Electronic Supplementary Information

A continuous flow investigation of sulfonyl chloride synthesis using *N*-chloroamides: optimization, kinetics and mechanism

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2 General Information

2.1 Materials and Methods

All materials were obtained from commercial suppliers (TCI, Sigma Aldrich, Alfa Aesar or VWR) and used without further purification unless otherwise noted. 1,3-Dichloro-5,5-dimethylhydantoin (DCH, **2**) was purchased from Alfa Aesar (98% purity) and used without further purification.

2.2 High Field NMR

NMR spectra were recorded on a Bruker 300 MHz instrument. ^{1}H and ^{13}C spectra were recorded at 300 MHz and 75 MHz, respectively, with a chemical shift relative to TMS expressed in parts per million (ppm). The samples were prepared in $CDCl_3$. The letters s, d, t and m are used to indicate singlet, doublet, triplet, and multiplet, respectively.

2.3 GC-FID Analysis

GC-FID analysis was performed on a Shimadzu GC FID 230 with a flame ionization detector, using an RTX-5MS column (30 m × 0.25 mm ID × 0.25 µm) and helium as carrier gas (40 cm sec^{-1} linear velocity). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C/min to 300 °C and kept constant at 300 °C for 4 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 quality).

2.4 GC-MS Analysis

GC-MS analysis was performed using a Shimadzu GCMS-QP2010 SE, using an RTX-5MS column (30 m × 0.25 mm × 0.25 µm) and helium as carrier gas with a linear velocity of 40 cm/sec. The injector temperature was set to 280 °C. After 1 min at 50 °C, the oven temperature was increased by 25 °C/min to 300 °C and then kept at 300 °C for 3 min. The mass detector was a quadrupole with pre rods and electron impact ionization. The following settings were used in the detector: ion source temperature 200 °C, interface temperature 310 °C, solvent cut time 2 min 30 sec, acquisition mode scan, mass range m/z = 50 till m/z = 400.

2.5 Typical GC-FID Chromatogram

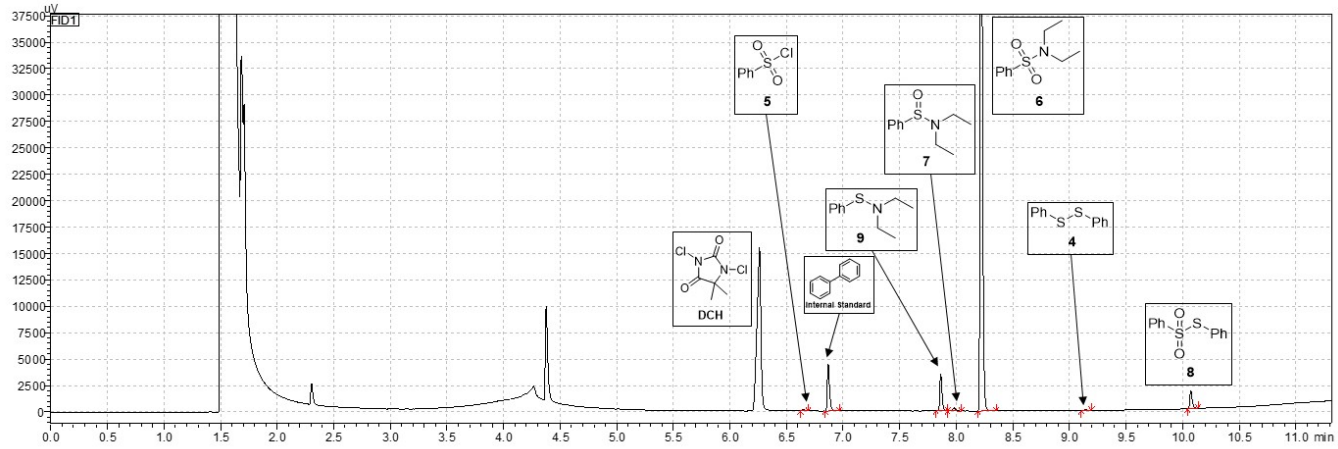


Fig. S1. Representative GC-FID chromatogram of the chlorosulfonylation reaction of diphenyl disulfide (**4**).

2.6 GC-FID Calibration

The quantity of the substrate, product, and intermediates were determined by GC-FID against biphenyl as an internal standard.

For this, calibration curves for diphenyl disulfide (**4**), biphenyl, *N*,*N*-diethylbenzenesulfonamide (**6**), and thiophenol (**4'**) were measured (see Fig. S2). The corresponding relative response factors were calculated.

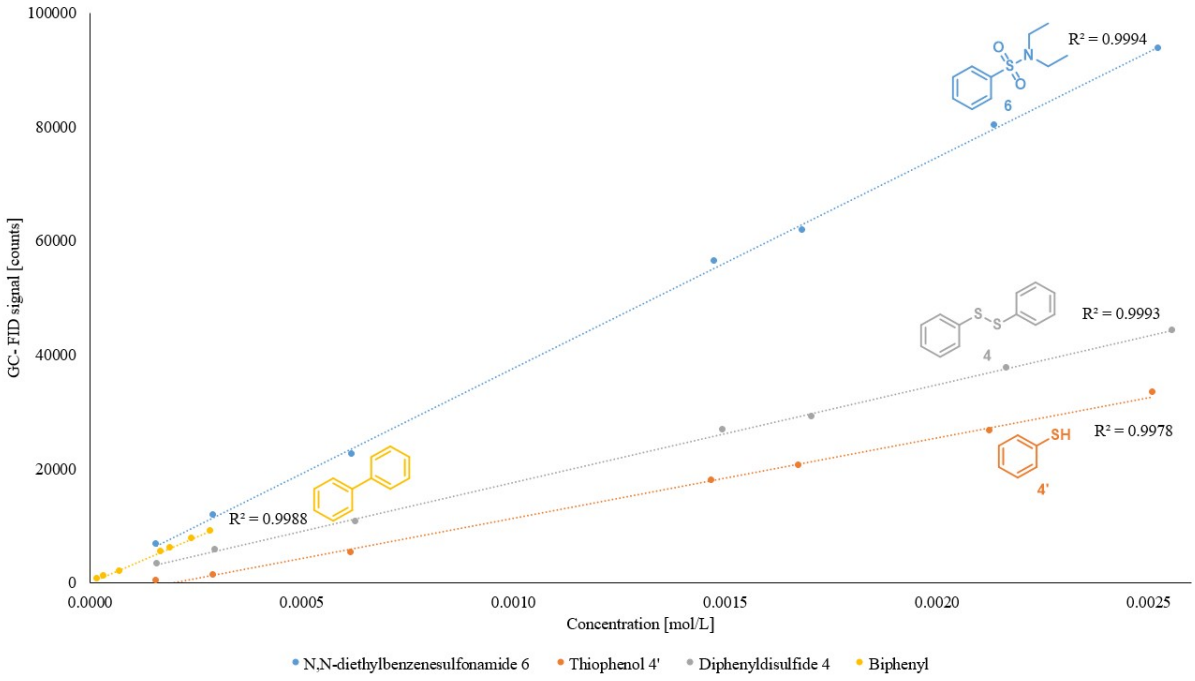


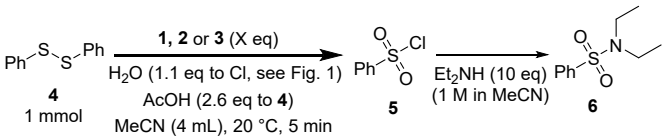
Fig. S2. GC-FID calibration graph for the analysis of the chlorosulfonylation reaction of diphenyl disulfide (**4**).

2.7 Flash Column Chromatography

Automated flash column chromatography was performed on a Biotage Isolera system using columns packed with KP-SIL, 60 Å (32-63 µm particle size) silica.

3 Initial Batch Experiments

3.1 Reagent Screenings



Scheme S1. Reaction scheme for the initial solvent screening in batch. 1 mmol scale using a 0.25 M substrate **4** solution. The experimental procedure is described below.

The obtained reaction mixtures from the experiments using NCS (**1**), DCH (**2**) and TCCA (**3**) can be seen in Fig. S3. By increasing the equivalents, which correlates to an increase in product content, the color fades from a strong yellow to a colorless solution. TCCA is insoluble in the used solvent system and a turbid solution was obtained.

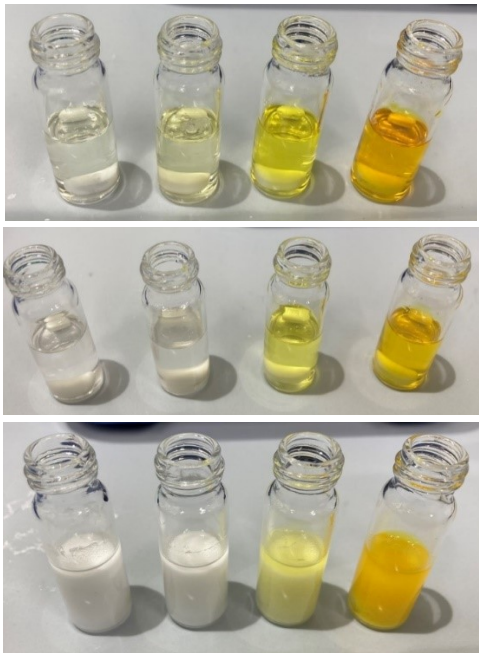


Fig. S3. Reaction mixtures of the reagent studies using NCS (1, top), DCH (2, middle), TCCA (3, bottom). From left to right following Cl equivalents were used: 5, 4, 2.5, 1.

Table S1. Measured values for the initial reagent screening. Values are determined by GC-FID using biphenyl as an internal standard. Chlorine equivalents were calculated as follows: 1 equiv. Cl was for NCS 1 equiv, for DCH 1/2 equiv and for TCCA 1/3 equiv.

Entry	Cl equiv.	Reagent	**4** [area%]	**6** [area%]	**7** [area%]	**8** [area%]	**9** [area%]
1	5	**NCS**	-	**98**	1	1	-
2	4	**NCS**	3	**63**	1	26	2
3	2.5	**NCS**	64	**2**	1	20	12
4	1	**NCS**	96	**-**	-	-	3
5	5	**DCH**	-	**97**	2	-	-
6	4	**DCH**	3	**68**	1	17	2
7	2.5	**DCH**	22	**28**	1	35	12
8	1	**DCH**	86	**-**	-	1	11
9	5	**TCCA**	-	**99**	-	1	-
10	4	**TCCA**	2	**62**	1	24	4
11	2.5	**TCCA**	28	**19**	1	39	13
12	1	**TCCA**	67	**6**	-	8	19

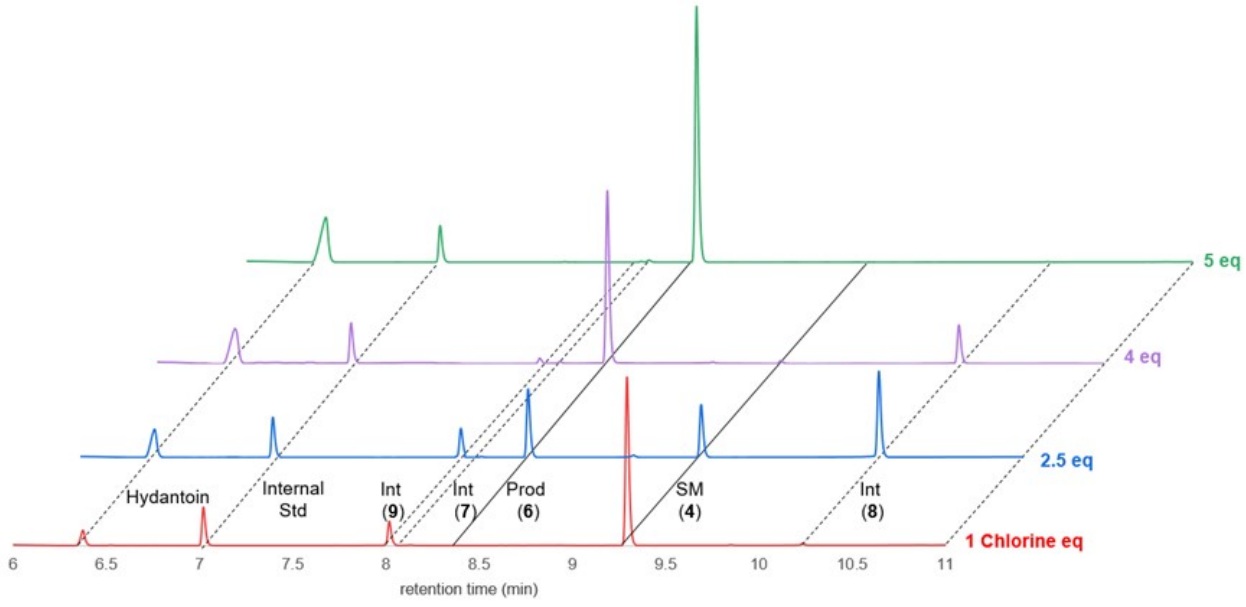
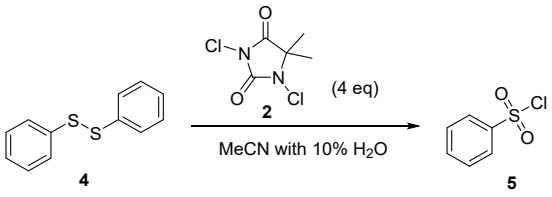


Fig. S4. GC-FID chromatograms for the chlorosulfonylation of diphenyl disulfide (**4**) with different equivalents of DCH (2).

