Efficient Continuous-Flow Bromination of Methylsulfones and Methanesulfonates and Continuous Synthesis of Hypobromite

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An efficient continuous-flow procedure for the synthesis of tribromomethylsulfones and tribromomethanesulfonates has been developed starting from the corresponding methylsulfones or methanesulfonates and potassium hypobromite using a biphasic reaction. Two different continuous-flow systems were used and compared for the bromination reaction. Different derivatives were synthesized in excellent isolated yields in very short reaction times using a small excess of potassium hypobromite. Hypobromite can be synthesized continuously leading to the continuous production of the brominated derivates. With the optimized flow conditions, a throughput of up to 53 g/day was obtained. The bromination reaction in flow has significant advantages compared to the corresponding batch process.

Keywords: continuous flow, methylsulfones, methanesulfonates, bromination, hypobromite

1. Introduction

The halomethylsulfonyl group is incorporated in several active biocides. Different patents describe the use of halomethylsulfonyl derivatives to protect paints, leather treatment liquids, coolants, metal cutting fluids, etc. against bacterial or fungal deterioration [1]. The AMICAL™ Preservatives of The Dow Chemical Company, for example, are useful for controlling microbial degradation in adhesives, paper coatings, plastics, textiles, and coatings. The active ingredient is *p*-tolyl diiodomethylsulfone [2].

Smith described the use of *p*-tolyl diiodomethylsulfone for the treatment of fungal or yeast infections of the skin [3]. Halomethylsulfonyl derivatives have also potential as herbicide or fungicide to protect agricultural products [4]. Other applications include, for example, antifouling paints for ships and fishing nets [5].

Halomethylsulfonyl derivatives find also application in the graphics industry. Trihalomethylsulfones **1** are used as polymerization initiator in lithographic printing plates (Figure 1) [6].

Several methods for the synthesis of phenyl trihalomethylsulfones are described in literature. The reaction of thiols or disulfides with halofluoromethanes and subsequent oxidation features the desired sulfones [7]. Farrar described the synthesis of trichloro- and tribromomethyl phenylsulfones starting from phenylthioacetic acid and sodium hypohalite [8]. Ochal et al. synthesized 4-chlorophenyl bromodichloromethylsulfone from chlorobenzene [9]. This group also developed the synthesis of phenyl trihalomethylsulfones using chlorination with sodium hypochlorite or bromination with sodium hypobromite or bromine chloride [10].

In our continuing efforts to use continuous-flow for reactions difficult to scale up, we evaluated the synthesis of tribromomethylsulfones and tribromomethanesulfonates using the biphasic reaction between methylsulfones or methanesulfonates and hypobromite [11]. Although this reaction is known in batch, no evaluation in continuous flow has been performed. However, performing this reaction in continuous flow is industrially relevant and has several advantages over the batch process. A continuous-flow process is inherently safer than the corresponding batch process due to the small internal volume associated with the continuous-flow reactors. This safety feature is important when working with toxic reagents. Moreover, continuous-flow reactors have excellent heat and mass transfer characteristics which can provide a significant improvement for biphasic reactions [12]. Scaling-up a continuous-flow process is very straightforward by the numbering-up concept compared to the scale-up of batch procedures which is often ambiguous [13].

2. Results and Discussion

Because of its industrial relevance, the reaction between 4-isopropoxyphenyl methylsulfone **2** and potassium hypobromite (KOBr) was chosen as generic reaction for the evaluation of the bromination of methylsulfones (Scheme 1). The reaction is performed in a biphasic water–toluene system with tetrabutylammonium bromide (TBABr) as phase transfer catalyst (PTC).

This reaction was first evaluated in batch for comparison. The KOBr solution was prepared by dropping Br_2 to an aqueous solution of potassium hydroxide (KOH) at 0 °C. This solution was subsequently added dropwise to a solution of 4-isopropoxyphenyl methylsulfone **2** and TBABr in toluene at 38 °C. The reaction required 22 h to reach completion. After work-up, the end product, 4-isopropoxyphenyl tribromomethyl sulfone **3**, was obtained with an isolated yield of 94%.

Two different reactor systems were evaluated for the optimization of the bromination reaction of 4-isopropoxyphenyl methylsulfone **2** in flow (Figure 2).

