steps leads to a significant time reduction and keeps the total inventory of hazardous azides low, thus effectively reducing the safety risks associated with these reagents [11]. Moreover, the use of superheated reaction conditions in combination with copper-based capillaries allows to further reduce the reaction time effectively [12]. Removal of the homogeneous Cu(I)-catalyst can also be achieved in flow leading to almost pure triazole compounds, which meet the stringent product purity requirements needed in the pharmaceutical industry [13, 14].

While the CuAAC has served as a benchmark reaction for flow chemistry in the past two decades, SuFEx has received much less scrutiny. Recently, our group developed an electrochemical approach to access the key sulfonyl fluoride starting materials [15]. The method involves an anodic oxidation process and uses widely available thiols or disulfides and KF as a cheap, safe and widely available fluorine source. Biphasic

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Scheme 1 Electrochemical oxidative coupling of thiophenol and KF in flow as a benchmark reaction. The reaction conditions displayed are the optimized parameters

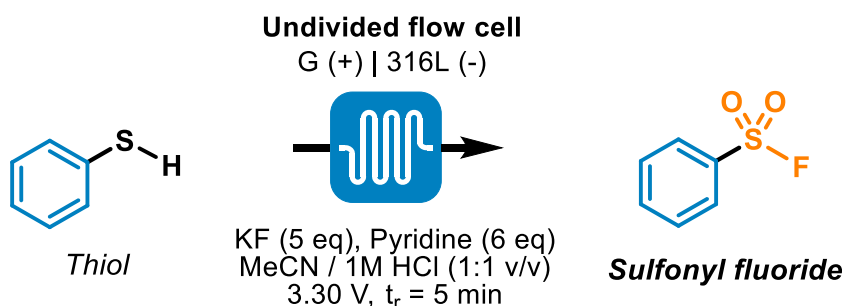
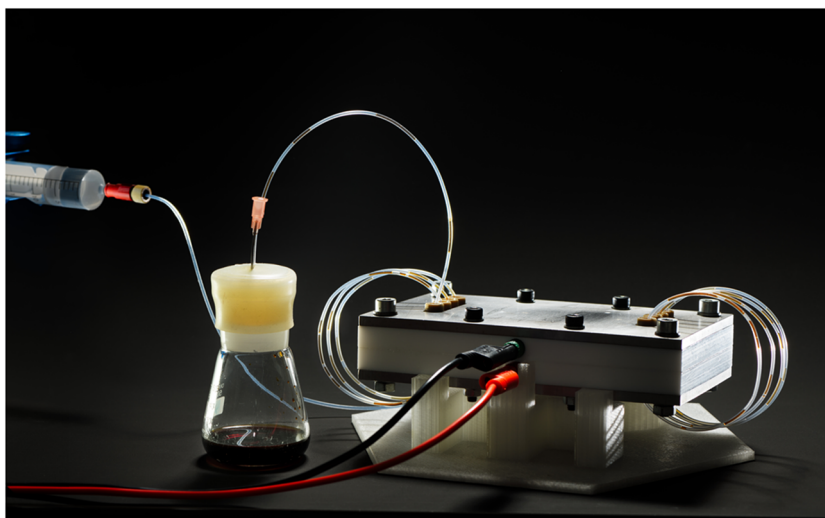


Fig. 1 Electrochemical flow reactor used for the multiphase sulfonyl fluoride synthesis through oxidative coupling of thiols and potassium fluoride (Courtesy of Bart van Overbeeke/ TU Eindhoven)



reaction conditions (acetonitrile/1 M HCl) are required and the reaction was carried out in batch. However, preliminary studies showed that the use of flow chemistry was of great benefit [16–20]. The reaction time could be reduced to the minute range in flow and no mass transfer limitations were observed. The reduced reaction time can be attributed to (i) the increased electrode surface-to-volume ratio, (ii) a high interfacial area between the organic and aqueous phase, and (iii) intensified mass transport due to multiphase fluid patterns.