3.2 Solvent/Reagent Studies

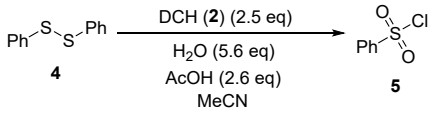
The chlorosulfonylation of diphenyl disulfide (**4**) was performed in acetonitrile with 10% water and four equivalents of DCH (**2**) (Scheme S2 and Fig. S5). This solvent system was not able to dissolve diphenyl disulfide (**4**) fully, although quantitative yield was reached after 1 min of reaction time. A high exotherm was observed during the reaction, heating the flask to a temperature close to the boiling point of the solvent mixture. This reaction demonstrated that using higher quantities of water resulted in solubility problems.



Scheme S2. Chlorosulfonylation of diphenyl disulfide in MeCN with 10% water.

Fig. S5. Chlorosulfonylation of diphenyl disulfide (**4**) in MeCN with 10% water. Left: before the addition of DCH, center: after adding DCH, right: 27 minutes reaction time.

Subsequently, acetonitrile was attempted with sufficient equivalents of water (to form HOCl) and acetic acid for quantitative yield (Scheme S3 & Fig. S6). A homogenous solution was observed throughout the whole reaction as the solid DCH could be dissolved immediately. Quantitative yield was reached after one min of reaction time. Additionally, a high exotherm was observed during the reaction.



Scheme S3. Chlorosulfonylation of diphenyl disulfide (**4**) in MeCN/AcOH/water.

Fig. S6. Chlorosulfonylation of diphenyl disulfide (**4**) in MeCN/AcOH/water. Left: before the addition of DCH (**2**), center: after adding DCH, right: 1:25 minutes reaction time.

Fig. S7. 0.86 M solution of DCH (**2**) in MeCN.

The identical experiment (Scheme S3) was repeated by adding a mixture of DCH (**2**) in acetonitrile (0.86 M), see Fig. S7. This solution was pumped to test it was possible in flow, and it worked successfully. It is important that the solution is stirred vigorously to prevent solids from settling.

4 Calorimetry Experiments

The determination of the heat of reaction (ΔH_{rxn}) was carried out using a Thermal Hazard Technology (THT) µRC Microreaction Calorimeter configured in titration mode. A 250 µL syringe was used to add the substrate **4** solution stepwise (10 × 25 µL injections). 0.250 M solution of diphenyl disulfide (**4**) in MeCN (250 µL) was prepared for addition via a syringe. A standard vial was prepared with a solution containing DCH (**2**) (0.632 M in MeCN), acetic acid (1 eq to DCH) and water (1.1 eq to DCH). The injections were performed by adding 250 µL **4** in 10 steps to the stirred solution (Table S2). Injections were made at 300 s intervals to enable stabilization of the calorimeter. Outlier results were removed for calculation of ΔH_{rxn}. The reaction exotherm was calculated with the remaining peaks and found between ΔH_{rxn} = −682 and −767 kJ/mol, giving an average of −725 kJ/mol. One reason for the deviation is due to the actual volume injected by the syringe. The measurement profile for entry 1 is shown in Fig. S8.

Table S2. Results measured in a batch microreaction calorimeter. Outliers were removed. [a]Injection 10 discarded, [b]Injection 1,2, 10 discarded, [c]Injection 3, 9, 10 discarded. Quantitative product yield was observed in all cases when the sample was tested by GC-FID post run.

Entry	T [°C]	Vial	Syringe	DCH (**2**) [eq]	Enthalpy [kJ/mol]	Mean Value ± STD [kJ/mol]
1[a]	25	DCH in MeCN, H_2O, AcOH	**4** in MeCN	5	-713, -722, -725, -706, -742, -733, -741, -756, -670	−723 ± 25
2[b]	40	DCH in MeCN, H_2O, AcOH	**4** in MeCN	5	-759, -687, -718, -649, -660, -654, -644	−682 ± 43
3[c]	40	DCH in MeCN, H_2O, AcOH	**4** in MeCN	3	-800, -821, -753, -851, -764, -683, -697	−767 ± 62
4	40	DCH in MeCN	MeCN, H_2O, AcOH	-	9, 9, 7, 5, 4, 3, 3, 2, 2, 1	4.5 ± 2.9

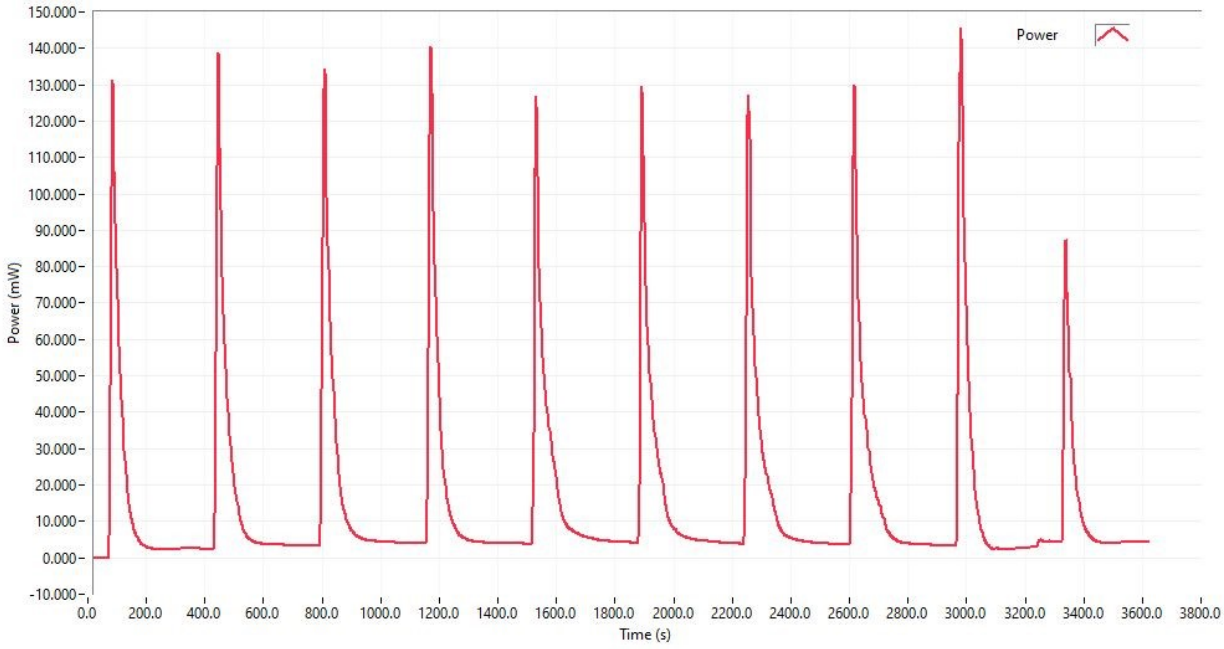


Fig. S8. Calorimetric profile obtained in entry 1. Injection 10 was an outlier.

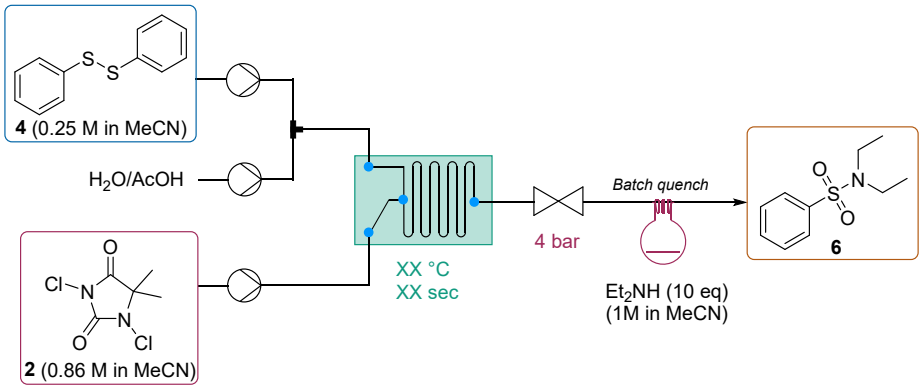
Subsequently, we calculated the adiabatic temperature rise ($\Delta T_{adiabatic}$) for the reaction. In this calculation we only consider the heat capacity of the solvent. A $\Delta T_{adiabatic}$ of 103 °C is estimated. Experimental observations showed that the reaction temperature rose to close to the boiling point of the solvent (82 °C). Thus, 103 °C is overestimating the experimental value, but can be explained by the heat transfer of the glass and the surrounding air.

$$\Delta T_{adiabatic} = -\frac{\Delta H_{reaction} * n_{diphenyl\ disulfide}}{c_{p,\,MeCN} * n_{MeCN}} = -\frac{-725\frac{kJ}{mol}\ 1\ mmol}{91.69\frac{J}{mol\ K}\ 76.6\ mmol} = 103\ K$$

5 General Flow Configurations

Standard PFA tubing (0.8 mm or 1.6 mm i.d.), PTFE or PEEK fittings and T-pieces were used in the flow setups. For pumping reagent solutions, syringe pumps (Syrris Asia) equipped with 1 and 0.5 mL syringes, or 0.5 and 0.25 mL were used, depending on the desired flow rate. All of the pumps were used with check valves (Upchurch, CV-3321) and internal pressure sensors. The pressure limit of the pumps was set to 20 bar. Above this pressure and the pumps would turn-off automatically for safety reasons. Before using the pumping systems, they were calibrated by pumping for a specified time and checking the mass balance. All pumps were found to dose within ± 2%.

5.1 Microstructured Flow Reactor Experiments



Scheme S4. Flow scheme for the chlorosulfonylation in the MMRS.

Initially, the chlorosulfonylation reaction was attempted in a Modular MicroReaction System (MMRS), manufactured by Ehrfeld Mikrotechnik (Wendelsheim, Germany), see 9 & Scheme S4. For the in- and outlets, 1/16" input connectors (0711-2-00224-F) in combination with heat exchangers (0309-4-0004-F) were used. To mix the substrate feed and the aqueous acetic acid, a simple T-piece constructed from Hastelloy C22 was used. A FlowPlate Lab (1701-3-0004-F) equipped with an SZ design Process Plate (1701-1642-HC, SZ mixer, nominal width 0.2 mm, Hastelloy C22) was used, and the temperature was controlled by a thermostat (Huber, Ministat 240). The liquid feeds were introduced at port 1 and port 2. The reaction mixture left the reactor at port 6 and then passed through a back pressure regulator BPR (Zaiput BPR-10) with 4 bar applied. The reaction mixture was reacted with 1 M Et_2NH solution in MeCN, corresponding to 10 equiv. The reaction mixture was collected in a flask.