In the initial flow experiments, a 1 M KOBr solution was prepared in batch by adding Br_2 to a 5.9 M KOH solution. The first reactor was a self-assembled system built up of perfluoroalkoxy (PFA)-tubing with a volume of 3 mL and a T- or Y-connector to combine both reagent streams (Figure 2a). Several reaction conditions were evaluated: reaction temperature, residence time, equivalents of PTC, and equivalents of KOBr. Besides this, also the type of mixer (T- or Y-connector) had an influence on the conversion. The reaction mixtures were analyzed by high-performance liquid chromatography–ultraviolet (HPLC–UV) (see Electronic Supplementary Material). The results for this series of optimization experiments are summarized in Table 1.

The side product formed during the reaction was the dibromo derivative due to incomplete conversion of the starting material **2**. Starting with a reaction temperature of 40 °C, a residence time of 15 min, 0.5 equiv. of TBABr, and a small excess of 3.3 equiv. of KOBr, the starting material was detected predominantly (entry a). If the residence time was prolonged to 30 min, again, mainly the

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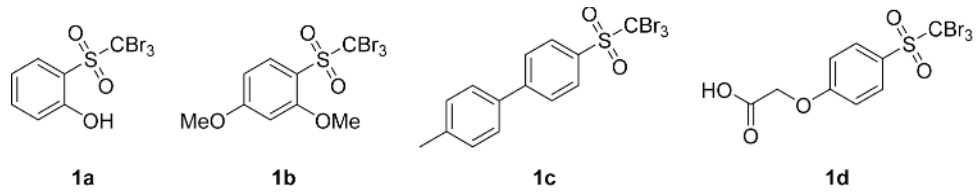
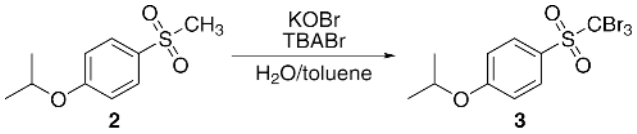


Figure 1. Trihalomethylsulfones as polymerization initiator in printing plates

Scheme 1. Bromination of 4-isopropoxyphenyl methylsulfone **2**



starting material was observed (entry b). In the next step, the reaction temperature was gradually increased to 60 °C, leading to better conversions (entries b–d). The next series of experiments was conducted with 6.7 equiv. of KOBr, leading to a lower amount of the dibromo intermediate (entry e). Changing the T-connector for a Y-connector led to plug flow with smaller plugs and, hence, a larger interfacial area (see Electronic Supplementary Material for an estimation of the interfacial area). This resulted in a higher amount of the end product **3** (entry f). Using stoichiometric amounts of PTC instead of 0.5 equiv. had no effect on the composition of the reaction mixture (entry g). In the last step, the reaction temperature was raised to 70 °C resulting in a higher conversion of the starting material **2** (entry h). In an attempt to further increase the conversion of the starting material **2**, the residence time was increased to 60 min, however, without any effect (entry i).

With a straightforward, self-assembled tube reactor system, full conversion of the substrate **2** to **3** was not possible. In the next series of experiments, the optimization procedure was repeated on a glass static mixer chip (Uniqsis®) (Figure 2b). The most optimal conditions for the self-assembled tube reactor system (Table 1, entry h) were used as starting point for the evaluation of the bromination reaction with the static mixer. In the first step, the influence of the residence time (and thus, flow rate) on the conversion was evaluated (Figure 3). However, because more efficient mixing is expected in the static mixer compared to the self-assembled system, experiments were started with a residence time of 15 min.

Starting the experiments with a residence time of 15 min, 86% end product was detected on HPLC–UV. However, when decreasing the residence time to 5 min, no starting material was observed and only traces of the dibrominated intermediate were detected. A further decrease of the residence time to 3 min led to almost full conversion of the starting material **2** into the tribrominated derivative **3** (based on HPLC–UV). In an attempt to increase the throughput, a residence time of 1 min was evaluated. However, this residence time was too short to reach full conversion. Based on these observations, an optimum in the residence time was observed. If the residence time is too low