In this manuscript, we provide a full investigation of all relevant process parameters in the flow-enabled

Table 1 Evaluation of different cathode materials in the electrochemical sulfonyl fluoride synthesis in flow

Entry	Counter electrode (cathode)	Yield (%) ^b
1	Stainless steel	92
2	Copper	38
3	Graphite	55
4	Nickel	46

[a] Reaction conditions: 0.1 M thiophenol, 0.6 M pyridine, 0.5 M KF, 3.30 V, 1 M HCl/CH₃CN (1:1 v/v), total flow rate 150 μ L/min, residence time 5 min, graphite anode. [b] GC-yield using GC-FID using an internal standard calibration method (biphenyl)

electrochemical oxidative coupling of thiols and fluoride yielding sulfonyl fluorides. Moreover, we have for the first time coupled the sulfonyl fluoride synthesis with a subsequent SuFEx click reaction in flow, which represents a particularly useful strategy to handle the most volatile sulfonyl fluoride reagents.

Table 2 Influence of the solvent system on the electrochemical sulfonyl fluoride synthesis in flow

Entry	Aqueous solvent	Organic solvent	Yield (%) ^b
1	H ₂ O	CH ₃ CN	78
2	0.5 M H ₂ SO ₄	CH ₃ CN	–
3	0.6 M HCl	CH ₃ CN	81
4	0.8 M HCl	CH ₃ CN	84
5	1.0 M HCl	CH₃CN	92
6	1.0 M HCl	THF	39
7	1.0 M HCl	CH ₃ OH	33
8	1.2 M HCl	CH ₃ CN	62
9	1.4 M HCl	CH ₃ CN	50

[a] Reaction conditions: 0.1 M thiophenol, 0.6 M pyridine, 0.5 M KF, 3.30 V, inorganic solvent/organic solvent (1:1 v/v), total flow rate 150 μ L/min, residence time 5 min, graphite anode and stainless steel cathode [b] GC-yield using GC-FID with internal standard (biphenyl)

Table 3 Amount of fluoride needed for the electrochemical sulfonyl fluoride synthesis in flow

Entry	Fluoride source	Yield (%) ^b
1	0.1 M KF	23
2	0.3 M KF	71
3	0.5 M KF	92
4	0.5 M NaF	–
5	0.5 M CsF	67
6	0.7 M KF	65
7	0.9 M KF	54

[a] Reaction conditions: 0.1 M thiophenol, 0.6 M pyridine, 3.30 V, 1 M HCl/CH₃CN (1:1 v/v), total flow rate 150 μL/min, residence time 5 min, graphite anode and stainless steel cathode. [b] GC-yield using GC-FID with internal standard (biphenyl)

Results and discussion

Initial experiments were carried out with thiophenol as the benchmark substrate and KF as the fluoride source (Scheme 1). It should be noted that all experiments described in this paper are carried out in a home-built electrochemical flow reactor (Fig. 1) [21]. At the cathode, hydrogen is generated as a benign and high value byproduct. In such a scenario, electrodes with a low hydrogen overpotential are typically preferred, e.g. platinum, copper or stainless steel [22]. From our previous experiments in batch, we found that a graphite anode and a stainless steel cathode worked optimal and this proved to be also the case in our flow experiments (Table 1, Entry 1). Other electrode materials as cathode, such as copper, graphite or nickel, did not lead to any improvement (Table 1, Entries 2–4).