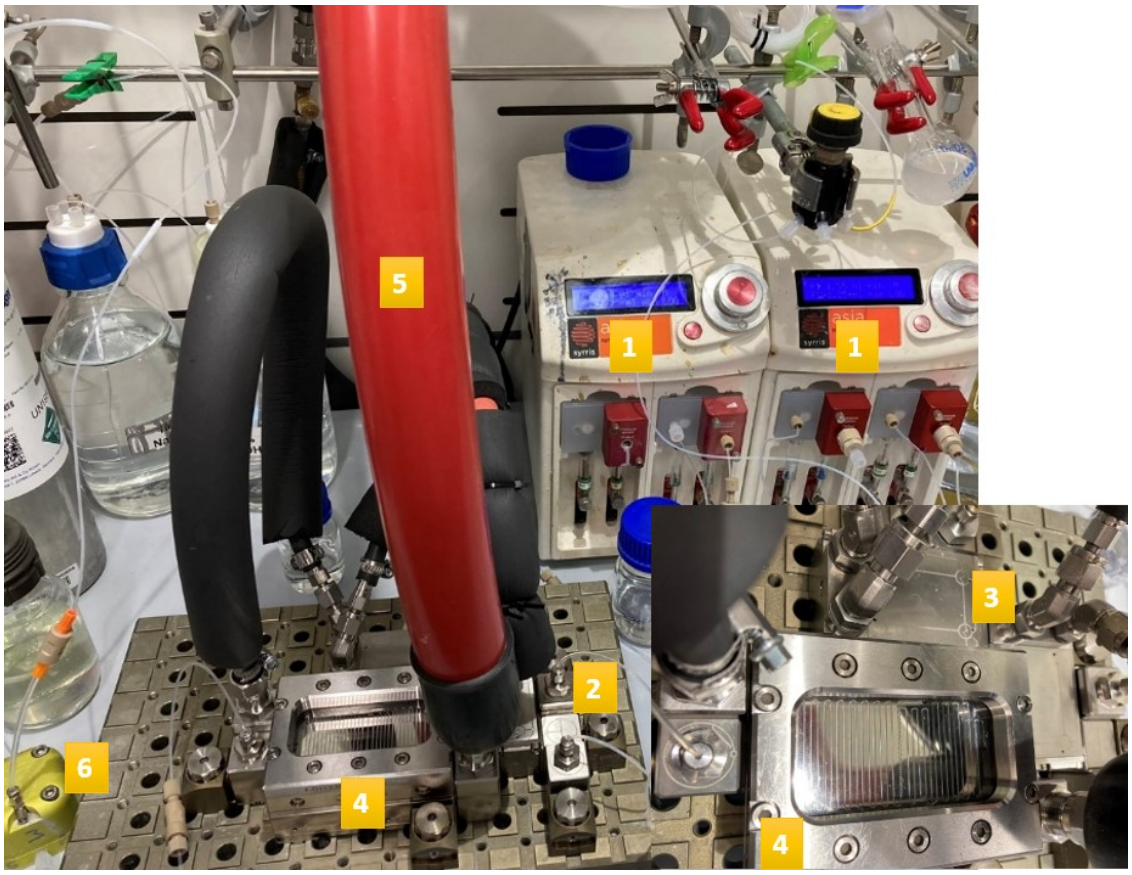


Fig. S9. MMRS Flow setup for the chlorosulfonylation. 1: Syrris Asia pumps, 2: T-mixer, 3: Heat exchanger, 4: SZ FlowPlate, 5: Thermostat, 6: Zaiput BPR-10

Similar behavior to the batch experiments was observed during the flow experiments. After a specific reaction time, a color change from intense yellow to colorless could be observed, when the reaction was successful (see 10). GC-FID analysis showed a trend that yellow solutions indicated a low yield and colorless mixtures represented higher yields. With this observation, an early prediction of the reaction success was possible.

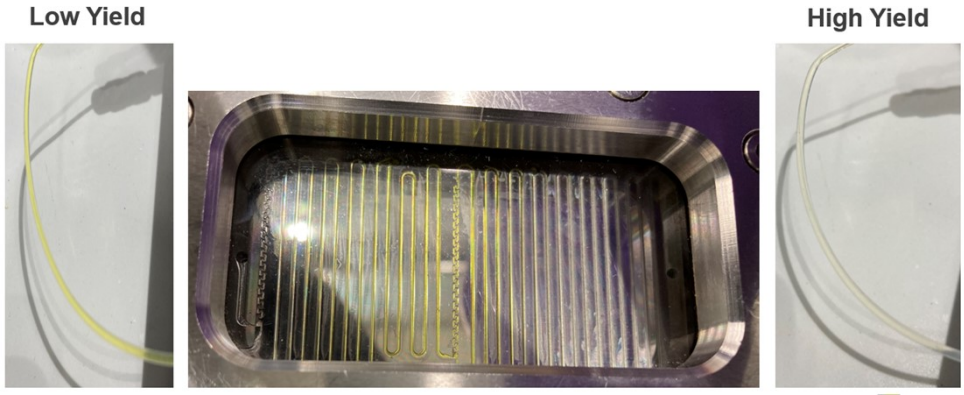


Fig. S10. Reactor observations during the chlorosulfonylation in the FlowPlate.

In the initial flow plate experiments, different temperatures, DCH equivalents, and residence times were investigated, see Table S3. At 5 °C, 27% substrate conversion, but almost no product was found. Increasing

the temperature to 20 °C led to 42% conversion, but only intermediate species were observed. Increasing the temperature to 40 °C gave complete conversion and 87% desired product yield was obtained, and 60 °C increased the yield further to 94%. These experiments showed that a specific temperature (>20 °C) is necessary to give elevated product formation.

In entries 5-7, the DCH (**2**) was varied between at 2, 2.6 and 3 equiv. Based on the proposed mechanism (shown in Scheme 5), 2.5 equivalents are necessary, which is supported by these experiments. The use of 3 equiv of DCH had no positive influence over 2.5 equiv.

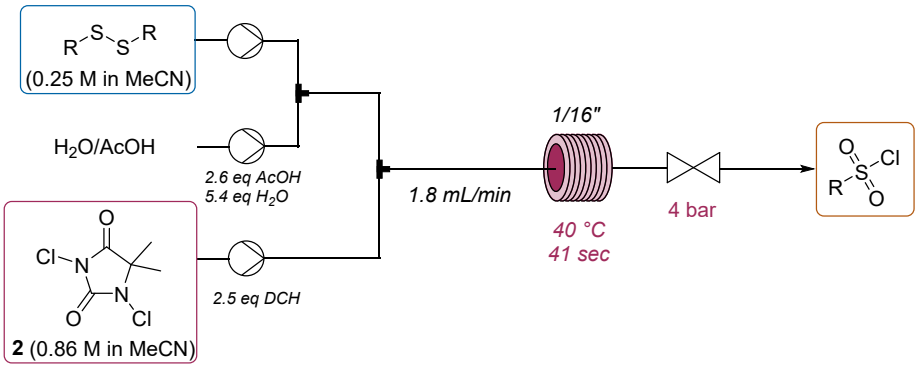
Afterwards, the residence time was varied between 24 and 97 seconds. These experiments showed a clear trend, and that a sufficient reaction time is necessary to achieve high yields. The experiments also indicated that the system was operating within a kinetic regime.

Unfortunately, acid formed within the reaction, leads to corrosion of Hastelloy C22 at elevated temperatures. Thus, the FlowPlate reactor was exchanged to T-pieces and PFA tubing for subsequent experiments.

Table S3. Results of the chlorosulfonylation experiments of diphenyl disulfide in the FlowPlate.

Entry	t_{res} [s]	T [°C]	DCH [equiv]	**6** [%]	**8** [%]	**7** [%]	**9** [%]	**4** [%]
1	48.4	**5**	2.6	**1**	6	15	5	73
2	48.4	**20**	2.6	**1**	10	25	7	58
3	48.4	**40**	2.6	**87**	7	3	3	-
4	48.4	**60**	2.6	**94**	1	-	3	-
5	52.8	40	**2**	**66**	12	11	10	1
6	48.4	40	**2.6**	**87**	7	3	3	-
7	44.7	40	**3**	**87**	8	3	1	1
8	**24.2**	40	2.6	**45**	16	32	7	1
9	**48.4**	40	2.6	**87**	7	3	3	-
10	**96.8**	40	2.6	**98**	-	1	-	-

5.2 Tubing Experiments



Scheme S5. Continuous flow scheme for the chlorosulfonylation in tubing.

The chlorosulfonylation reaction was performed in a reactor coil constructed of PFA tubing. The tubing was submerged in a heated water bath for temperature control. Simple T-pieces made of PTFE or PFA were used to mix the feeds. Initially, the substrate and the aqueous acetic acid feeds were mixed, which then subsequently mixed with the DCH feed. After the heated coil, the mixture was passed through a BPR (Zaiput BPR-10) with 4 bar applied. The reaction mixture was quenched with 1 M Et_2NH solution in MeCN, corresponding to 10 equiv. The reaction mixture was collected in a flask.

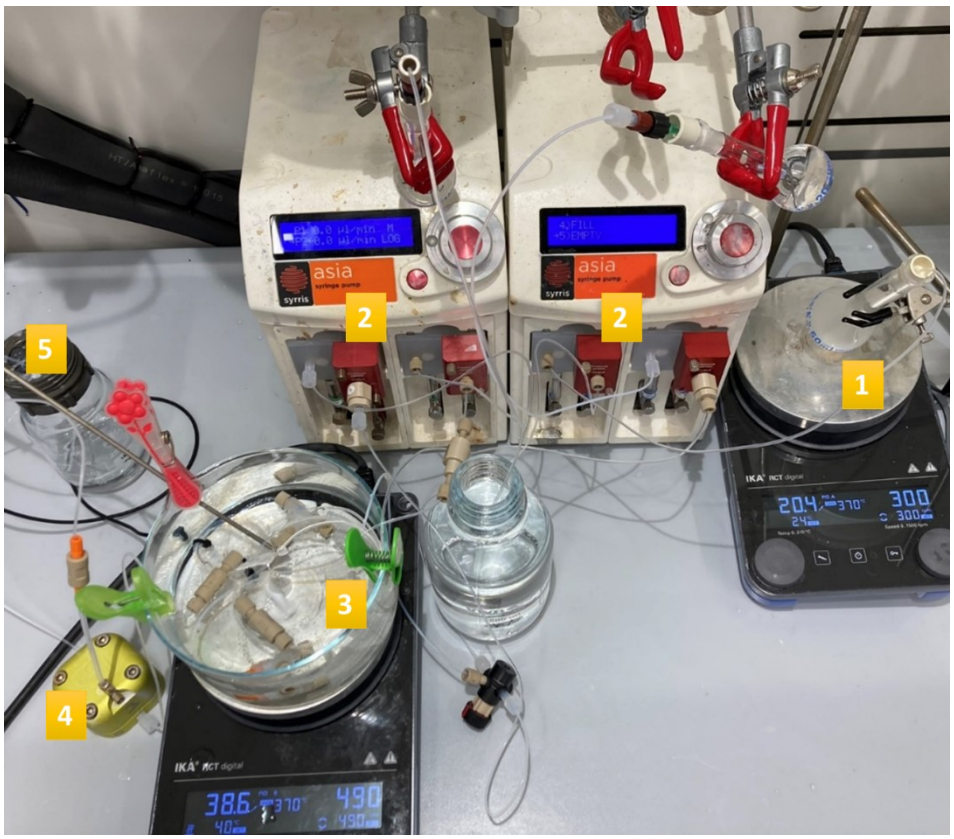


Fig. S11. Reaction setup for the chlorosulfonylation experiments in plastic tubing.

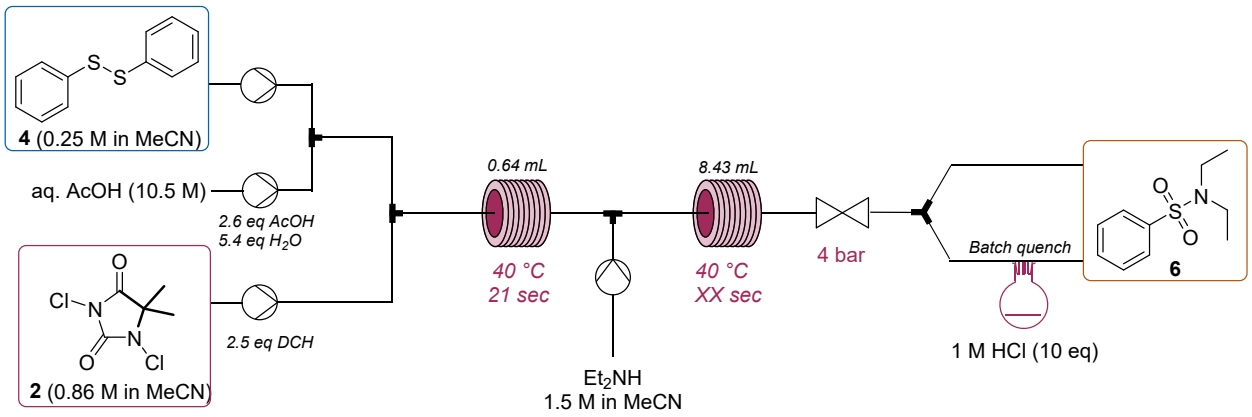
5.2.1 Reproducibility

A set of conditions were repeated several times during the study to assess the reproducibility of the experiments. The results are shown in Table S4.

Table S4. Reproducibility experiments. Conditions: 1/16 "tubing with 639 µL internal volume, 1.8 mL/min total flow rate, 41 s residence time, 40 °C, 2.5 equiv. DCH, 5.4 eq. water. Results are determined by GC-FID using biphenyl as an internal standard.

Entry	Date of exp.	Time of exp.	**4** [%]	**6** [%]	**8** [%]	**7** [%]	**9** [%]
1	24/01/22	1 pm	-	**95**	-	1	4
2	01/03/22	8 am	-	**92**	1	6	1
3	08/03/22	8 am	3	**96**	-	-	-
4	08/03/22	9 am	-	**92**	1	6	1
5	04/02/22	10 am	-	**96**	2	1	1
6	04/02/22	3 pm	-	**96**	2	1	1

5.3 Amination in flow



Scheme S6. Flow scheme for the telescoped chlorosulfonylation reaction followed by the amination reaction.

