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Electrochemical Synthesis of Sulfonamides in Single-Pass Flow

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An electrochemical multicomponent synthesis of sulfonamides at room temperature in single-pass flow is presented. In contrast to batch-type electrolysis, an undivided flow cell setup with a stainless-steel cathode and either a boron-doped diamond (BDD) anode or a glassy carbon anode can be employed. Simply by using SO_2 stock solutions, less atom-economic sulfur dioxide surrogates can be avoided. Moreover, no additional supporting electrolytes are required due to the in-situ generation of amidosulfinates, which also serve as intermediate for this transformation. This protocol allows sulfonamides to be synthesized directly from non-prefunctionalized electron-rich arenes with amines and SO_2. In total, 10 examples are demonstrated with isolated yields up to 92%. The robust scalability of this electrosynthesis with an easy downstream processing was also proven.

Introduction

Sulfonamides are an important class of compounds in medicinal chemistry,[1] agrochemistry,[2] and other life science applications.[3] Remarkably, 25% of all sulfur-containing drugs approved by the U.S. Food and Drug Administration (FDA) in 2018 involve sulfonamide functionalities.[4] Several of them can be found in the List of Essential Medicines of the World Health Organization (WHO).[5] Gerhard Domagk received the Nobel Prize in 1939 for his discovery of the antibacterial effect of the sulfonamide Prontosil.[6] Additionally, sulfonamide functionalities can be found in polymers,[7] dyes,[8] solvents,[9] fungicides,[10] insecticides,[11] plasticizers,[12] and electrolytes for batteries.[13] This broad variety of application makes it evident that efficient methods for the synthesis of sulfonamides are required. Especially, the direct introduction of a sulfonamide functionality into non-pre-functionalized (hetero)arenes is of current research interest.[14] Sulfonamides are traditionally synthesized in two steps by reaction of an aromatic compound with chlorosulfuric acid to a sulfonyl chloride intermediate, which then reacts with an amine to the sulfonamide product,[15] as shown in Figure 1. Noteworthy, these sulfonyl chlorides are usually obtained as regioisomeric mixture. Moreover, this synthesis suffers from further drawbacks, such as the low overall atom economy and necessity of harsh reaction conditions.[16] In 2019, the Noël group reported the synthesis of sulfonamides in single-pass flow by electrochemical oxidative coupling of amines and thiols.[17] Despite the usefulness of this method, toxic thiophenols, which are of limited availability, are required as starting materials. In 2021, our group reported the first direct synthesis of sulfonamides from non-prefunctionalized (hetero)-arenes, amines and SO_2.[18] Inexpensive stock solutions of sulfur dioxide omit the need for non-atom economic and expensive SO_2 surrogates. This synthetic approach demonstrates several advantages organic electrosynthesis can offer:[19] (i) The reaction is carried out with comparably mild reaction conditions; (ii) electricity, preferably from renewable sources, is used as an inexpensive redox agent, preventing the generation of toxic reagent waste; (iii) metal-free reaction conditions. This protocol is a representative example of the recent progress in the area of electrochemical incorporation of SO_2 into organic molecules. It illustrates that organic electrosynthesis can offer new chemical reactivity and enable novel reaction pathways.[20] Just as with organic electrosynthesis, increasing attention is paid to the field of flow chemistry, which offers several benefits over reactions in batch:[21] Flow chemistry provides unique ways of precisely

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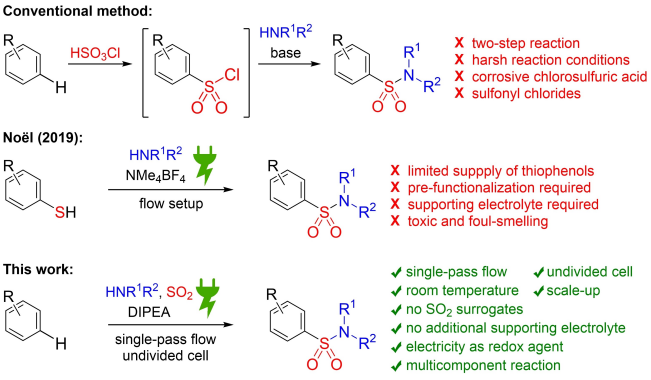