Next, we investigated the influence of the solvent system (Table 2). As the organic phase, acetonitrile was selected as

Table 4 Importance of the Phase Transfer Catalyst in the electrochemical sulfonyl fluoride synthesis in flow

Entry	Phase Transfer Catalyst	Yield (%) ^b
1	0.1 M pyridine	60
2	0.2 M pyridine	67
3	0.3 M pyridine	78
4	0.4 M pyridine	83
5	0.5 M pyridine	87
6	0.6 M pyridine	92
7	0.6 M n-Bu ₄ NBr	35
8	0.6 M n-Bu ₄ NCl	66
9	0.7 M pyridine	91
10	0.8 M pyridine	85

[a] Reaction conditions: 0.1 M thiophenol, 0.5 M KF, 3.30 V, 1 M HCl/CH₃CN (1:1 v/v), total flow rate 150 μL/min, residence time 5 min, graphite anode and stainless steel cathode. [b] GC-yield using GC-FID with internal standard (biphenyl)

the optimal solvent. Lower yields for the target product were obtained in other common organic solvents, such as THF or methanol (Table 2, Entries 6–7). The presence of acid provided in general higher yields compared to non-acidic reaction mixtures (Table 2, Entry 1). However, the presence of sulfuric acid proved to be detrimental for the reaction as no product formation was observed (Table 2, Entry 2).

Next, we investigated the influence of the fluoride source on the reaction outcome (Table 3). As shown in our previous work [15], the reaction worked well with alkali fluorides but also with Selectfluor. The use of Selectfluor was not further considered due to low atom efficiency and its higher price compared to alkali fluorides. The reaction worked best with 5 equivalents of KF (Table 3, Entry 4). While only one equivalent is needed for the reaction, the remaining 4 equivalents served as a cheap supporting electrolyte. Increasing the

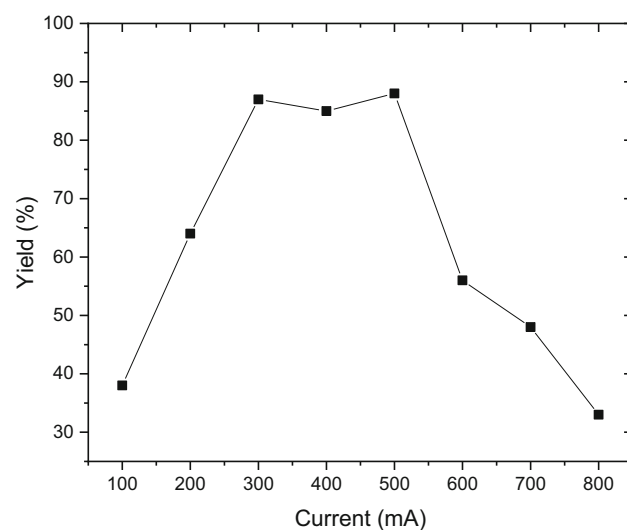
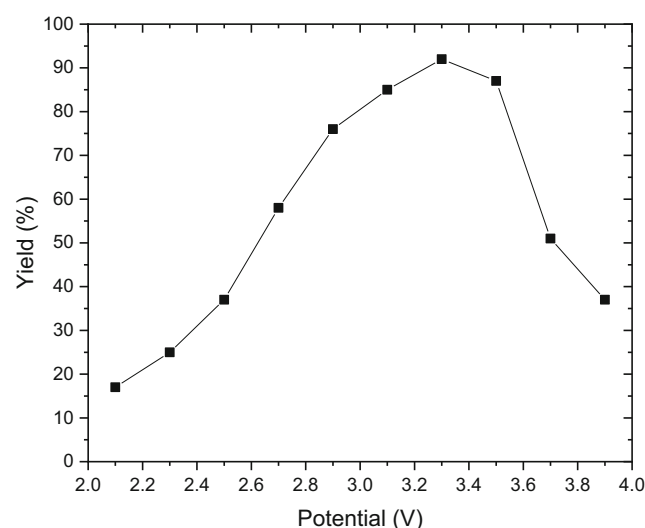


Fig. 2 Electrochemical sulfonyl fluoride synthesis in flow. (top) Potentiostatic reaction conditions, (bottom) galvanostatic reaction conditions. GC-yield using GC-FID with internal standard (biphenyl)