Experiments were executed to show the feasibility of also performing the amination step within a continuous flow configuration to form a sulfonamide as a telescoped process. The optimized conditions from the chlorosulfonylation were taken shown in Scheme 3. After 41 seconds of residence time for the chlorosulfonylation step, Et_2NH (1.5 M in MeCN) was introduced using a T-piece. After that, a second coil (1/16", 8.43 mL) at 40 °C was used, giving residence times between 146 and 180 seconds. For each set of conditions, two samples were taken under steady-state conditions (3 reactor volumes worth of material). One was measured directly on the GC-FID, and the second one was quenched with ten equivalents of HCl (1 M). The results are shown in Table S5. As discussed in the main manuscript, six amine equivalents were insufficient as high amounts of sulfonyl chloride **5** remained, which confirmed that additional amine was necessary. In entries 2_1 and 2_2, 8.6 equiv of amine provided the sulfonamide in high yield. Increasing the

amount of amine (entries 3_1 and 3_2) further than 8.6 equiv did not further improve the product yield. Thus, the feasibility of forming sulfonamides in a telescoped manner using continuous flow technique was demonstrated.

Table S5. Results for the telescoped flow protocol to form sulfonamide **6**. Conditions as described in Scheme S6. Results are determined by GC-FID using biphenyl as an internal standard.

	Et_2NH [eq]	$t_{res,\ amine}$ [sec]	Batch HCl quench	**5** [%]	**6** [%]	**8** [%]	**7** [%]	**9** [%]
1_1	6.0	180	-	36.7	**52.8**	6.3	3.2	0.3
1_2	6.0	180	10 eq	46.0	**46.0**	2.8	-	-
2_1	8.6	156	-	-	**94.4**	1.9	2.6	0.2
2_2	8.6	156	10 eq	3.3	**94.5**	1.0	-	-
3_1	10.0	146	-	-	**90.2**	3.2	4.9	1.2
3_2	10.0	146	10 eq	4.7	**93.3**	1.3	-	-

6 Data Kinetic Profiling

Figures 2-6 in the main manuscript were drawn using the experimental data shown below.

- Fig. 2: a (entries 1-9), b (1-9), c (10-23), d (25-32)
- Fig. 3: entries 1-9
- Fig. 4: entries 10-21
- Fig. 5: entries 1-9, 43-49, 50-56
- Fig. 6: entries 1-9, 33-42

Table S6. Data for the temporal kinetic profiles. [a] Reactor types: A - 1/16" diameter & 639 µL; B - 1/16" diameter & 539 µL; C – 1/16" diameter & 1288 µL. [b] ½ concentration → 0.07 M product after the reactor. [c] 10% 5 added to the substrate feed. [d] 20% 5 added to the substrate feed.

Entry	Reactor[a]	t_{res} [sec]	T [°C]	DCH [equiv.]	Water [equiv.]	4 [%]	6 [%]	8 [%]	7 [%]	9 [%]
1	A	16	30	2.5	5.4	40	9	2	30	18
2	B	25	30	2.5	5.4	36	5	3	31	24
3	A	27	30	2.5	5.4	16	10	3	41	30
4	A	33	30	2.5	5.4	-	38	11	36	16
5	B	34	30	2.5	5.4	-	53	3	34	10
6	A	41	30	2.5	5.4	-	81	2	15	1
7	A	41	30	2.5	5.4	-	83	2	14	1
8	B	44	30	2.5	5.4	-	97	1	1	1
9	A	55	30	2.5	5.4	-	98	1	-	-
10	B	15	40	2.5	5.4	33	5	2	36	25
11	A	16	40	2.5	5.4	30	6	6	40	18
12	B	19	40	2.5	5.4	17	4	11	59	8

13	B	22	40	2.5	5.4	7	11	3	42	36
14	A	27	40	2.5	5.4	2	49	9	30	10
15	A	27	40	2.5	5.4	1	50	5	30	13
16	C	31	40	2.5	5.4	-	71	6	14	8
17	B	36	40	2.5	5.4	-	81	2	15	2
18	A	41	40	2.5	5.4	-	96	-	1	3
19	A	41	40	2.5	5.4	-	96	3	1	1
20	A	41	40	2.5	5.4	-	96	3	-	1
21	C	58	40	2.5	5.4	-	98	1	1	-
22	C	61	40	2.5	5.4	-	97	1	1	-
23	C	63	40	2.5	5.4	-	97	1	1	1
24	A	82	40	2.5	5.4	-	99	-	-	-
25	B	15	50	2.5	5.4	5	17	4	48	26
26	B	17	50	2.5	5.4	-	35	5	42	19
27	A	21	50	2.5	5.4	-	64	3	26	7
28	A	27	50	2.5	5.4	-	74	3	22	1
29	A	41	50	2.5	5.4	-	91	2	4	3
30	A	41	50	2.5	5.4	-	91	2	4	3
31	A	48	50	2.5	5.4	-	91	2	4	3
32	A	55	50	2.5	5.4	-	91	2	4	3
33[b]	A	16	30	2.53	10.76	77	-	1	16	6
34[b]	A	20	30	2.53	10.76	69	1	2	18	10
35[b]	A	27	30	2.53	10.76	62	1	2	21	13

36[b]	A	32	30	2.53	10.76	55	2	7	31	6
37[b]	A	37	30	2.53	10.76	51	2	7	26	14
38[b]	A	41	30	2.53	10.76	43	3	10	33	12
39[b]	A	54	30	2.53	10.76	-	48	18	31	4
40[b]	A	60	30	2.53	10.76	-	89	5	5	1
41[b]	A	68	30	2.53	10.76	-	93	3	4	-
42[b]	A	77	30	2.53	10.76	-	92	4	4	1
43[c]	A	16	30	2.5	5.43	-	9	6	36	17
44[c]	A	21	30	2.5	5.43	-	25	7	38	14
45[c]	A	23	30	2.5	5.43	-	39	15	44	2
46[c]	A	27	30	2.5	5.43	-	54	5	30	11
47[c]	A	33	30	2.5	5.43	-	66	3	22	9
48[c]	A	37	30	2.5	5.43	-	78	3	15	4
49[c]	A	55	30	2.5	5.43	-	94	1	5	-
50[d]	A	16	30	2.51	5.44	11	15	10	42	22
51[d]	A	21	30	2.51	5.44	-	34	11	40	15
52[d]	A	24	30	2.51	5.44	-	45	7	37	10
53[d]	A	27	30	2.51	5.44	-	62	5	23	10
54[d]	A	33	30	2.51	5.44	-	72	3	17	8
55[d]	A	37	30	2.51	5.44	-	81	2	13	4
56[d]	A	55	30	2.51	5.44	-	91	1	7	1

7 General Procedures

7.1 Chlorosulfonylation Batch Procedures

An exemplary batch procedure is described below. If not otherwise noted, batch experiments were executed using this procedure.

Substrate (1 mmol) was dissolved in acetonitrile (4 mL, 0.25 M). Then acetic acid (150 µL, 2.6 eq) and water (100 µL, 5.4 eq) were added. The 4 mL screw cap vial was placed in a metal block at room temperature and stirred heavily (min. 500 rpm) using a magnetic stirrer. Subsequently, the reagent, e.g. 1,3-dichloro-5,5-dimethyl hydantoin (**2**), was slowly added as a solid, whilst maintaining the reaction temperature below the boiling point. After five min, 10 µL reaction mixture was diluted in 990 µL acetonitrile and analyzed by GC analysis. For the amination, Et_2NH (1 M in MeCN) was added to the GC vial in excess (10 equiv).

7.2 Chlorosulfonylation Flow Experiments

All feed solutions were prepared in volumetric flasks. *Example substrate feed preparation:* diphenyl disulfide (**4**) (5.53 g, 25.3 mmol) and biphenyl (0.390 g, 2.53 mmol) were dissolved in MeCN (100 mL, 0.253 M **4**). *Example reagent feed preparation:* 1,3-Dichloro-5,5-dimethyl hydantoin (DCH, **2**) (16.7 g, 84.8 mmol) was dissolved in MeCN (100 mL, 0.848 M **2**). This feed mixture was continuously stirred. *Example amidation feed preparation:* Diethylamine (2.19 g, 29.9 mmol) was dissolved in MeCN (30.0 mL, 0.998 M). After mixing, the flasks were sealed, and a needle sucked out the feed solution through tubing directly into the pump.

Before running the reactions, the system was flushed with technical grade MeCN for 10 min. After the experiments, the setup was rinsed with MeCN and stored under isopropanol.

The reaction outlet was collected in 4 mL vials containing a specific amount of quench solution and a stirring bar for a defined time depending on the flow rate (between 9 to 30 seconds) after reaching steady-state (minimum of three reactor volumes). For every set of conditions, three fractions were collected and analyzed on the GC.

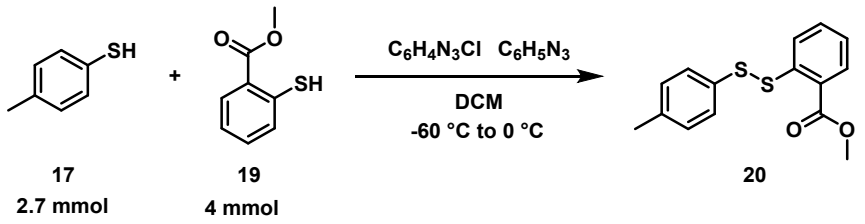
A 20 µL quenched reaction mixture was diluted in 1 mL acetonitrile for GC analysis. All the compounds were quantified using GC-FID using biphenyl as internal standard. The same samples were analyzed by GC-MS using their molecular weights for identification. Isolated compounds were characterized by NMR analysis. NMR samples were prepared in $CDCl_3$.

Within the substrate scope, no quench reaction was performed. The reaction outlet was collected in a round bottom flask for between 6.5 to 12 minutes, depending on the scale of the reaction. To check the performance of the reaction a quenched sample was taken before and after the product collection.

The following isolation procedure was used for the substrate scope and the long run experiment: the obtained solution was concentrated to near dryness under vacuum at 30 °C. The crude product was diluted with CH_2Cl_2 (15 mL), and aqueous saturated $NaHCO_3$ (10 mL) was added. The mixture was stirred for 15 minutes, and the organic phase was washed with brine (2 ×10 mL). The organic phase was dried over

Na_2SO_4 and filtered. The organic solvent was evaporated and dried at 2 mbar at 40 °C to afford the desired sulfonyl chloride products.

7.3 Synthesis of an Unsymmetrical Disulfide



Scheme S7. Synthesis of an unsymmetrical disulfide.

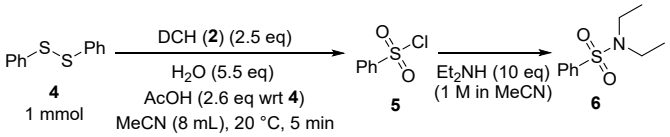
The synthesis of methyl 2-(*p*-tolyldisulfaneyl)benzoate (**21**) was conducted based on a procedure published by Hunter *et al*.[1]

To a stirred solution of 1-chlorobenzotriazole (0.611 g, 4.00 mmol) and benzotriazole (0.331 g, 2.78 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added dropwise a solution of methyl thiosalicylate (**19**) (0.680 g, 4.04 mmol) in CH_2Cl_2 (2 mL). The solution was allowed to stir for 3 h with slow warming to -20 °C. 4-methylbenzenthiol (**17**) (0.336 g, 2.70 mmol) in CH_2Cl_2 (2 mL) was then added slowly at -20 °C and the solution was stirred at 0 °C for 30 min. The reaction was then quenched with a solution of $Na_2S_2O_3$ (0.508 g in 10 mL water) together with saturated aqueous $NaHCO_3$ (20 mL), with rapid stirring at 0 °C for 20 min before being extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography using cyclohexane/EtOAc (linear gradient from 0 to 18% EtOAc) to afford **20** (0.621 g, 2.14 mmol, 80%) as a white solid. The main side product was dimethyl-2,2'-dithiobisbenzoate (**23**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, *J* = 2.1 Hz, 2H), 7.52 (m, *J* = 3.4 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.25 (q, *J* = 5.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.98 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.3, 125.4, 125.9, 126.9, 127.7, 129.9, 131.4, 132.7, 133.0, 137.1, 141.5, 166.8. GC-MS analysis: m/z 270 confirmed.

7.4 Batch Experiments to Compare with a Phase Transfer Catalyst

To test the role of the product in the autocatalytic cycle two batch experiments were executed in parallel, one with the developed standard conditions and one using Bu_3MeNCl to show the increase in reaction rate.