Figure 1. Synthetic approaches to sulfonamides.

controlling both conventional and electrochemical reaction parameters,[22] it allows for greater control of stoichiometry as well as reaction time,[23] and it can also increase selectivity and reproducibility of reactions.[24] Based on previous studies, we further developed the batch protocol into flow by employing an undivided flow cell setup in single-pass mode. To our delight, no separator between the electrodes is required, which is not feasible in batch-type electrolysis. Additionally, the electrochemical flow reaction is not disturbed by a disruptive hydrogen evolution reaction, as SO_2 is reduced cathodically as counter reaction.[25]

Results and Discussion

To investigate the reaction in single-pass flow, the conditions for the test reaction displayed in Figure 2 were optimized.

Unless stated otherwise, the yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. The standard conditions gave a yield of 72% (Table 1, entry 1). To our delight, a similar yield of 71% (entry 2) was obtained when using glassy carbon instead of boron-doped diamond (BDD) as anode material. This is beneficial, as glassy carbon is a significantly less expensive alternative to BDD.[26] Employing graphite as anode material resulted in a much lower yield of only 35% (entry 3). When using BDD as material for both the anode and the cathode, no trace of product formation was detected (entry 4). In this case, the reaction mixture decomposed during electrolysis and no other product could be found. Using glassy carbon as anode and cathode material resulted in a yield of 45% (entry 5). Such a setup allows the reaction to be carried out with a metal-free electrode material for both anode and cathode. However, all further optimization experiments were carried out using stainless steel as cathode material because of the higher yield (entry 1 and 2). Next, the influence of the reaction temperature was investigated. Cooling the flow cell to 10 °C decreased the yield to 55% (entry 6). Increasing the temperature to 35 °C or 50 °C resulted in 34% (entry 7) and 14% (entry 8) yield, respectively. These results indicate that the reaction is best carried out at room temperature, which is beneficial because no external heating or cooling of the undivided flow cell is required. Thereafter, the amount of applied charge and the current density were optimized. In those experiments the flow rate had to be adjusted to control the required applied charge for the specified current density. The application of only 3.0 *F* instead of 4.0 *F* resulted in 53% yield (entry 9). Increasing the amount of applied charge from 4.0 *F* to 6.0 *F* resulted in 55% yield (entry 10). Changing the current density from 12.0 mA cm^{-2} to 18.0 mA cm^{-2} (entry 11), 24.0 mA cm^{-2} (entry 12) or 30.0 mA cm^{-2} (entry 13) resulted in yields of 59%, 61%, and 64%, respectively, which are all inferior to the standard reaction conditions. Using 24.0 mA cm^{-2} in combination with an increase of applied charge to 6.0 *F* (entry 14) or 8.0 *F* (entry 15) gave 25% and 48% yield, respectively. Based on these results, all subsequent optimization was carried out using 4.0 *F* and 12.0 mA cm^{-2}. When increasing the amount of morpholine to 6.0 equivalents (entry 16), no change in yield was observed. Using 6.0 equivalents of DIPEA, a slightly higher yield of 75% was found (entry 17). A further increase of yield was observed when a higher amount of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was used in combination with an additional amount of base: For a ratio of HFIP/MeCN 2:1 (vol%) and 6.0 equivalents

Table 1. Optimization of the test reaction.