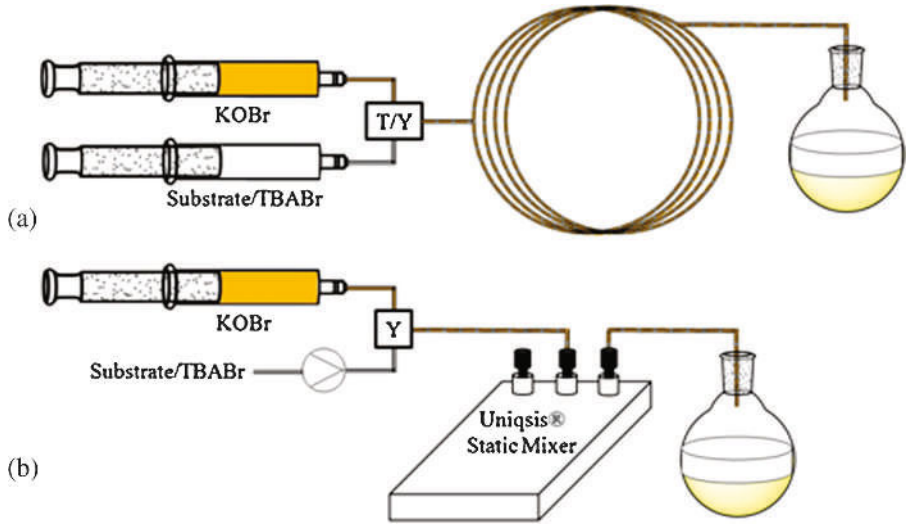


Figure 2. Schematic representation of the continuous-flow setup: (a) self-assembled tube reactor and (b) Uniqsis® static mixer

Table 1. Overview of the results for the self-assembled tube reactor

Entry	T^a (°C)	RT[a] (min)	PTC (equiv.)	KOBr[b] (equiv.)	T/Y mixer	Reaction mixture composition (%)		
						RCH_3	$RCHBr_2$	$RCBr_3$
a	40	15	0.5	3.3	T	95	2	3
b	40	30	0.5	3.3	T	91	2	7
c	50	30	0.5	3.3	T	75	4	21
d	60	30	0.5	3.3	T	61	4	35
e	60	30	0.5	6.7	T	60	2	38
f	60	30	0.5	6.7	Y	39	2	59
g	60	30	1	6.7	Y	44	2	54
h	70	30	0.5	6.7	Y	27	2	71
i	70	60	0.5	6.7	Y	35	2	63

[a] T = temperature, RT = residence time.
[b] A solution of 0.3 M (resp. 0.15 M) starting material was used for the reaction with 3.3 (resp. 6.7) equiv. of KOBr.

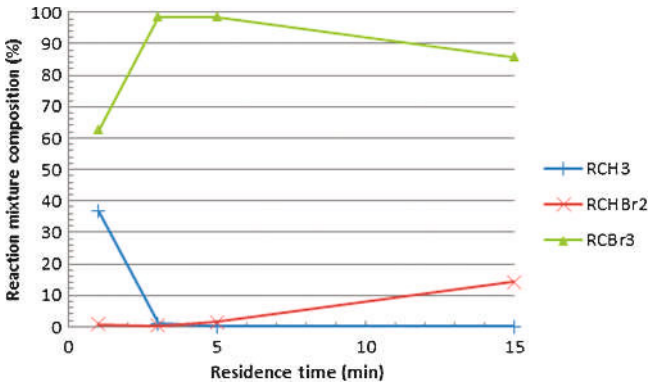


Figure 3. Influence of the residence time on the reaction mixture composition. Conditions: 70 °C, 6.7 equiv. of KOBr, and 0.5 equiv. of TBABr (reaction mixture composition based on HPLC–UV [254.8 nm]; see Electronic Supplementary Material)

(flow rate too high), the reaction cannot reach full conversion. If the residence time is too high (flow rate too low), less efficient mixing is observed.

In the next step, the influence of the reaction temperature on the conversion was determined (Figure 4).

In order to obtain full conversion of the starting material into the tribrominated derivative, a reaction temperature of 85 °C is required.

In the last step of the optimization, the amount of KOBr was reduced (Figure 5). Full conversion of the starting material **2** was observed with as little as 4 equiv. of KOBr. Lower amounts of KOBr resulted in incomplete conversion.

When both reactor systems are compared, the Uniqsis® glass static mixer is superior to the self-assembled tube reactor. The mixing characteristics of the static mixer result in the formation of an emulsion and, hence, very efficient contact between the water phase (KOBr) and the toluene phase (starting material) resulting in full conversion of the starting material. In the self-assembled tube reactor, a plug flow is observed having a smaller interfacial area in comparison to the formed emulsion in the Uniqsis® system. In the mesoreactor, a longer residence time and more KOBr are required for the conversion of the starting material. The optimized conditions were used to synthesize a library of tribromomethylsulfones and tribromomethanesulfonates with the Uniqsis® static mixer (Table 2). For comparison purposes, the reactions were also evaluated in batch. Unless otherwise stated in Table 2, no purification of the end product was necessary.