7.4.1 Standard Conditions



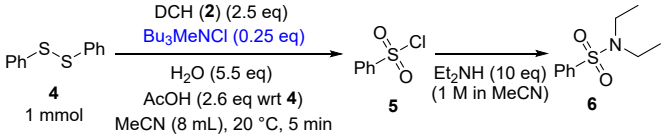
Scheme S8. Reaction scheme for the chlorosulfonylation in batch. 1 mmol scale using a 0.25 M substrate solution. The experimental procedure is described below.

The standard batch procedure was executed as described below. The obtained yields of **6** after the quench with diethylamine are shown in Table S7. The reaction went to completion within 45 seconds reaction time.

Table S7. Measured values for the chlorosulfonylation of diphenyl disulfide (**4**) in batch. Values are determined by GC-FID compared to biphenyl as an internal standard. Reaction time is defined until taking a sample and putting it into Et_2NH (1 M in MeCN).

Reaction time [sec]	**4** [%]	**6** [%]	**7** [%]	**8** [%]	**9** [%]
15	63	6	20	-	11
30	12	17	42	1	27
45	-	98	-	-	-
60	-	99	-	-	-
300	-	99	-	-	-

7.4.2 Addition of Bu_3MeNCl



Scheme S9. Reaction scheme for the chlorosulfonylation in batch when adding Bu_3MeNCl in catalytic amounts (0.25 eq). 1 mmol scale using a 0.25 M substrate solution. The experimental procedure is described below.

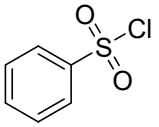
To show the potential influence of a R-Cl bond in the system on the reaction rate, Bu_3MeNCl was added in a catalytic amount (0.25 eq). The standard batch procedure was executed as described below. The obtained yields of **6** after the quench with diethylamine are shown in Table S8. The reaction went to completion within 15 seconds reaction time. Unfortunately, the ability to sample before 15 seconds reaction time was not possible in batch, so all samples showed quantitative yield for product **6**. We found that the reaction is significantly faster when adding Bu_3MeNCl to the reaction mixture.

Table S8. Measured values for the chlorosulfonylation of diphenyl disulfide (**4**) in batch. Values are determined by GC-FID compared to biphenyl as an internal standard. Reaction time is defined until taking a sample and putting it into Et_2NH (1 M in MeCN).

Reaction time [s]	**4** [%]	**6** [%]	**7** [%]	**8** [%]	**9** [%]
15	1	98	-	-	1
30	1	98	-	-	-
45	1	98	-	-	-
300	1	99	-	-	-

8 Compound Characterization

Benzenesulfonyl chloride (5)



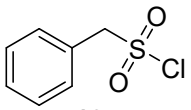
5

Colorless oil

Diphenyl disulfide: 89% yield Thiophenol: 73% yield

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, *J* = 2.4 Hz, 2H), 7.78 (m, *J* = 2.7 Hz, 1H), 7.65 (m, *J* = 3.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.0, 129.8, 135.3, 144.4. GC-MS analysis: m/z 176 confirmed.

Phenylmethanesulfonyl chloride (10a)



10a

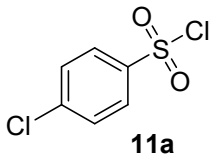
White solid

94% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 5H), 4.89 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.9, 126.2, 129.2, 130.3, 131.4. GC-MS analysis: m/z 190 confirmed.

4-Chlorobenzenesulfonyl chloride (11a)

11 was not fully soluble in acetonitrile at 0.25 M. The concentration was reduced to 0.1 M.



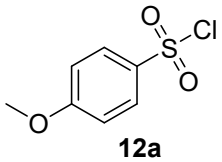
11a

White solid

74% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.5, 130.1, 142.2, 142.6. GC-MS analysis: m/z 210 confirmed.

4-Methoxybenzenesulfonyl chloride (12a)



12a

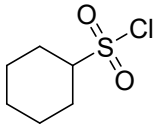
White solid

Bis(4-methoxydiphenyl) disulfide: 61% 4-methoxybenzene thiol: 74%

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.1 Hz, 2H), 7.06 (d, *J* = 9.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 114.8, 129.6, 136.0, 164.9. GC-MS analysis: m/z 206 confirmed.

Cyclohexanesulfonyl chloride (13a)

13 was not soluble in acetonitrile at 0.25 M, a biphasic l/l solution was obtained. Thus, the concentration was reduced to 0.1 M and 3% PhMe was added to obtain a single phase.



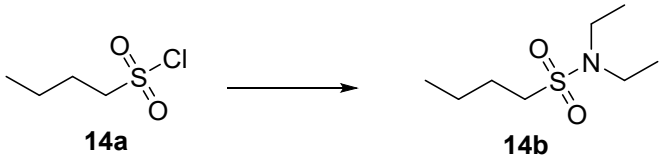
13a

Colorless oil

Dicyclohexyl disulfide: 76% Cyclohexanethiol: 75%

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (m, *J* = 3.9 Hz, 1H), 2.43 (m, *J* = 3.8 Hz, 2H), 2.01 (m, *J* = 4.2 Hz, 2H), 1.73 (m, *J* = 5.0 Hz, 3H), 1.35 (m, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 25.0, 27.2, 74.9. GC-MS analysis: m/z 182 confirmed.

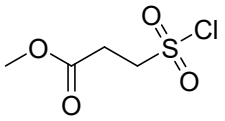
***n*Butylsulfonyl chloride (14a)**



14a **14b**

Compound was not isolated, because of the very similar boiling point to MeCN. The reaction was validated by GC-FID & GC-MS analysis after reaction with Et_2NH, showing a peak-to-peak reaction from **14a** to **14b**. The spectra are shown in the spectra section, showing an m/z peak at 193.

Methyl-3-chlorosulfonylpropanoate (15a)



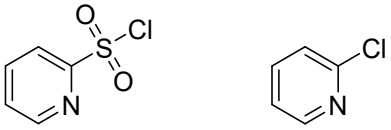
15a

Yellow oil

72% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (t, *J* = 7.4 Hz, 2H), 3.77 (s, 3H), 3.06 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.0, 52.7, 60.1, 169.2. GC-MS analysis: m/z 186 confirmed.

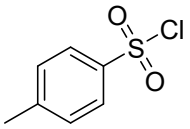
Pyridine-2-sulfonyl Chloride (16a) and side product 2-chloropyridine (16b)



16a **16b**

A mixture of pyridine-2-sulfonyl chloride and 2-chloropyridine was obtained. The masses were confirmed by GC-MS analysis.

4-Methylbenzenesulfonyl chloride (17a)



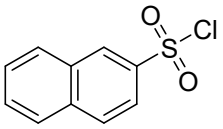
17a

white solid

68% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 2.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 127.0, 130.3, 141.7, 146.9. GC-MS analysis: m/z 190 confirmed.

Naphtalene-2-sulfonyl chloride (18a)



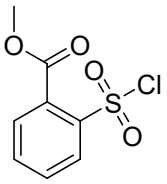
18a

Yellow solid

95% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.1 Hz, 1H), 8.03 (m, *J* = 7.0 Hz, 4H), 7.74 (m, *J* = 3.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.3, 128.2, 128.4, 128.9, 129.9, 130.3, 130.4, 131.7, 135.8, 141.1. GC-MS analysis: m/z 223 confirmed.

Methyl-2-chlorosulfonylbenzoate (19a)