#	Deviation from standard reaction conditions[a]	Yield [%][b]
1	none	72
2	glassy carbon | | stainless steel	71
3	graphite | | stainless steel	35
4	BDD | | BDD	0
5	glassy carbon | | glassy carbon	45
6	10 °C	55
7	35 °C	34
8	50 °C	14
9	3.0 *F*, 200 µL min^{-1}	53
10	6.0 *F*, 100 µL min^{-1}	55
11	18.0 mA cm^{-2}, 224 µL min^{-1}	59
12	24.0 mA cm^{-2}, 298 µL min^{-1}	61
13	30.0 mA cm^{-2}, 373 µL min^{-1}	64
14	24.0 mA cm^{-2}, 6.0 *F*, 200 µL min^{-1}	25
15	24.0 mA cm^{-2}, 8.0 *F*, 149 µL min^{-1}	48
16	6.0 equiv. morpholine	72
17	6.0 equiv. DIPEA	75
18	HFIP/MeCN 2:1, 6.0 equiv. DIPEA, 1.8 mmol scale	88 (84% isolated)
19	HFIP/MeCN 2:1, 6.0 equiv. DIPEA, 1.8 mmol scale, glassy carbon | | stainless steel	88 (86% isolated)
20	HFIP/MeCN 2:1, 8.0 equiv. DIPEA	70
21	HFIP/MeCN 2:1, 8.0 equiv. DIPEA, 20.0 equiv. SO_2	60
22	HFIP/MeCN 2:1, 6.0 equiv. pyridine, no DIPEA	46
23	HFIP (no MeCN), 6.0 equiv. DIPEA, 224 µL min^{-1}, c(1,4-dimethoxybenzene) = 0.10 mol L^{-1}	10
24	No electricity	0

[a] The standard reaction conditions are the conditions shown in Figure 2. More details can be found in the Supporting Information. BDD: boron-doped diamond. DIPEA: *N*,*N*-diisopropylethylamine, HFIP: 1,1,1,3,3,3-hexafluoropropan-2-ol. [b] Unless stated otherwise, the yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

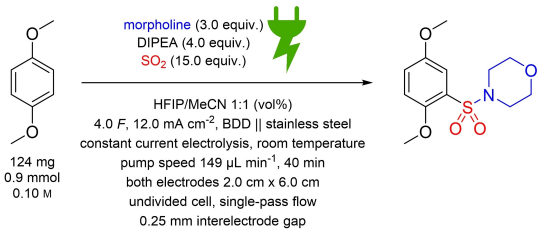

Figure 2. The test reaction used for optimization.

of DIPEA, an isolated yield of 84% was obtained (entry 18, 88% NMR yield). These conditions were tested again with glassy carbon as anode material instead of BDD, which gave an even slightly higher isolated yield of 86% (entry 19, 88% NMR yield). Those two reactions (entry 18 and 19) were carried out in 1.8 mmol scale. Increasing the amount of DIPEA further up to 8.0 equivalents resulted in a decrease of yield to 70% (entry 20). When adjusting the amount of sulfur dioxide to 20.0 equiv., with 8.0 equiv. DIPEA, a yield of 60% was obtained (entry 21). The use of pyridine instead of DIPEA resulted a yield of only 46% (entry 22). The use of HFIP as solvent without any MeCN, in combination with 6.0 equiv. of DIPEA was tested. For this experiment, the concentration of the starting material had to be lowered to 0.10 mol L^{-1} because of the lower solubility of SO_2 in HFIP compared with its splendid solubility in MeCN. This resulted in a yield of only 10% (entry 23). In general, the concentration of the starting material should be kept as high as possible because of the increased space-time yield in flow electrolysis. No product formation was found when no electricity was applied (entry 24).