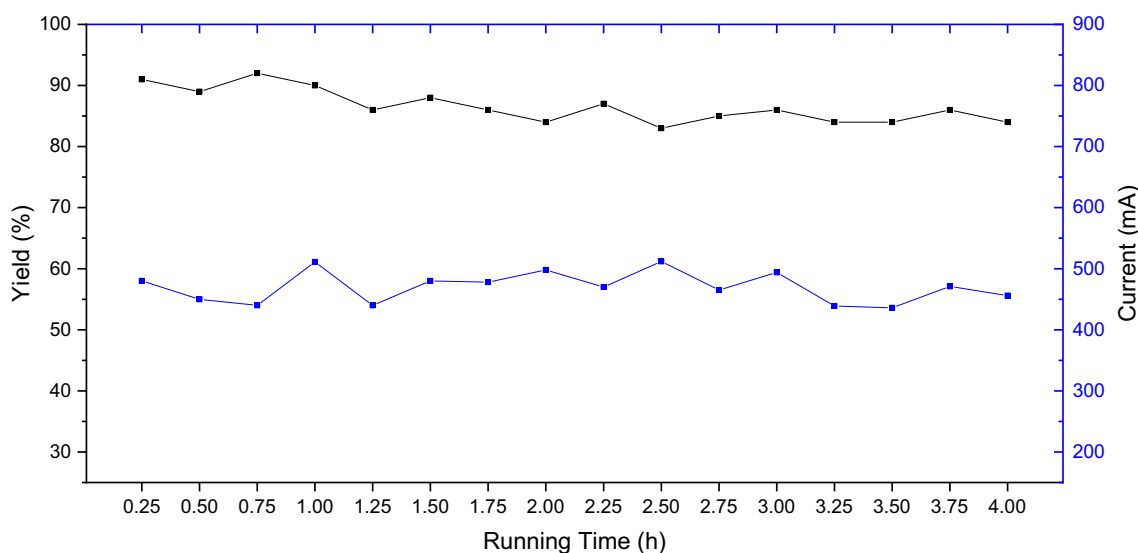


Fig. 3 Stability test (4 h operation time) for the reaction (conditions are those from Scheme 1) with a 5 min residence time. GC-yield using GC-FID with internal standard (biphenyl)

amount of KF did not lead to further improvements (Table 3, Entries 6–7).

The electrochemical oxidative coupling of thiols and potassium fluoride requires the addition of pyridine to obtain high yields. It is possible that pyridine functions either as an electron mediator [23] or as a phase transfer catalyst. From our mechanistic investigations [15], we believe that at least pyridine functions partly as a phase transfer catalyst (Table 4). Screening the concentration of pyridine, we found that the best results were obtained with 0.6–0.7 M pyridine (Table 4, Entries 6 and 9). Other phase transfer catalysts, such as tetrabutyl ammonium bromide and chloride were less effective (Table 4, Entries 7–8).

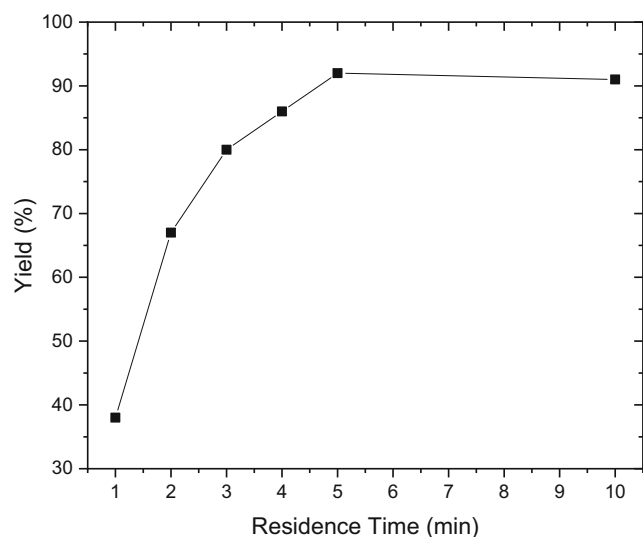


Fig. 4 Influence of the residence time on the electro-oxidative fluorination of thiophenol to benzenesulfonyl fluoride. GC-yield using GC-FID with internal standard (biphenyl)