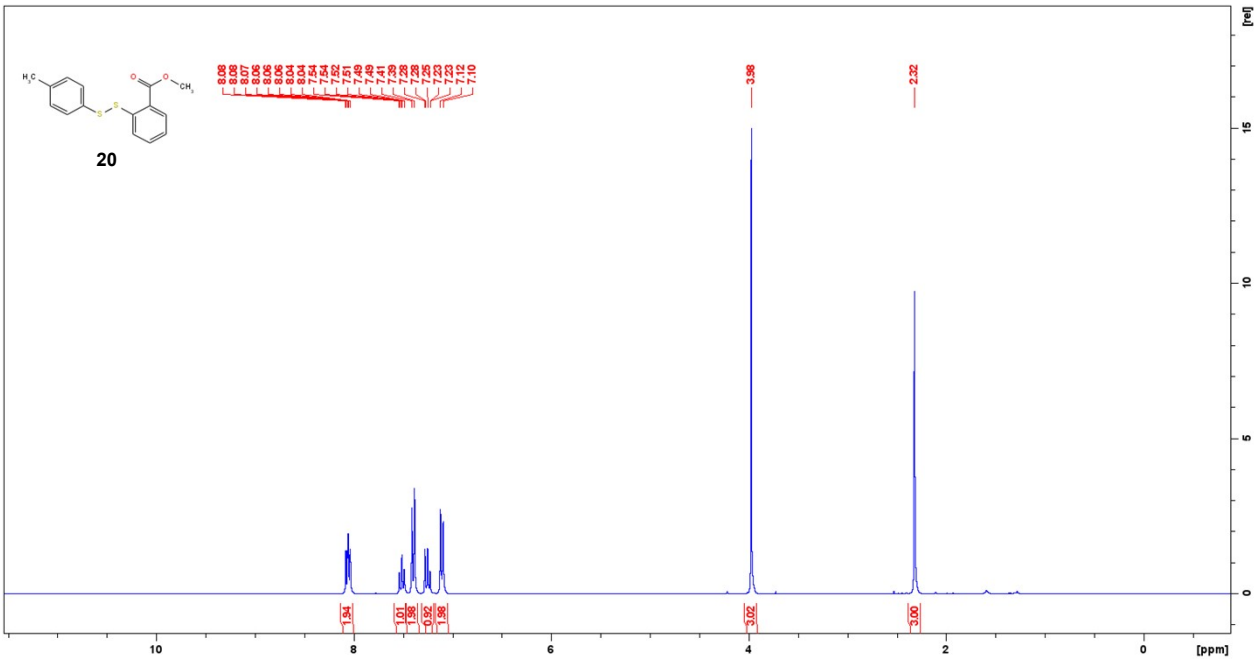
19a

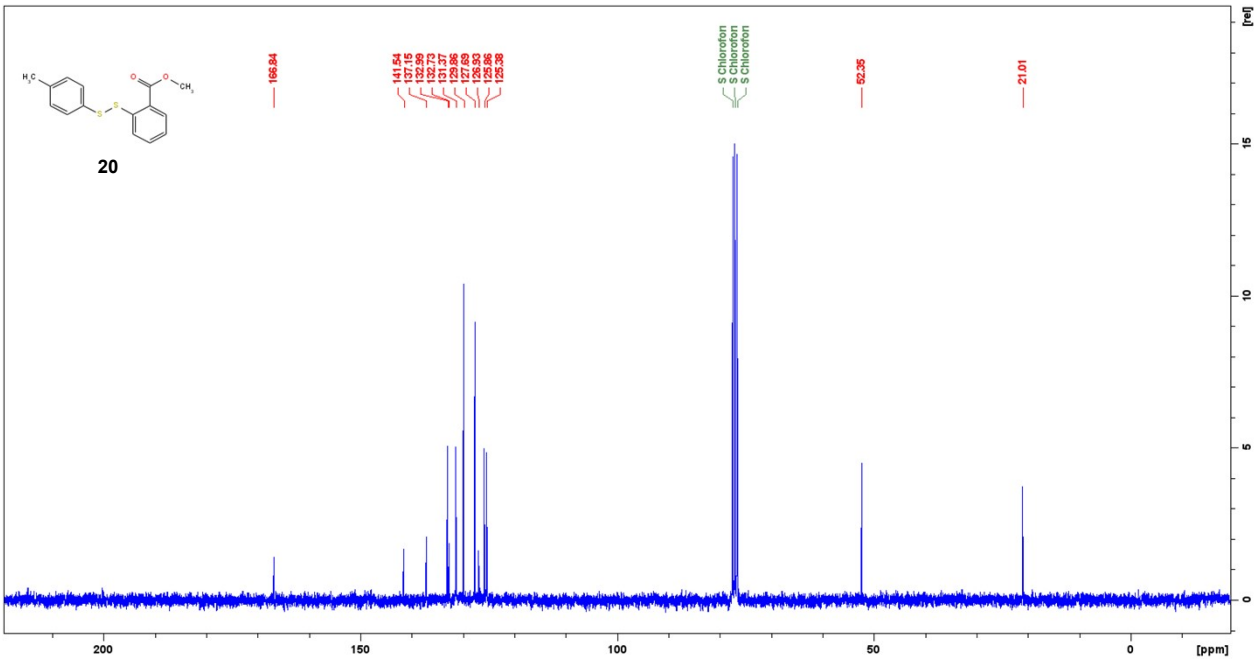
White solid

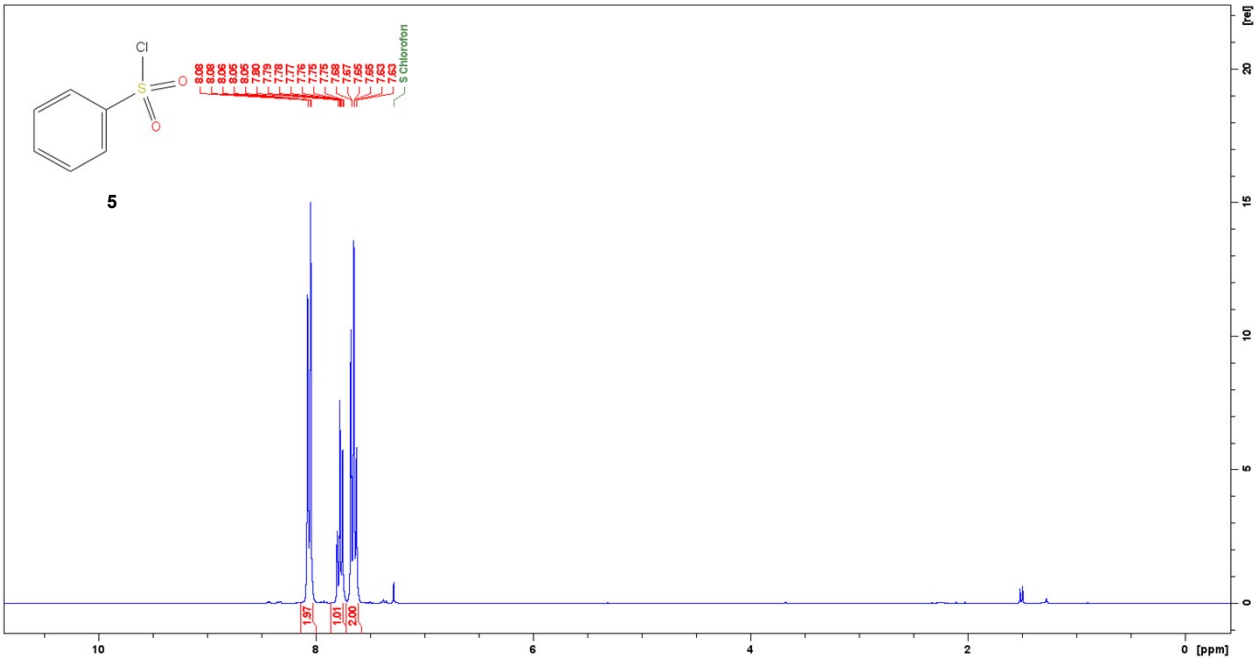
95% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.78 (m, *J* = 3.9 Hz, 3H), 4.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.4, 129.1, 130.1, 131.5, 132.3, 135.2, 141.6, 166.3. GC-MS analysis: m/z 234 confirmed.

9 GC-FID, GC-MS & NMR Spectra






Cl
S
O
O
5
8.08
8.08
8.06
8.06
8.05
8.05
7.80
7.79
7.78
7.77
7.76
7.75
7.75
7.68
7.67
7.66
7.65
7.63
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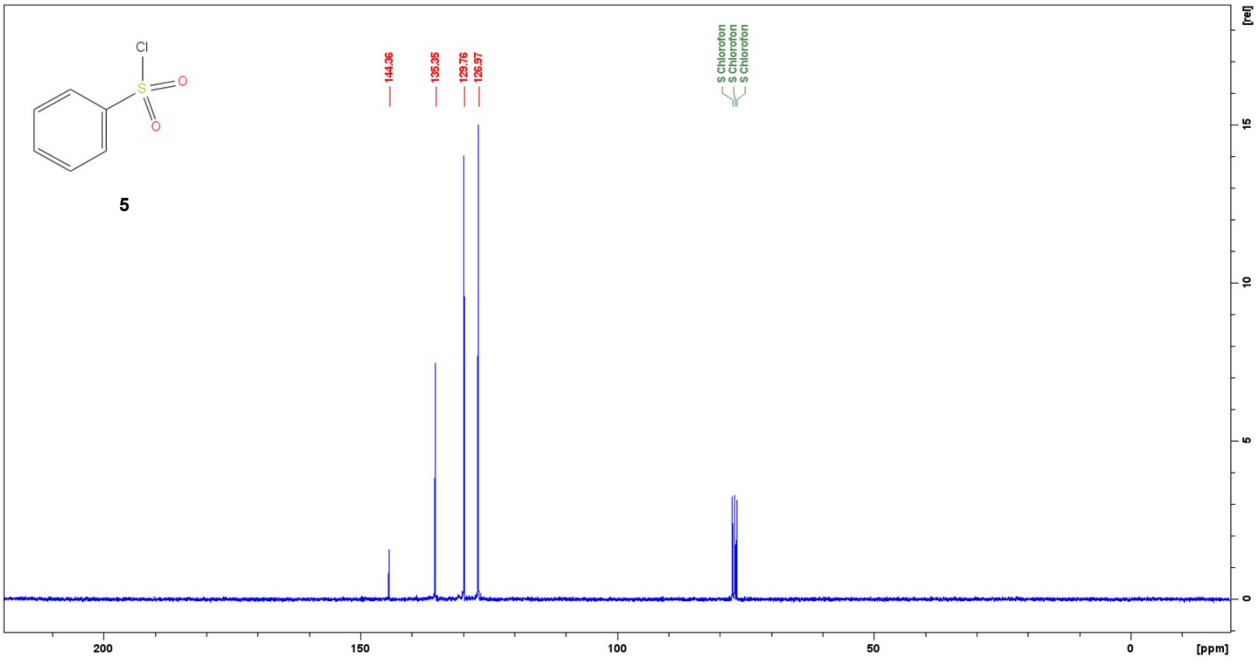
2
0 [ppm]
[rel]
20
15
10
5
0


Cl
S
O
O
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135.35
129.76
128.97
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S Chloroform
S Chloroform
200
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50
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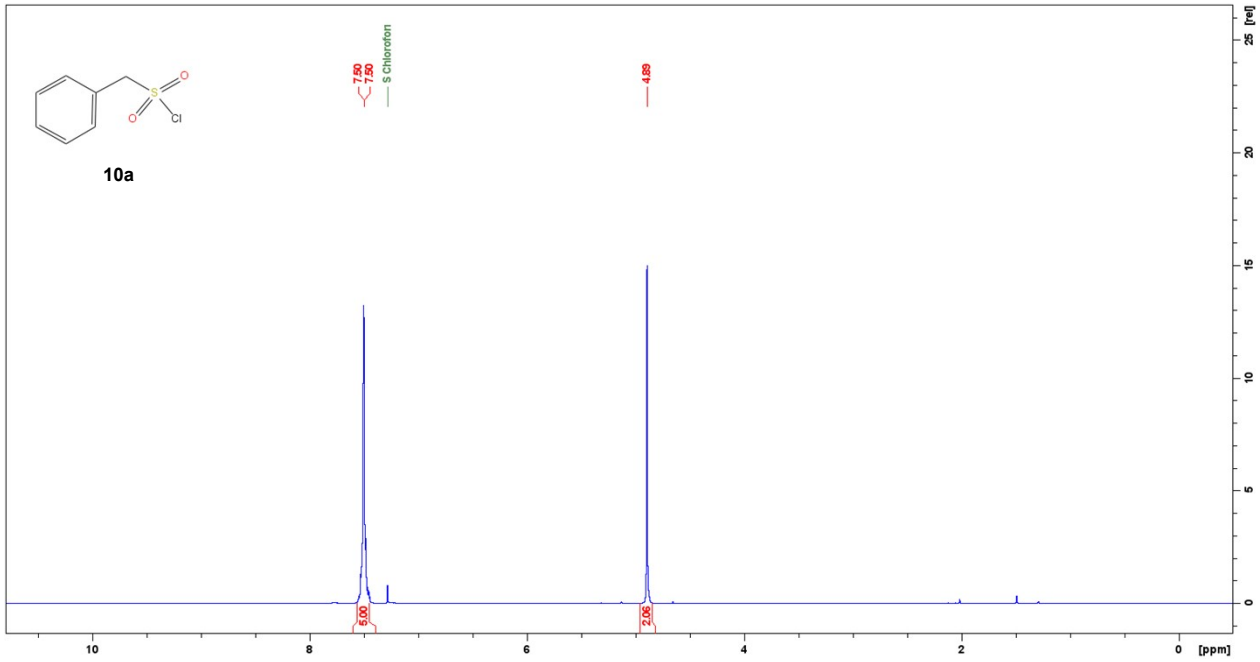
[rel]
15
10
5
0


10a
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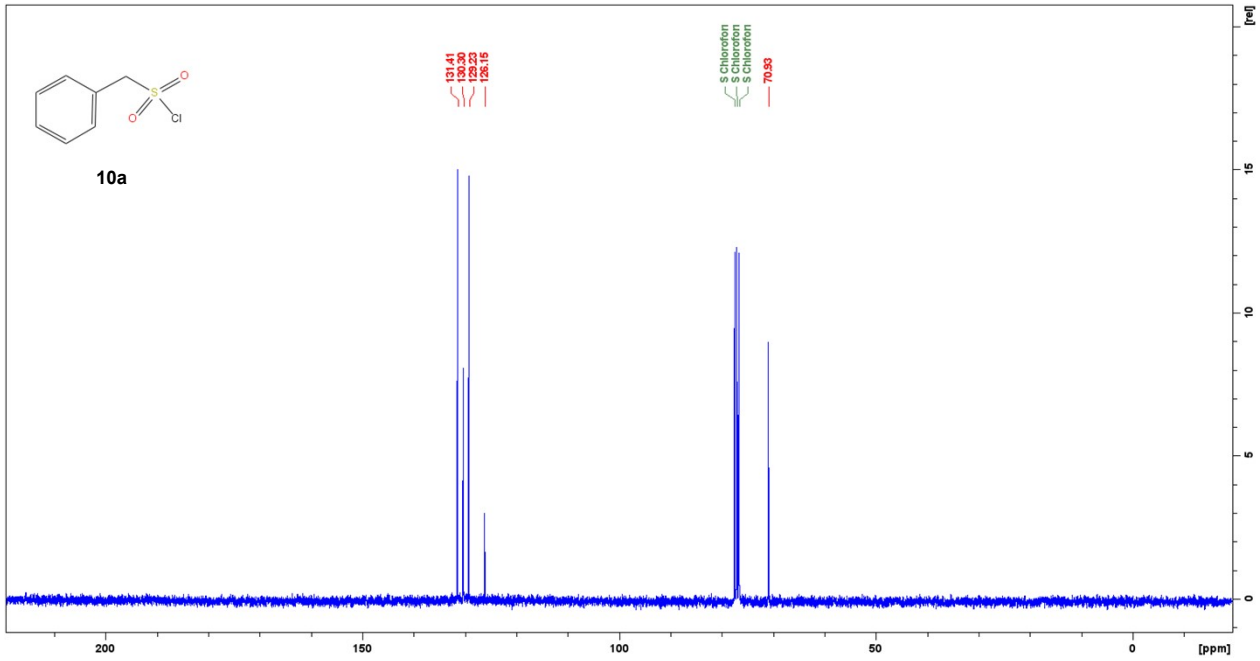
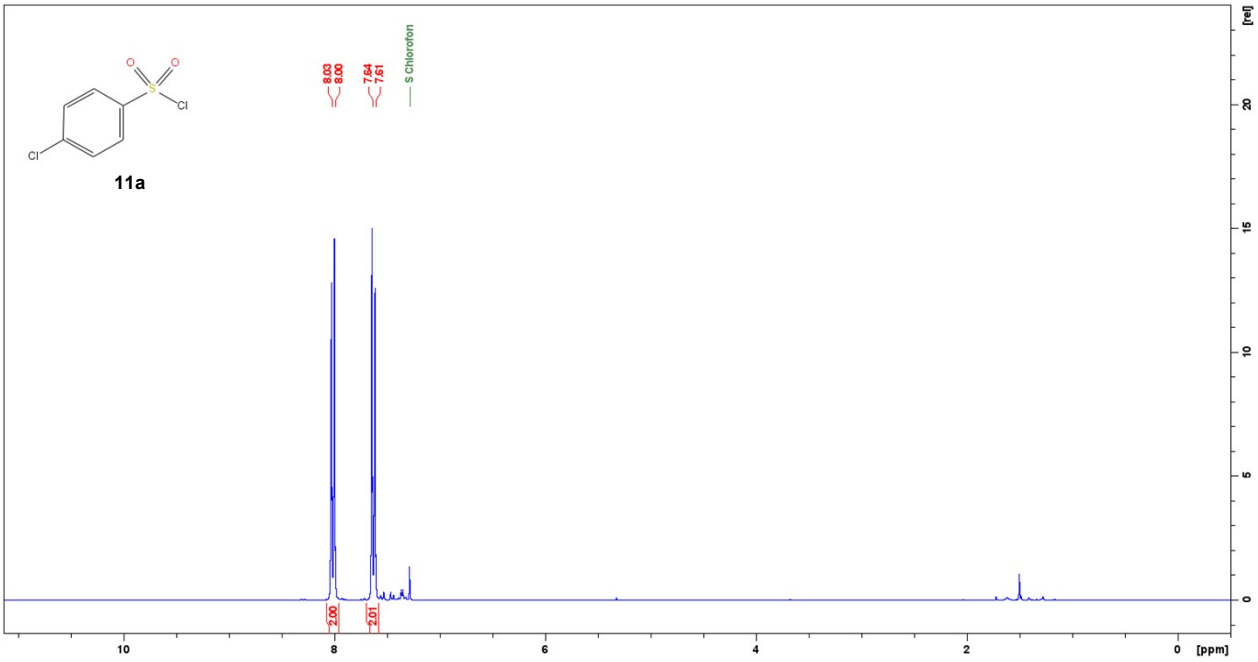
7.50
S Chloroform
4.89
5.00
2.06
[rel]
[ppm]