Excellent and comparable yields were obtained for the tribromination of methylsulfones and methanesulfonates using

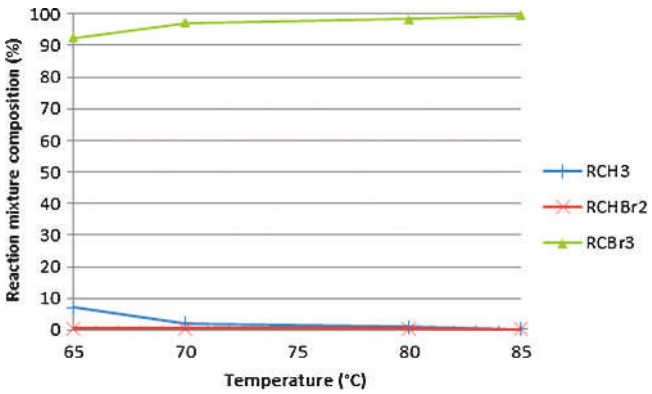


Figure 4. Influence of temperature on the reaction mixture composition. Conditions: 3 min residence time, 6.7 equiv. of KOBr, and 0.5 equiv. of TBABr (reaction mixture composition based on HPLC–UV [254.8 nm]; see Electronic Supplementary Material)

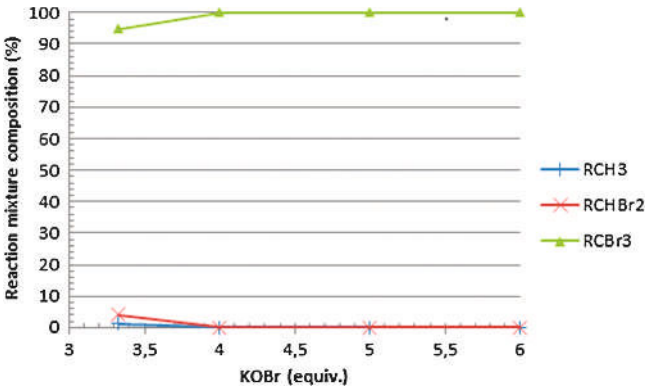
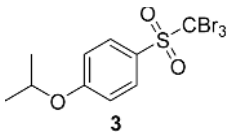
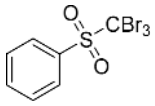
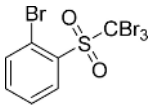
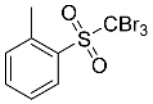
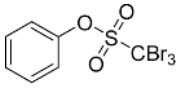
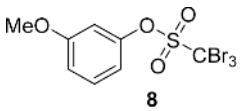
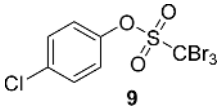


Figure 5. Influence of KOBr on the reaction mixture composition. Conditions: 3 min residence time, 85 °C, and 0.5 equiv. of TBABr (reaction mixture composition based on HPLC–UV [254.8 nm]; see Electronic Supplementary Material)

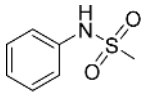
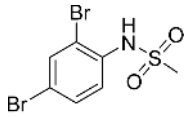
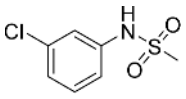
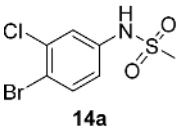
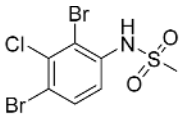
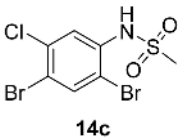
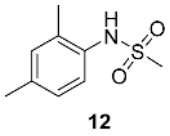
batch or flow conditions (Table 2). In batch, no further purification of the end product was necessary after work-up of the reaction mixture. In flow, purification was sometimes required. Lower yields were mainly caused by losses during work-up of the reaction mixture. For compound **5** (Table 2, entry 3), a lot of

Table 2. Overview of synthesized tribromomethylsulfones and tribromomethanesulfonates

Entry	Compound	Flow		Batch
		Isolated yield (%)	Isolated throughput (g/day)	Isolated yield (%)
1	 **3**	Quantitative	53	94
2	 **4**	87	40	82
3	 **5**	48[a]	26	49
4	 **6**	77[b]	37	69
5	 **7**	87[b]	41	88
6	 **8**	83[b]	42	84
7	 **9**	84[b]	43	89

[a] Purification: recrystallization.
[b] Purification: column chromatography.

Table 3. Bromination of *N*-aryl methanesulfonamides

Substrate	Products formed
 **10**	 **13**
 **11**	 **14a**  **14b**  **14c** **14a:14b:14c** 0.2:1:0.8
 **12**	CRM[a]

[a] Complex reaction mixture.

side products were observed under flow conditions. These products could not be identified but the formation of side products is possible due to incomplete bromination of the methylsulfone group or due to bromination of the aromatic ring.