Reaction scope

In all reactions, only sulfonamides were found as products, as shown in Figure 3, and no side products could be isolated. The highest isolated yield was obtained for 1,4-dimethoxybenzene, which gave sulfonamide **1** in 84% isolated yield when BDD was employed as anode material and 86% for a glassy carbon anode. 1,2-Dimethoxybenzene gave the two possible sulfonamide isomers **2a** and **2b** in isolated yields of 41% and 14% (combined yield: 55%), respectively with reaction conditions [c] and only 12% for **2a** and 9% for **2b** (combined yield: 21%) by conditions [a]. For all halogen-containing substrates, the major product was the isomer wherein the sulfonamide moiety is located in position para to the halo substituent: For 1-bromo-2,5-dimethoxybenzene, product **3a** was obtained in 53% isolated yield and isomer **3b** in 19% (combined yield: 72%). With 1,4-dimethoxy-2,3-dimethyl-benzene as starting material, product **4** was found in 26% isolated yield with reaction conditions [d] and 25% isolated yield with conditions [a]. Sulfonamide **5a** was found as major product in 50% isolated yield and isomer **5b** as minor product with 11% for 1-chloro-2,5-dimethoxybenzene as substrate (combined yield: 61%). With reaction conditions [c], for 1-fluoro-2,5-dimethoxybenzene, **6a** was found in 56% isolated yield and **6b** in 11% (combined yield: 67%). With conditions [a], **6a** and **6b** were obtained in only 13% and 8%, respectively (combined yield: 21%). For 1,4-benzodioxane, the two possible sulfonamides **7a** and **7b** were isolated in yields of 41% and 14% (combined yield: 55%), respectively for reaction conditions [c]. With conditions [a], only 23% of **7a** and 10% of **7b** (combined yield: 33%) was isolated.

As shown in Figure 4, other amines have been successfully employed in the synthesis of sulfonamides. The use of azepane gave sulfonamide **8** in 43% isolated yield. Using dibutylamine or diisobutylamine resulted in isolated yields of 31% for product **9** and 66% for **10**, respectively.

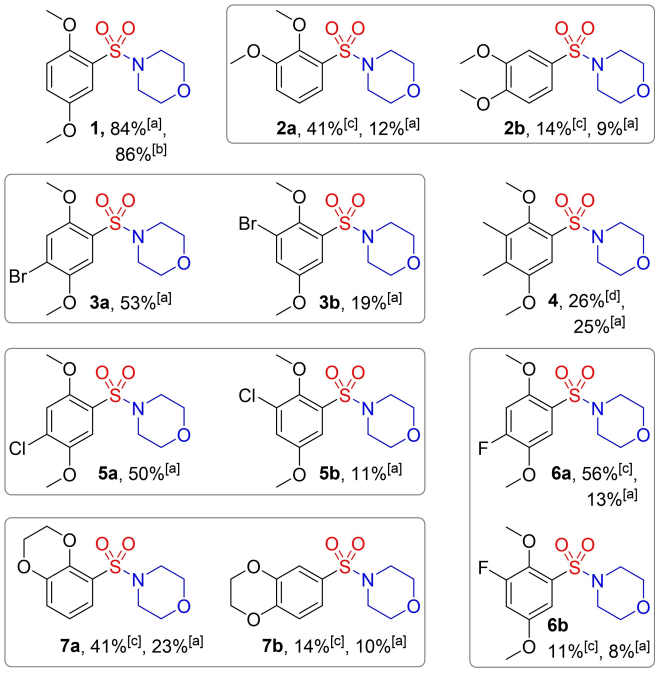

Figure 3. The scope. [a] Reaction conditions: starting material (1.8 mmol, 0.15 mol L^{-1}), morpholine (3.0 equiv.), DIPEA (6.0 equiv.), SO_2 (15.0 equiv., 2.25 mol L^{-1}), HFIP (1.10 mL), MeCN (1.12 mL), HFIP/MeCN 2:1 (vol%), amount of applied charge $Q = 4.0$ *F*, current density $j = 12.0$ mA cm^{-2}, room temperature, BDD anode (2.0 cm×6.0 cm), stainless steel cathode (2.0 cm×6.0 cm), undivided cell, pumping rate: 149 µL min^{-1}, constant current electrolysis, single-pass flow, interelectrode gap: 0.25 mm. [b] Deviations from conditions [a]: glassy carbon instead of BDD. [c] Deviations from conditions [a]: starting material (2.4 mmol, 0.10 mol L^{-1}), DIPEA (4.0 equiv.), HFIP/MeCN 1:1 (vol%), amount of applied charge $Q = 3.5$ *F*. [d] Deviations from conditions [a]: starting material (1.5 mmol, 0.13 mol L^{-1}). More details can be found in the Supporting Information.