10a
131.41
130.30
129.23
126.15
S Chloroform
S Chloroform
S Chloroform
70.93
[rel]
[ppm]


11a
8.03
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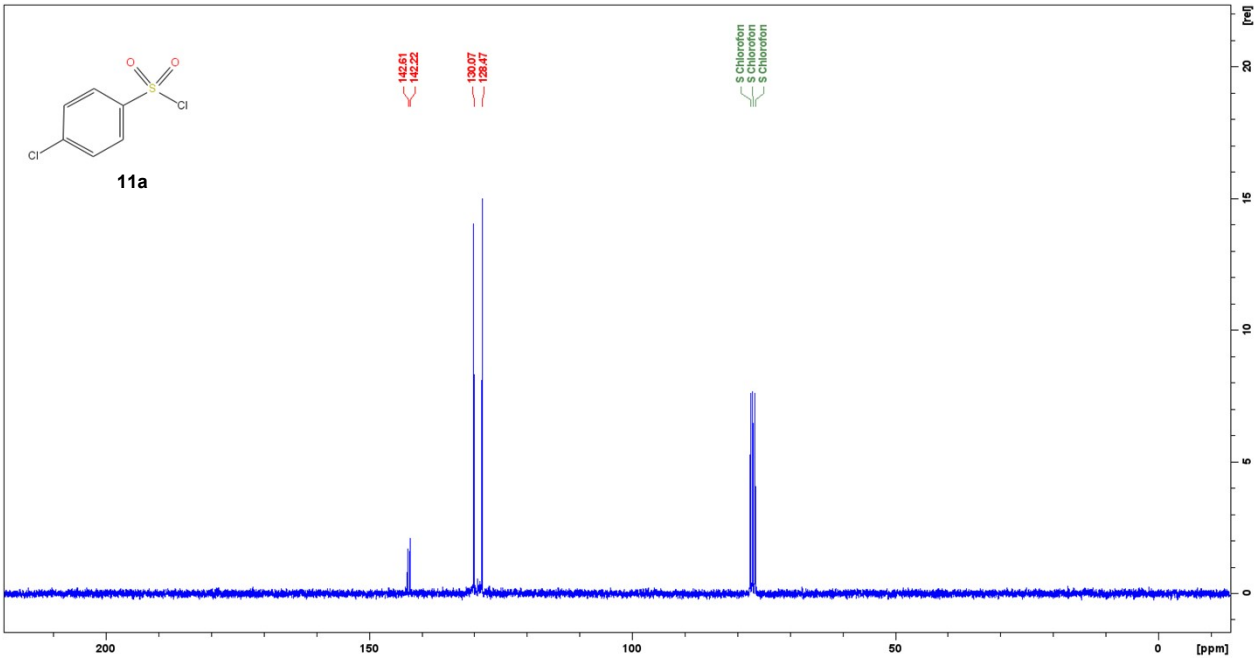
7.64
7.61
S Chloroform
2.00
2.01
[rel]
[ppm]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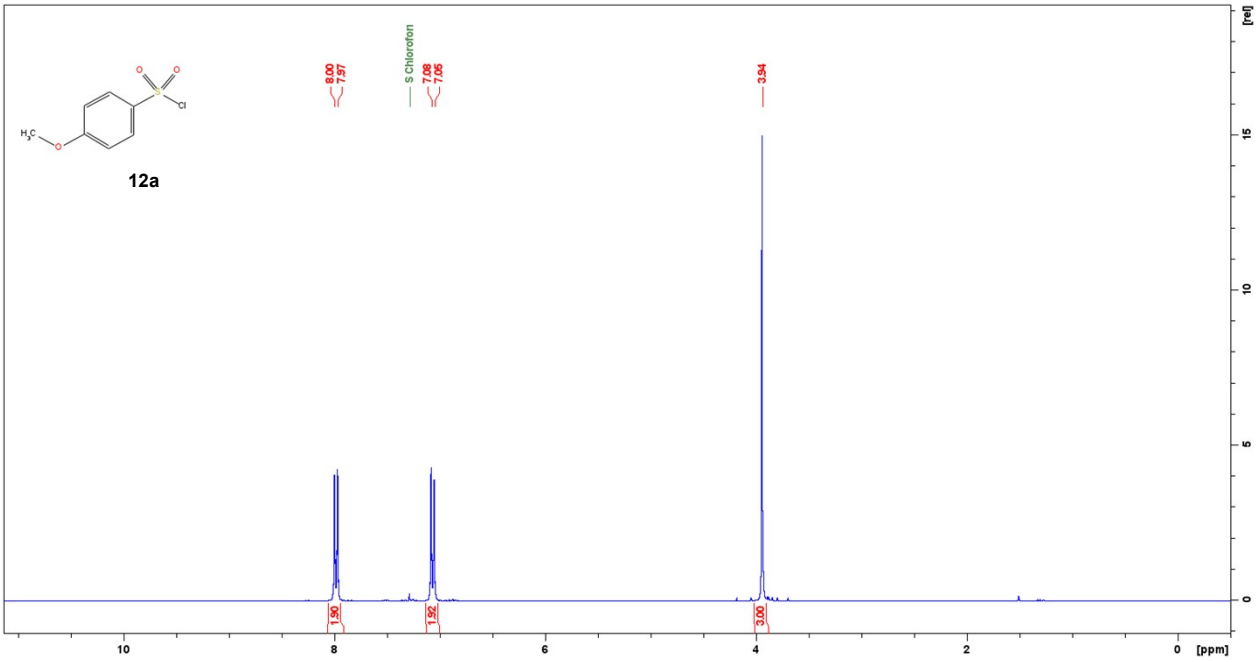
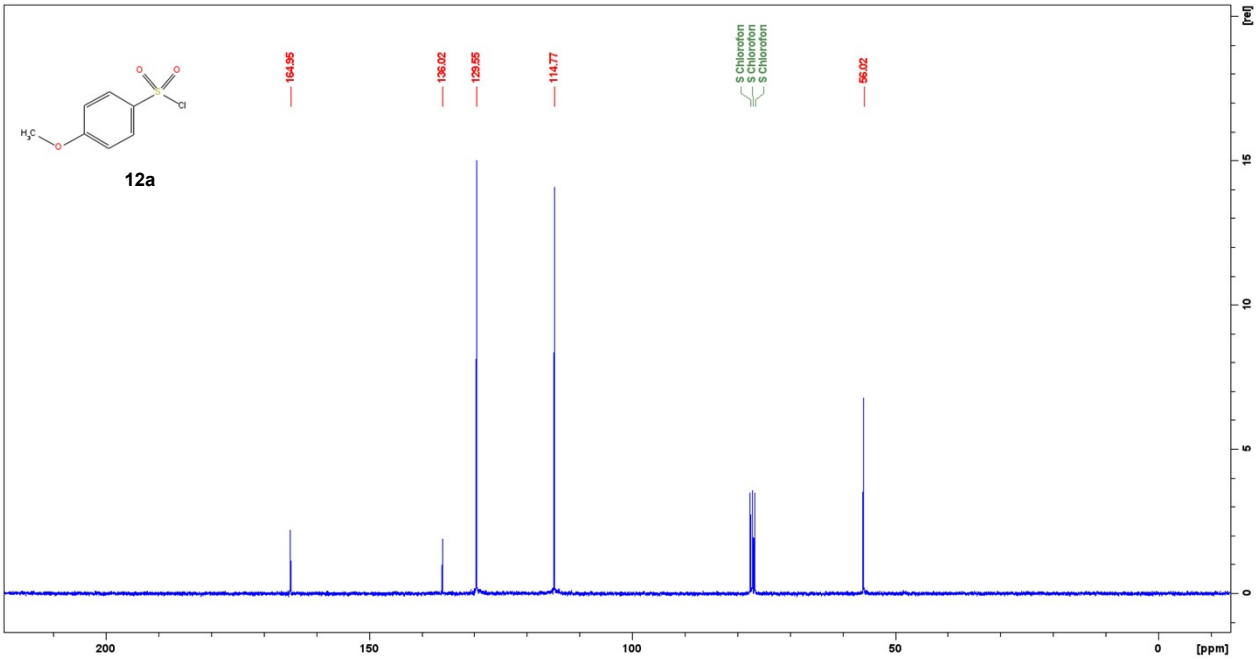
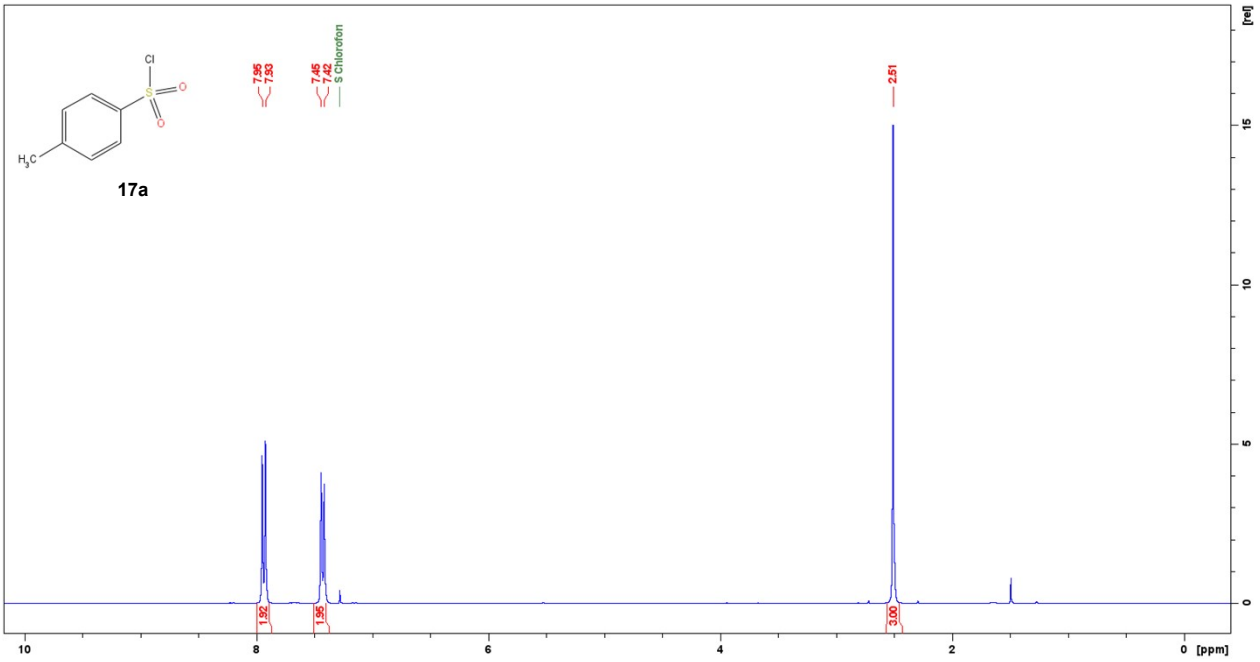
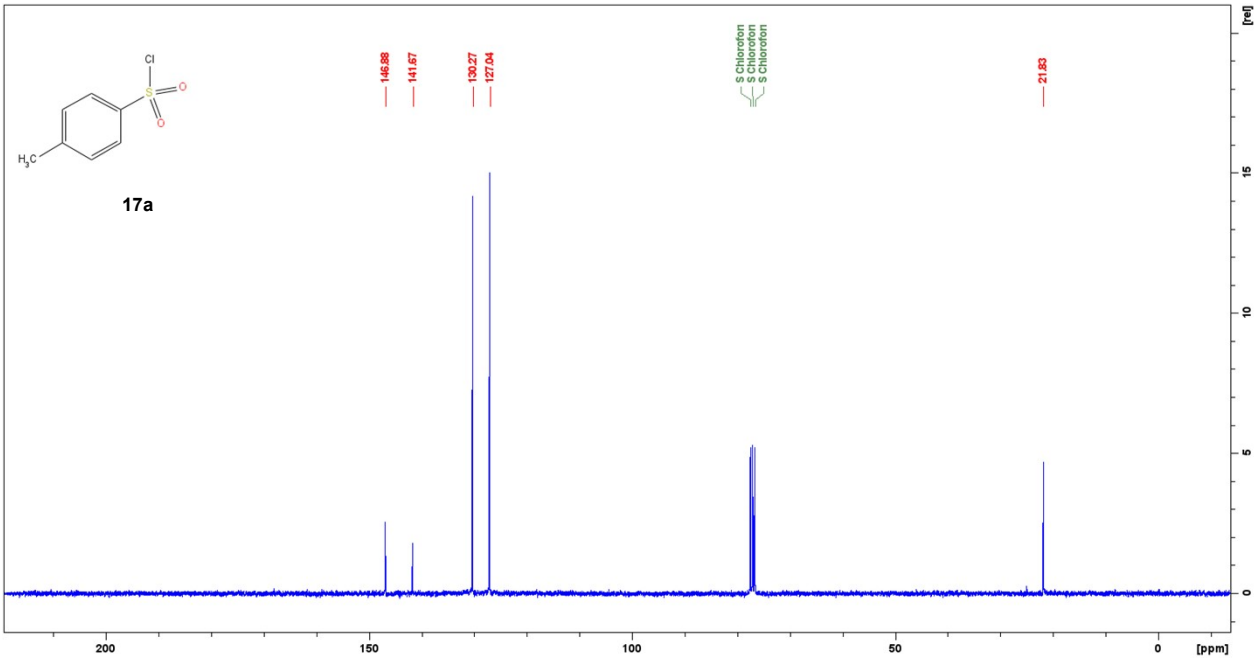
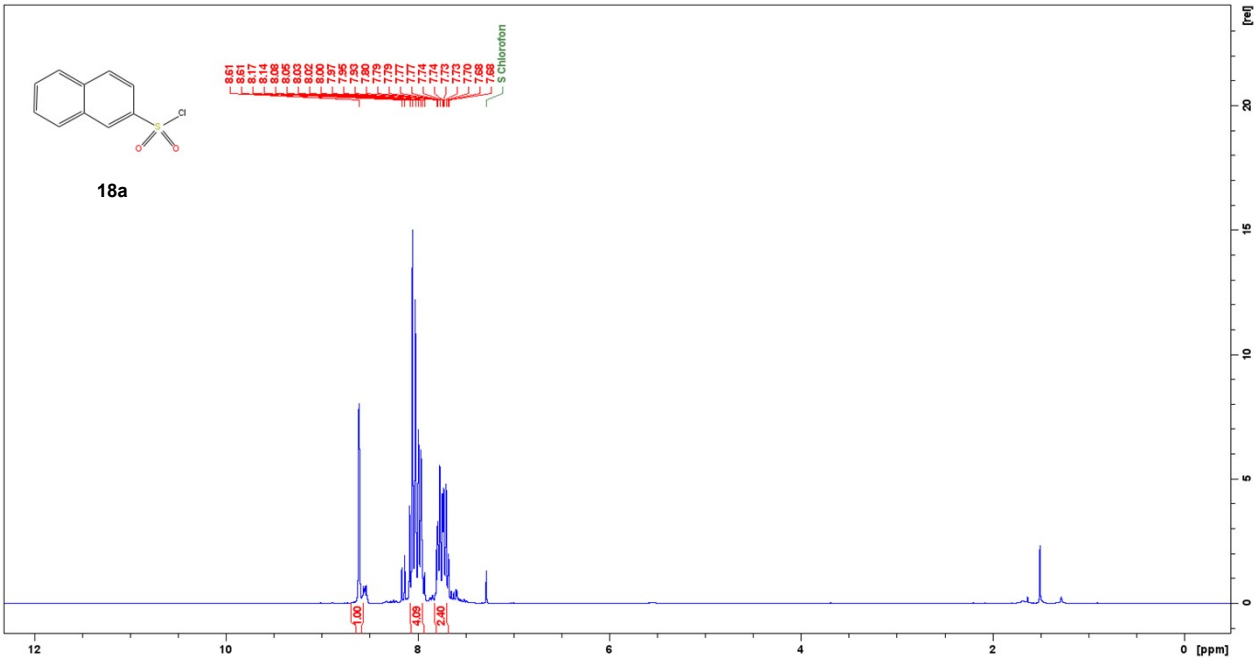
142.61
142.22
130.07
129.47
S Chloroform
S Chloroform
S Chloroform
[rel]
[ppm]