The optimized flow procedure was also evaluated for the bromination of *N*-aryl methanesulfonamides. Three different *N*-aryl methanesulfonamides were evaluated in flow: *N*-phenyl methanesulfonamide, *N*-3-chlorophenyl methanesulfonamide, and *N*-2,4-dimethylphenyl methanesulfonamide. However, for these substrates, bromination of the aromatic system occurred. Table 3 gives an overview of the products detected in the reaction mixtures based on proton nuclear magnetic resonance (^{1}H-NMR). Monobromination of the aromatic ring of *N*-aryl methanesulfonamides has been reported using Br_2 or bromosuccinimide [14].

In the next step, we focused on the continuous-flow synthesis of hypobromite in order to combine the synthesis of hypobromite with the subsequent bromination reaction. The flow rates of Br_2 and the KOH solution are determined by the stoichiometric ratio and residence time for the subsequent bromination reaction. In the first series of trials, the synthesis of KOBr in flow was evaluated in a self-assembled tube reactor, analogous to the system shown in Figure 2a, in view of the corrosiveness of the reagents. The reaction conditions with the highest conversion for the bromination in the self-assembled tube reactor were used to determine the flow rate of Br_2 and aq. KOH. Pure bromine (5 μL/min) and a 5.9 M KOH solution (0.1 mL/min) were mixed in a T-mixer before entering a tube reactor of 0.5 mL at 0 °C. However, after the T-mixer, inefficient mixing was observed (plug flow of bromine and the KOH solution) resulting in insufficient formation of KOBr for the subsequent bromination reaction. Probably, the large difference in flow rate between pure bromine and the KOH solution causes this inefficient mixing (flow ratio Br_2:KOH = 1:20). However, after optimizing the bromination reaction on the static mixer, we evaluated again the formation of hypobromite in the self-assembled tube reactor. The optimized conditions in the static mixer require a flow of 0.33 mL/min of a 1-M KOBr solution which in turn requires a flow of 17 μL/min Br_2 and 0.313 mL/min aq. KOH. Because previous results were not satisfying when neat Br_2 was used, Br_2 was diluted in order to obtain a better flow ratio. Different solvents were evaluated: CH_2Cl_2, $ClCH_2CH_2Cl$, tBuOH, and CH_3CN. Observing the color change of both the aqueous and organic phase, hypobromite is formed when mixing both solutions. However, an unstable emulsion was formed when mixing the biphasic hypobromite solution with the solution of the starting material in the static mixer resulting in irreproducible results.

In the second attempt, the glass static mixer was used to prepare the KOBr solution starting from a 5.9-M KOH solution and pure Br_2. In this case, efficient mixing of the bromine and KOH solution was obtained but a white precipitate was formed during the reaction leading to blockage of the mixer chip. Decreasing the concentration of the KOH solution to 5 M and, hence, the equivalents of KOH used did not resolve this problem.

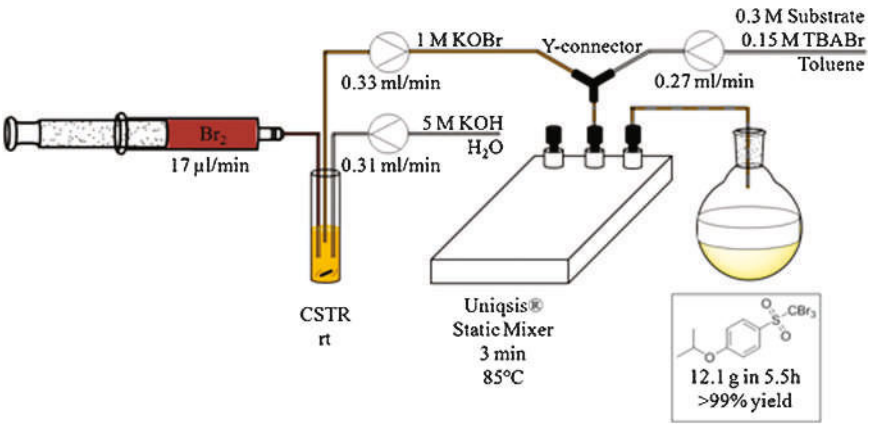


Figure 6. Continuous production of hypobromite and subsequent bromination

Table 4. Isolated yields during course of operation

Time interval (min)	Isolated yield (%)
0–60	98
60–120	quant.
120–180	quant.
180–240	quant.
240–330	quant.