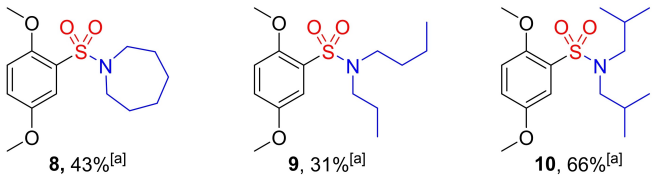

Figure 4. Other amines which have been tested. [a] Reaction conditions: starting material (1.8 mmol, 0.15 mol L^{-1}), morpholine (3.0 equiv.), DIPEA (6.0 equiv.), SO_2 (15.0 equiv., 2.25 mol L^{-1}), HFIP (1.10 mL), MeCN (1.12 mL), HFIP/MeCN 2:1 (vol%), amount of applied charge $Q = 4.0$ *F*, current density $j = 12.0$ mA cm^{-2}, room temperature, BDD anode (2.0 cm×6.0 cm), stainless steel cathode (2.0 cm×6.0 cm), undivided cell, pumping rate: 149 µL min^{-1}, constant current electrolysis, single-pass flow, interelectrode gap: 0.25 mm. More details can be found in the Supporting Information.

Scale-up

To demonstrate the scalability of this method, the reaction was carried out in an 8-fold scale up from 1.8 mmol to 14.4 mmol starting material. In the first scale-up experiment, an isolated yield of 86% of the sulfonamide product **1** could be achieved

(Table 2, entry 1), which is the same yield that was obtained when the reaction was carried out in 1.8 mmol scale. In addition, 14% of the unconsumed starting material (SM) could be recovered during purification via flash column chromatography. Dividing the mass of isolated product by electrolysis time results in a productivity of 0.33 g/h. To improve the space-time yield of the scale-up reaction, another 8-fold scale-up experiment was carried out in a larger flow cell (Table 2, entry 2). The modular cell employed in the scale-up reaction was previously described,[27] and more information about the flow cells can be found in the Supporting Information. This cell has an electrode surface that is 4 times the size of the small flow cell: both electrodes have a surface of 48 cm^2. In order to obtain the same current density and amount of applied charge, a higher electric current is applied in combination with a higher pumping rate, which decreases the reaction time (see Supporting Information for more details). In this experiment, BDD was used as anode material. To our delight, sulfonamide **1** was obtained in 92% isolated yield (Table 2, entry 2), and 8% starting material was recovered during purification using flash column chromatography. For this reaction, 1.43 g/h of product can be obtained, which means that both isolated yield and space-time yield are improved. In Figure 5, the experimental setup of entry 2 in Table 2 is displayed.

Table 2. Scale-up reactions.

#	Deviation from the standard reaction conditions[a]	Isolated Yield [%]	Recovered SM [%]	Productivity [g/h]
1	14.4 mmol scale, glassy carbon | | stainless steel	86	14	0.33
2	14.4 mmol scale, both electrodes each 48 cm^2	92	8	1.43

[a] The standard reaction conditions are the conditions shown in Figure 2.