Electrochemical transformations can be carried out either potentiostatic (constant potential) or galvanostatic (constant current). Under both scenarios, excellent yields could be obtained in flow as can be seen from Fig. 2. However, the highest yield and the most stable operation was observed under potentiostatic reaction conditions with GC yields up to 92%. Galvanostatic reactions provide a constant current and thus the reaction rate is constant until complete conversion is obtained. In contrast, potentiostatic operation keeps the cell potential constant and is of high interest to obtain high and tunable reaction selectivity [24]. While galvanostatic operation is preferred in batch, potentiostatic reaction conditions in flow are in our experience equally fast [25, 26]. We believe this has to do with the fact that the conversion increases along the channel length and thus a constant supply of electrons is maintained the entire time. Indeed, during a four-hour stability test, we saw that the current remained constant between 400 and 500 mA (Fig. 3). This is in contrast with batch potentiostatic experiments where the supply of electrons decreases when the conversion increases (less product needs to be converted, thus higher potential and lower current). This leads to slower reaction rates towards the end of the reaction and thus full conversion is harder to reach. In batch, this is often solved by adding large amounts of supporting electrolyte.

While the reaction required 24–36 h in batch to reach full conversion [15], the reaction can be completed in only 5 min in flow (Figs. 4 and 5). Such intensified reaction conditions can be attributed to the short diffusion distances to the electrode surface, the intensified mass transport due to multiphase flow patterns and the increased interfacial area.

Next, we investigated the scalability of our flow protocol. Since electrochemical transformations are surface reactions,

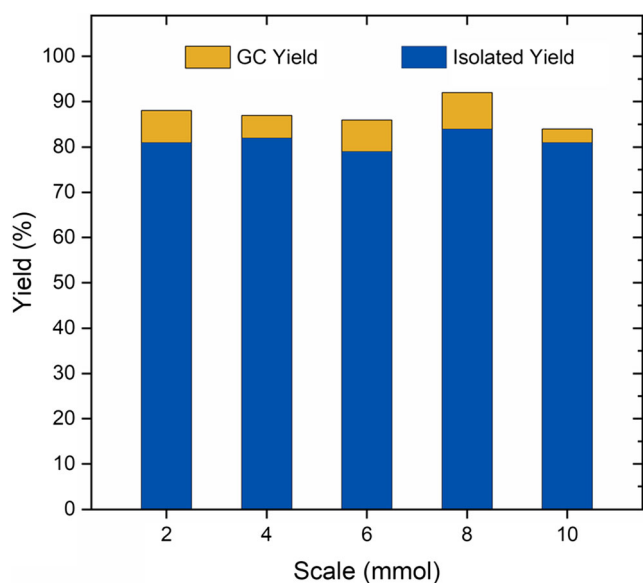


Fig. 5 Scale-up test (2 mmol to 10 mmol scale) for the reaction with 5 min residence time. Conditions, see Scheme 1. Yields reported are those of isolated products