Finally, the flow equivalent of a continuous stirred tank reactor was used to prepare the KOBr solution. Bromine and the KOH solution were pumped in a vial containing a rotating stirring bar. Bromine reacts immediately with the KOH solution resulting in the instantaneous formation of hypobromite. When a 5.9-M KOH solution was used, a turbid reaction mixture was obtained. Lowering the concentration of the KOH solution to 5 M solved the problem and resulted in a transparent, yellow KOBr solution. To proof the concept, this flow setup was used to brominate 4-isopropoxyphenyl methylsulfone **2**. After reaching steady state, the reactor was run for 5.5 h and the isolated yield was determined for different time intervals (Figure 6, Table 4).

After reaching steady state, full conversion of the starting material was obtained. The work-up and purification of the end-product is very straightforward since only diluting the organic phase with Et_2O and washing with water is required. From Table 4, it is clear that stable conditions and excellent isolated yields are obtained. Compared to the batch process, the continuous-flow bromination in a glass static mixer is much faster due to the formation of an emulsion and the efficient heat and mass transfer in the biphasic system. Moreover, the formation of hypobromite can be directly coupled to the subsequent bromination reaction. Using this experimental setup, a safe, efficient, and scalable bromination is possible with a production of up to 53 g/day.

3. Conclusion

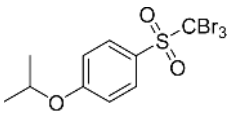
The developed continuous-flow bromination of methylsulfones and methanesulfonates forms an industrially relevant procedure for the synthesis of tribromomethylsulfones and tribromomethanesulfonates. Different halogenated methylsulfones and methanesulfonates were synthesized in excellent isolated yields. When using *N*-aryl methanesulfonamides, bromination of the aromatic system occurs. When both reactor systems are compared, the static mixer is superior to the self-assembled tube reactor due to the formation of an emulsion in the static mixer. The bromination reaction is completed in only 3 min in a glass static mixer compared to 22 h for the corresponding batch process using only a small excess of sodium hypobromite. Using the flow equivalent of a continuous stirred tank reactor, hypobromite can be prepared continuously and subsequently used in the bromination reaction. Quantitative conversion is obtained and leads to a throughput up to 53 g/day. In this way, a very efficient and safe method is developed for the bromination of methylsulfones and methanesulfonates.

4. Experimental

4.1. Batch Procedures

4.1.1. Synthesis of Starting Materials. Noncommercial starting materials were prepared based on literature procedures [15]. Methanesulfonates were prepared using the following procedure (experimental procedure for the synthesis of phenyl methanesulfonate; the synthesis of other methanesulfonates is analogous). To a stirred solution of 5 g phenol (53.12 mmol, 1 equiv.) and 5.9 g Et_3N (58.4 mmol, 1.1 equiv.) in CH_2Cl_2, 6.7 g methanesulfonyl chloride (58.4 mmol, 1.1 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred 1 h at 0 °C and 1 h at room temperature and subsequently diluted with EtOAc. The organic phase was washed with water and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, 8.69 g phenyl methanesulfonate (50.46 mmol) was isolated (95%). Spectral data of all synthesized starting materials are in comparison with literature [16].

4.1.2. Synthesis of 4-Isopropoxyphenyl Tribromomethylsulfone 3. Approximately 13.08 g KOH (233.23 mmol, 20 equiv.) was dissolved in 30 mL H_2O, and the solution was cooled to 0 °C. Subsequently, 2.4 mL Br_2 (46.65 mmol, 4 equiv.) was added dropwise resulting in the formation of a yellow KOBr solution. Meanwhile, 2.5 g 4-isopropoxyphenyl methylsulfone (11.7 mmol, 1 equiv.) and 1.88 g TBABr (5.83 mmol, 0.5 equiv.) were dissolved in 40 mL toluene. The reaction mixture was heated to 50–60 °C in order to dissolve all TBABr. In the next step, the KOBr solution was added dropwise to the solution of the starting material and PTC at 38 °C over a period of 7 min. Subsequently, the reaction mixture was stirred vigorously during 22 h at 38 °C. Et_2O and H_2O were added to the reaction mixture after which the organic phase was washed with H_2O and brine. The organic phase was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. Approximately 4.98 g 4-isopropoxyphenyl tribromomethylsulfone (11.04 mmol) was isolated (94%). No further purification of the end product was necessary.