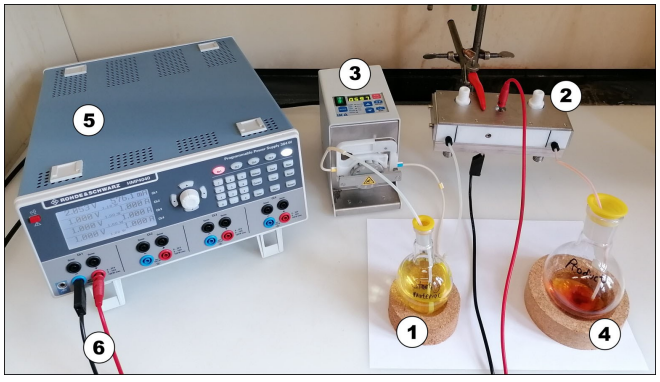

Figure 5. A simple experimental setup: The reaction solution is prepared in a round bottom flask (1) and then directly pumped out of there through the undivided electrolysis cell (2) once by using a peristaltic pump (3). The solution coming from the outlet of the electrolysis cell is collected again in a round bottom flask (4). The anode and cathode of the electrolysis cell are connected to a galvanostat (5) with wires (6). More details can be found in the Supporting Information.

Recycling of the electrolyte (reaction medium)

The HFIP/MeCN solvent mixture used in the reaction can be recycled simply by using vacuum distillation into a cooling trap, as shown in Figure 6. For the scale-up experiment of entry 2 in Table 2, 84 vol% of the HFIP/MeCN 2:1 solvent mixture was recovered, which contained 0.8 mol L^{-1} sulfur dioxide. This recovered solvent mixture was purged again with SO_2 to obtain a new stock solution, which was then used in a reaction of the same conditions as entry 19 in Table 1 (see Supporting Information for more details). To our delight, an isolated yield of 86% for sulfonamide **1** was obtained when using the recycled solvent mixture. This clearly demonstrates that the reaction medium can be recycled and re-used easily.

Mechanism

As displayed in Figure 7, it is postulated that this dehydrogenative reaction proceeds vial electrochemical C–H activation. The amine **11** reacts as a Lewis base with SO_2, forming the Lewis acid-base adduct **12**. Deprotonation of **12** with a base forms amidosulfinate species **13**. This amidosulfinate acts as both the nucleophile and as supporting electrolyte. The formation of **13** is promoted by the hydrogen bonding power of HFIP. In addition, the hydrogen bonding triggers an exclusive reactivity of the sulfur center as solvent effect.[28] HFIP and amine mixtures show an unusually high electrical conductivity.[29] Consequently, there is no need for an additional supporting electrolyte in the solution, which simplifies the reaction and the workup. After the initial anodic oxidation of the arene **14** to cationic radical intermediate **15**,[30] the amidosulfinate acts as a nucleophile on it. The subsequent oxidation of **15** results in loss of a proton and rearomatization to form the sulfonamide product **16**. At the cathode, sulfur dioxide is reduced as counter reaction.[25] Noteworthy, all components except the target compound sulfonamide are volatile, facilitating work up and translation into application.[31]

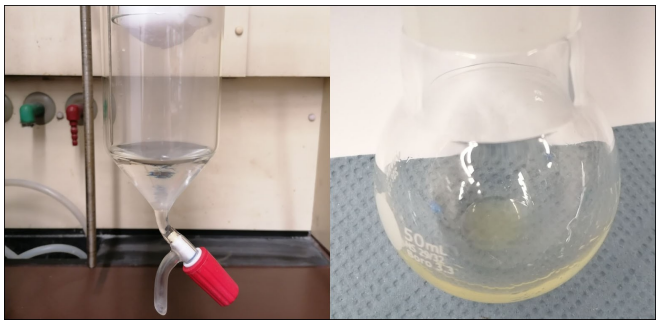

Figure 6. Left: Easy recovery of the HFIP/MeCN solvent mixture from the crude reaction medium using vacuum distillation/condensation into a cooling trap. Right: Isolated sulfonamide product of the reaction which used a SO_2 stock solution that was made from recovered HFIP/MeCN (see Supporting Information for more details).