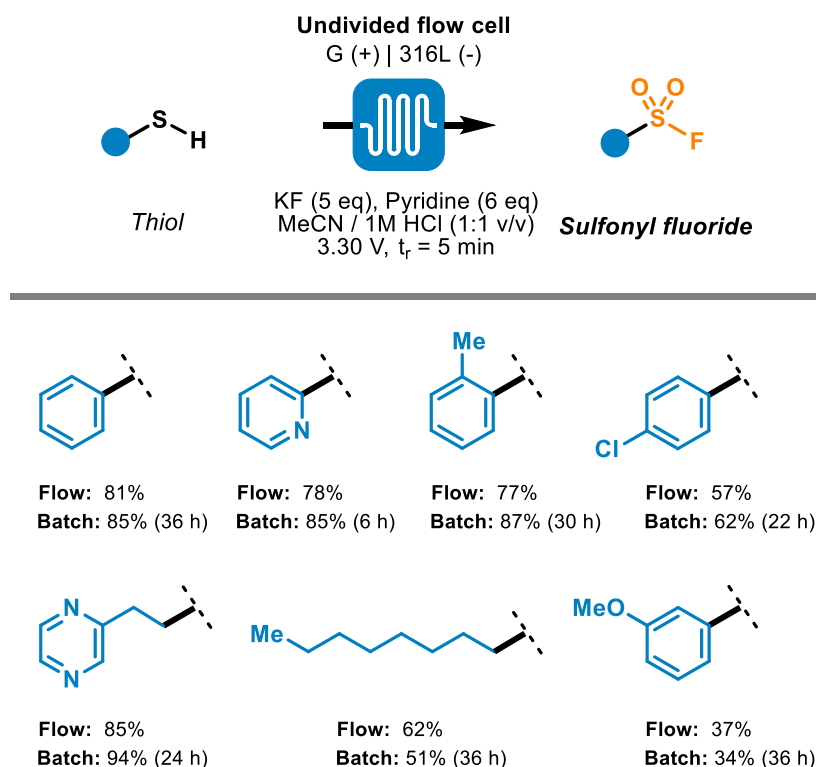
scale-up in batch can be regarded as very challenging. Typically, the electrode size is increased and larger amounts of supporting electrolyte are required to cope with the increase in Ohmic drop. Therefore, nearly all industrial electrochemical processes are carried out as flow processes in narrow-gap cells (inter-electrode gap = 0.5–10 mm) which are numbered-up depending on the targeted throughput [16]. As can be seen

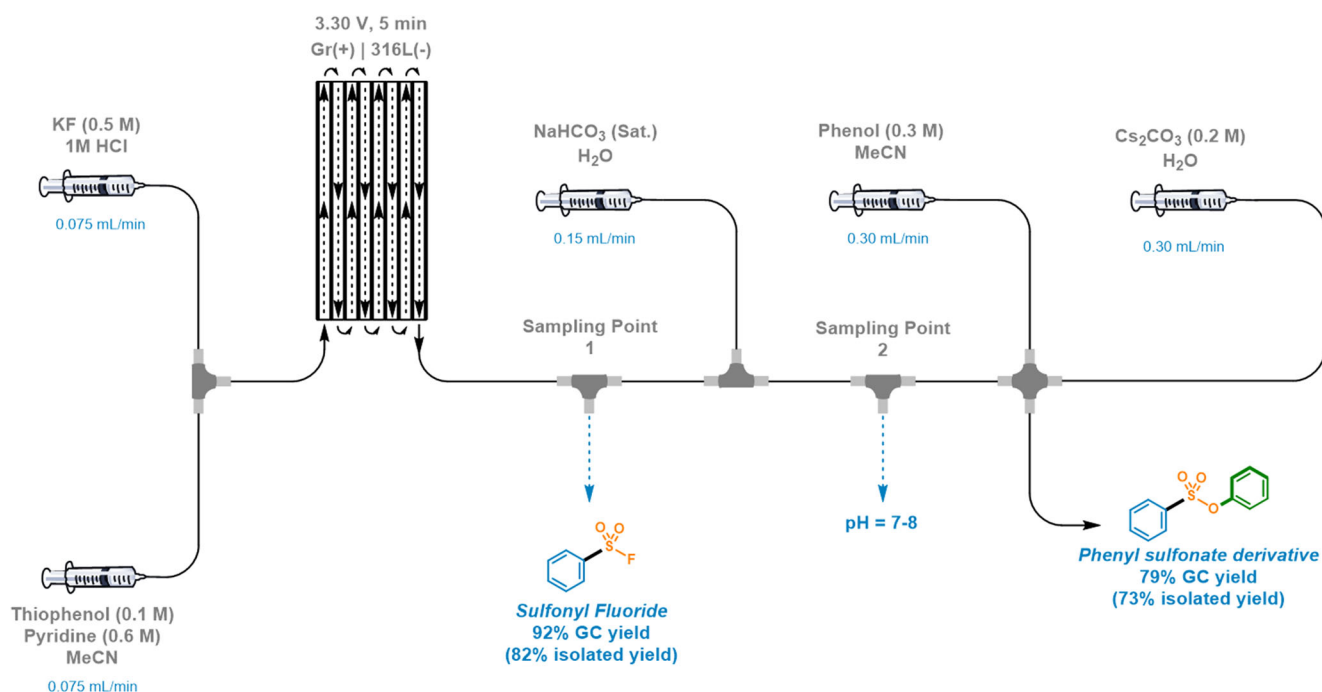
from Fig. 5, the GC and isolated yields remained constant from 2 mmol to 10 mmol scale, showing proof that the reaction is scalable but also provides stable output for longer periods of time.