3

4-Isopropoxyphenyl Tribromomethyl Sulfone 3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (6H, d, J = 6.07 Hz, 2 × CH_3); 4.70 (1H, septet, J = 6.07 Hz, C<u>H</u>$(CH_3)_2$); 7.00–7.04 (2H, m, 2 × CH_{arom}); 8.11–8.14 (2H, m, 2 × CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 21.79 (2 × CH_3); 51.82 (C_qBr_3); 70.99 (<u>C</u>H$(CH_3)_2$); 115.24 (2 × CH_{arom}); 118.12 (C_qS); 135.97 (2 × CH_{arom}); 164.18 (C_q0). IR (cm^{-1}): ν_{max}: 1152, 1346 (RSO_2R). MS: m/z (%): 467.8 ([M +NH_4]$^+$, 100); 469.8 ([M+NH_4]$^+$, 100). Melting point: T_m = 126 °C. Chromatography: PE–EtOAc (95:5) R_f = 0.10. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 94% (white crystals).

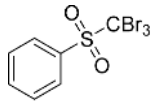
4.2. Continuous-Flow Process. The following solutions are prepared in advance:

1. A 1 M KOBr solution is prepared by dropping 1.28 mL Br_2 to 25 mL of a 5.9 M aq. KOH solution at 0 °C.
2. A solution of 0.3 M substrate and 0.15 M TBABr is prepared by dissolving 2.57 g 4-isopropoxyphenyl methylsulfone and 1.93 g TBABr in toluene until a total volume of 40 mL is obtained. The solution is heated to 50–60 °C in order to dissolve all TBABr and is pumped at this temperature through the reactor.

The glass static mixer is rinsed by pumping water and toluene through the reactor. Subsequently, the reactor is heated to 85 °C and both reagent solutions are pumped through the mixer block at a total flow rate of 0.6 mL/min (F_{KOBr} = 0.33 mL/min; $F_{Substrate/TBABr}$ = 0.27 mL/min) and, thus, a residence time of 3 min and a ratio KOBr–substrate of 4. After reaching steady state (11 min), a sample was collected for 45 min. After collection, the sample was diluted with water and Et_2O. The organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure. Approximately 1.64 g 4-isopropoxyphenyl tribromomethylsulfone was isolated (quantitative yield). No further purification of the end product was necessary.

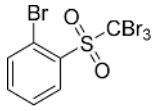
The synthesis of the other derivatives is analogous. Each time, a sample was collected for 40 to 45 min and worked up.

In some cases, the end product needs further purification (recrystallization from MeOH or column chromatography) as stated underneath.



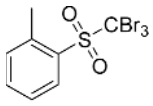
4

Phenyl Tribromomethyl Sulfone 4. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62–7.67 (2H, m, 2 × CH_{arom}); 7.78–7.83 (1H, m, CH_{arom}); 8.24–8.27 (2H, m, 2 × CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 50.55 (C_qBr_3); 128.56 ($C_{q,arom}$); 128.82 (2 × CH_{arom}); 133.64 (2 × CH_{arom}); 135.76 (CH_{arom}). IR (cm^{-1}): ν_{max}: 1152, 1334 (RSO_2R). MS: m/z (%): 409.8 ($[M+NH_4]^+$, 100); 411.7 ($[M+NH_4]^+$, 100). Melting point: T_m = 149 °C. Chromatography: PE–EtOAc (95:5) R_f = 0.14. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 87% (pale white crystals).



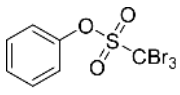
5

2-Bromophenyl Tribromomethyl Sulfone 5. Purification: recrystallization from MeOH. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56–7.61 (2H, m, 2 × CH_{arom}); 7.86–7.90 (1H, m, CH_{arom}); 8.45–8.50 (1H, m, CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 50.74 (C_qBr_3); 125.69 ($C_{q,arom}$); 127.43 (CH_{arom}); 128.40 ($C_{q,arom}$); 136.45 (CH_{arom}); 137.10 (CH_{arom}); 138.19 (CH_{arom}). IR (cm^{-1}): ν_{max}: 1158, 1343 (RSO_2R). MS: m/z (%): 489.7 ($[M+NH_4]^+$, 100); 487.7 ($[M+NH_4]^+$, 65); 411.7 ($[M+NH_4]^+$, 65). Melting point: T_m = 109 °C. Chromatography: PE–EtOAc (95:5) R_f = 0.12. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 48% (brownish solid).



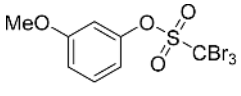
6

2-Methylphenyltribromomethyl Sulfone 6. Purification: column chromatography (70:30, PE–EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.91 (3H, s, CH_3); 7.41–7.45 (2H, m, 2 × CH_{arom}); 7.65 (1H, txd, J_1 = 7.6 Hz, J_2 = 1.3 Hz, CH_{arom}); 8.32 (1H, ~d, J = 8.1 Hz, CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 22.62 (CH_3); 52.50 (C_qBr_3); 126.19 (CH_{arom}); 127.04 (C_qS); 133.50 (CH_{arom}); 135.76 (CH_{arom}); 136.29 (CH_{arom}); 143.48 (C_qCH_3). IR (cm^{-1}): ν_{max}: 1155, 1332 (RSO_2R). MS: m/z (%): 423.8 ($[M+NH_4]^+$, 100); 425.8 ($[M+NH_4]^+$, 100). Melting point: T_m = 102 °C. Chromatography: PE–EtOAc (95:5) R_f = 0.17. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 77% (pale white solid).