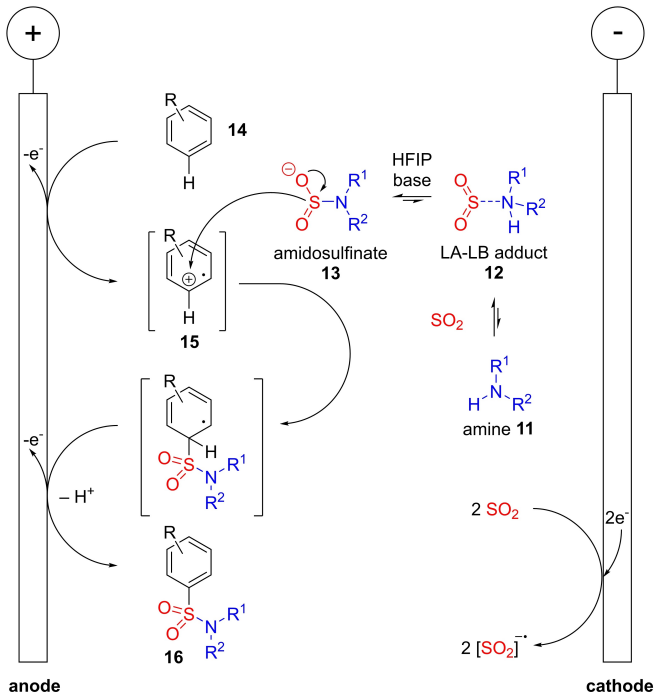

Figure 7. Proposed reaction mechanism.

Conclusions

A method for the electrochemical synthesis of sulfonamides at room temperature in single-pass flow with an undivided cell was developed. Sulfur dioxide stock solutions as atom-economic source of SO_2 are utilized and the use of electricity omits the application of expensive redox agents. The amount of HFIP and base in the reaction solution could be identified as major parameters to optimize the yield. Either BDD or glassy carbon can be chosen as anode material. In total, 10 examples were demonstrated with isolated yields up to 92%. Beneficially, the reagents and electrolyte components are volatile. Consequently, the down-stream processing is strongly facilitated. It has been demonstrated that the HFIP/MeCN solvent mixture can be recovered and re-used for further electrolysis runs. The scalability of the electrolysis was demonstrated in an 8-fold upscaled electrolysis. The space-time yield of the scale-up reaction could be improved by using a larger flow cell. This method allows sulfonamides to be synthesized electrochemically in a continuous process.

Experimental Section

Standard reaction conditions: 1,4-dimethoxybenzene (124 mg, 0.9 mmol, 0.15 mol L^{-1}) was dissolved in MeCN (1.12 mL) and HFIP (1.10 mL). Then, morpholine (3.0 equiv., 2.7 mmol, 0.24 mL) and DIPEA (4.0 equiv., 3.6 mmol, 0.61 mL) was added. To this, a stock solution of SO_2 in HFIP/MeCN 1:1 (15.0 equiv. SO_2, 13.5 mmol, 2.25 mol L^{-1} SO_2 in solution) was added. During addition the reaction solution was cooled, as some heat-up is expected. The peristaltic pump was calibrated with acetonitrile before every experiment. BDD was used as anode material and stainless steel as cathode material. A Teflon spacer of thickness 0.25 mm was used. The reaction solution is pumped through the electrolysis cell and the electrolysis was started (4.0 *F*, 149 µL min^{-1}, 12.0 mA cm^{-2}). For isolation of the product, a saturated aqueous solution of $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed using a rotary evaporator. The crude extract was adsorbed on silica and the product(s) were isolated using flash column chromatography.

Supporting Information

Detailed information on experimental setup, general procedures, reaction optimization, scale-up, and product characterization can be found in the Supporting Information, including NMR spectra. The authors have cited additional references within the Supporting Information.[32–36]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: electrolysis · microreactors · multicomponent reactions · radical reactions · sulfonamides

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