With the optimal reaction conditions in hand, we commenced evaluating the flow protocol for the conversion of a diverse set of thiols (Scheme 2). In most scenarios, the yields were comparable with the batch protocol. It should be noted that no individual optimization was carried out, this explains that in some cases a slightly lower yield was obtained compared to individually optimized batch examples. Nevertheless, the results shown in Scheme 2 show clearly that the batch protocols can be seamlessly translated to flow.

Some of the corresponding sulfonyl fluorides presented in Scheme 2 are volatile and therefore difficult to isolate on small scale. Immediate conversion of these compounds in a follow-up SuFEx-type transformation is therefore recommended. In flow, this can be easily achieved by combining the individual steps in a single, uninterrupted flow protocol [27]. Hereto, the sulfonyl fluoride product (92% GC yield, 82% isolated yield) exiting the electrochemical reactor is first quenched with a saturated NaHCO_3 solution as the SuFEx reaction requires to be carried out at neutral pH (Scheme 3). Sampling points were added in our design to verify the yield of the sulfonyl fluoride (Scheme 3, Sampling point 1) and the pH (Scheme 3, Sampling point 2). Next, the neutralized reaction stream was merged with a reagent stream containing phenol and a stream containing additional Cs_2CO_3 . Within 30 s, we observed a

Scheme 2 Flow synthesis of sulfonyl fluorides and comparison with the batch protocol. Reaction conditions in flow: 0.1 M thiol, 0.6 M pyridine, 0.5 M KF, 3.30 V, 1 M HCl/ CH_3CN (1:1 v/v), total flow rate 150 $\mu\text{L}/\text{min}$, residence time 5 min; Reaction conditions in batch: 2 mmol thiol, 10 mmol KF, 8 mmol pyridine, 10 mL CH_3CN , 10 mL 1 M HCl, 3.20 V. Yields reported are those of isolated products





Scheme 3 Multistep reaction sequence in flow combining the electrochemical sulfonyl fluoride synthesis with the follow-up SuFEx reaction to yield phenyl sulfonate derivatives

clean conversion to the corresponding phenyl sulfonate derivative (73% isolated yield) using this telescoped flow process. Moreover, this example highlights the clear advantage of combining the reagent synthesis and the subsequent SuFEx click reaction in a telescoped fashion in terms of isolation, time and labor reduction. Further, we believe this process should be amenable to applications in high throughput experimentation [28, 29].

In conclusion, a continuous-flow protocol for the electrochemical oxidative coupling of thiols and KF to prepare sulfonyl fluorides was developed. The flow protocol leads to significant shorter reaction times (5 min in flow vs. 6–36 h in batch) and proves to be scalable (up to 10 mmol). Moreover, the flow sulfonyl fluoride synthesis can be readily telescoped into a SuFEx follow up reaction, without the need for intermediate purification. Ultimately, we believe that this flow protocol will be useful for those in academia and industry, interested in SuFEx click chemistry.

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