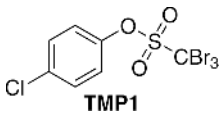
7

Phenyl Tribromomethanesulfonate 7. Purification: column chromatography (97.5:2.5, PE–EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33–7.37 (1H, m, CH_{arom}); 7.41–7.46 (4H, m, 4 × CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 37.82 (C_qCBr_3); 121.37 (2 × CH_{arom}); 127.75 (CH_{arom}); 129.92 (2 × CH_{arom}); 151.06 (C_qOS). IR (cm^{-1}): ν_{max}: 1192, 1379 ($ROSO_2R$). MS: no ionization observed. Chromatography: PE–EtOAc (95:5) R_f = 0.25. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 87% (brownish liquid).



8

3-Methoxyphenyl Tribromomethanesulfonate 8. Purification: column chromatography (97.5:2.5, PE–EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.83 (3H, s, CH_3O); 6.89 (1H, dxd, J_1 = 8.32 Hz, J_2 = 2.32 Hz, CH_{arom}); 6.95 (1H, t, J = 2.32 Hz, CH_{arom}); 7.02 (1H, dxd, J_1 = 8.32 Hz, J_2 = 2.32 Hz, CH_{arom}); 7.33 (1H, t, J = 8.32 Hz, CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 37.84 (C_qCBr_3); 55.66 (CH_3O); 107.50 (CH_{arom}); 113.42 (CH_{arom}); 113.55 (CH_{arom}); 130.23 (CH_{arom}); 151.70 (C_qOS); 160.60 (C_qOCH_3). IR (cm^{-1}): ν_{max}: 1181, 1385 ($ROSO_2R$). MS: no ionization observed. Melting point: T_m = 97 °C. Chromatography: PE–EtOAc (95:5) R_f = 0.37. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 83% (white solid).



TMP1

4-Chlorophenyl Tribromomethanesulfonate 9. Purification: column chromatography (95:5, PE–EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36–7.44 (4H, m, 4 × CH_{arom}). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 37.47 (C_qCBr_3); 122.83 (2 × CH_{arom}); 130.04 (2 × CH_{arom}); 133.52 (C_qCl); 149.50 (C_qOS). IR (cm^{-1}): ν_{max}: 1194, 1391 ($ROSO_2R$). MS: no ionization observed. Melting point: T_m = 58 °C. Chromatography: PE–EtOAc (95:5) R_f = 0.22. HRMS (ESI or APCI): no ionization observed. Elementary analysis: degradation of compound. Yield: 84% (pale white solid).

4.3. Synthesis of KOBr in Flow. The following solutions are prepared in advance:

1. 5 M KOH in H_2O
2. 0.3 M 4-isopropoxyphenyl methylsulfone and 0.15 M TBABr in toluene. The solution is heated to 50–60 °C in order to dissolve all TBABr and is pumped at this temperature through the reactor.

The glass static mixer is rinsed by pumping water and toluene through the reactor. Subsequently, the reactor is heated to 85 °C. Bromine (17 μL/min) and the KOH solution (0.31mL/min) are pumped in a vial at room temperature containing a rotating stirring bar. Hence, a 1 M KOBr solution is obtained. After building up a buffer volume, the KOBr solution is pumped through the mixer block together with the solution containing the substrate and PTC at a total flow rate of 0.6 mL/min (F_{KOBr} = 0.33 mL/min; $F_{Substrate/TBABr}$ = 0.27 mL/min) and, thus, a residence time of 3 min and a ratio KOBr–substrate of 4. The complete system was run for 30 min before collection started. Isolated yields were determined at different time intervals. Each time, the samples were diluted with water and Et_2O. Subsequently, the organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure (Table 4 gives an overview of the isolated yields in the different time intervals). No further purification of the end product was necessary.

Supporting Information

Electronic Supplementary Material (ESM) (detailed description and photographs of the experimental setup, calculation of the interfacial area of the plug flow, and copy of the ^{1}H- and ^{13}C-spectra) associated with this article is available in the online version at doi:10.1556/JFC-D-14-00006.

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