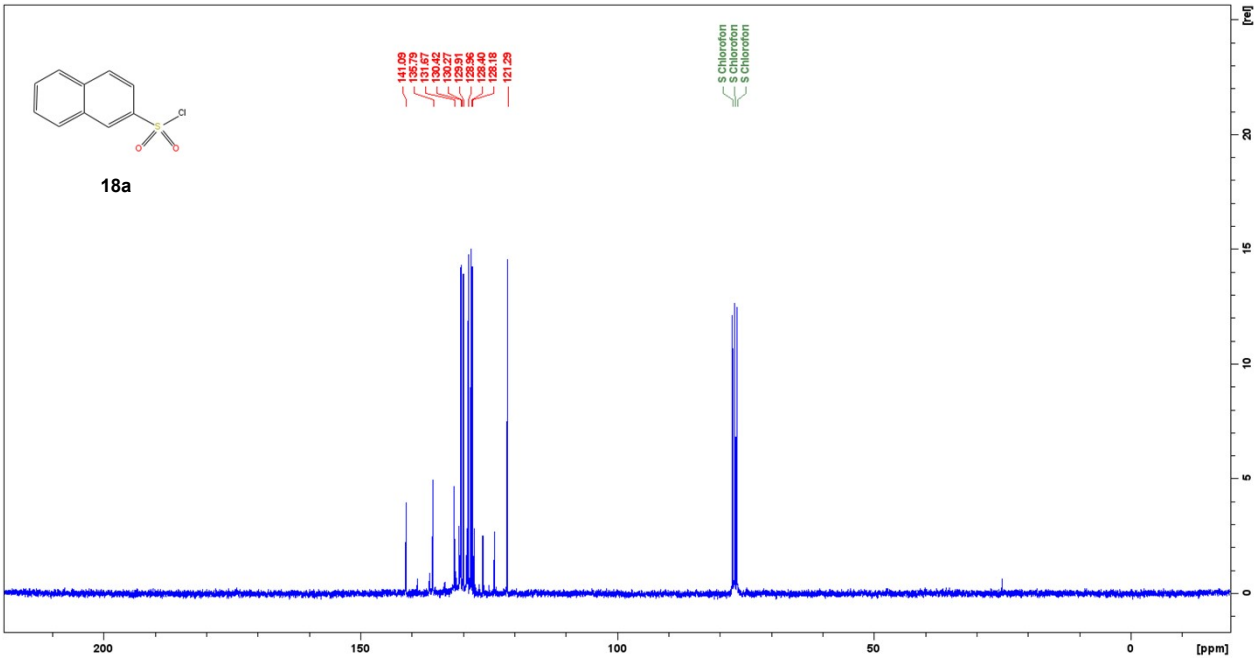

12a
8.00
7.97
S Chlorofori
7.08
7.05
3.94
1.90
1.92
3.00
[rel]
[ppm]

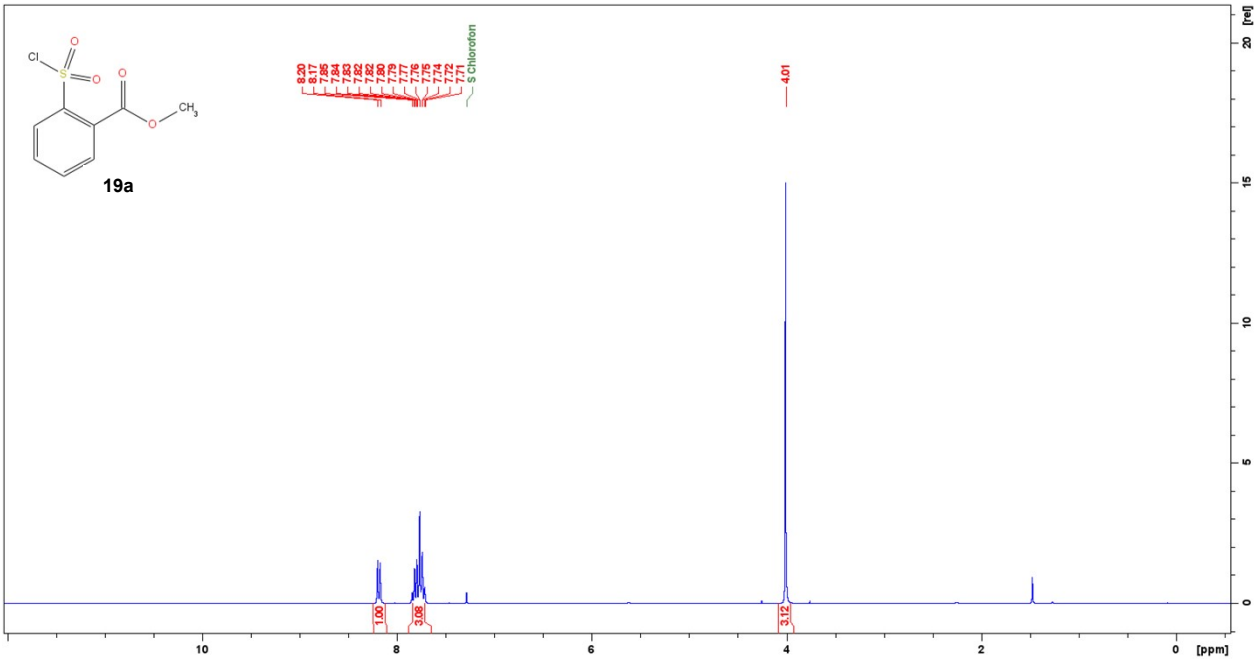

12a
164.95
136.02
129.55
114.77
S Chlorofori
S Chlorofori
S Chlorofori
55.02
[rel]
[ppm]

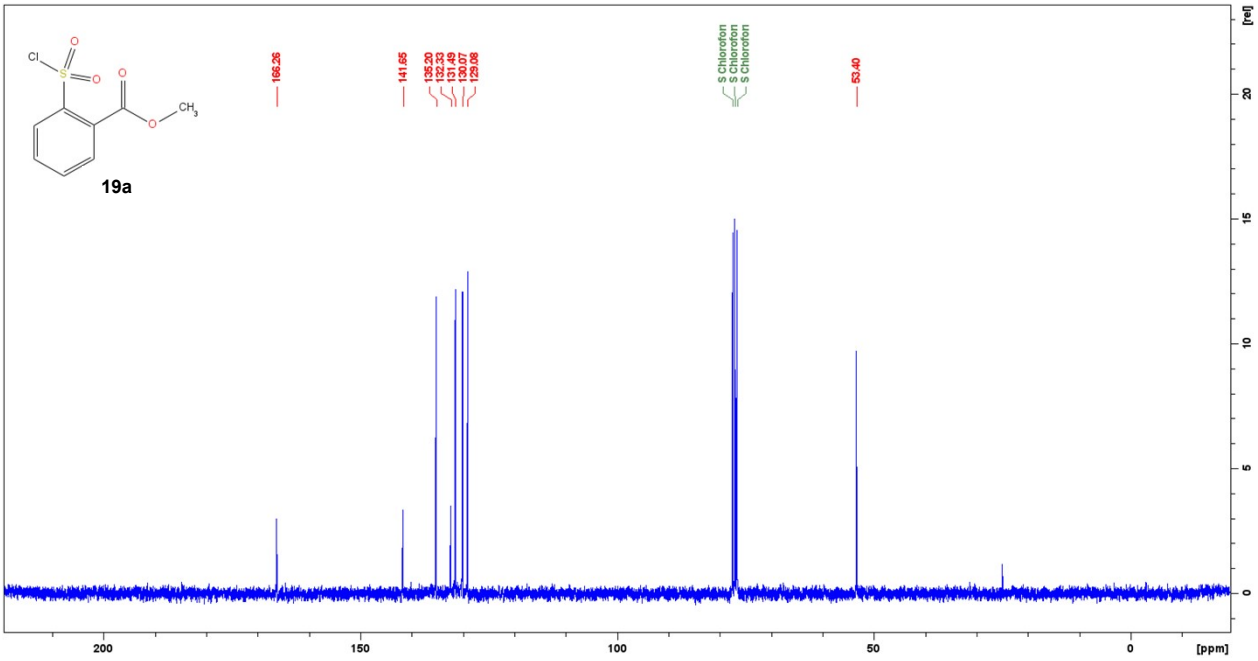

17a
7.95
7.93
7.45
7.42
S Chloroform
2.51
1.92
1.95
3.00
[rel]
[ppm]

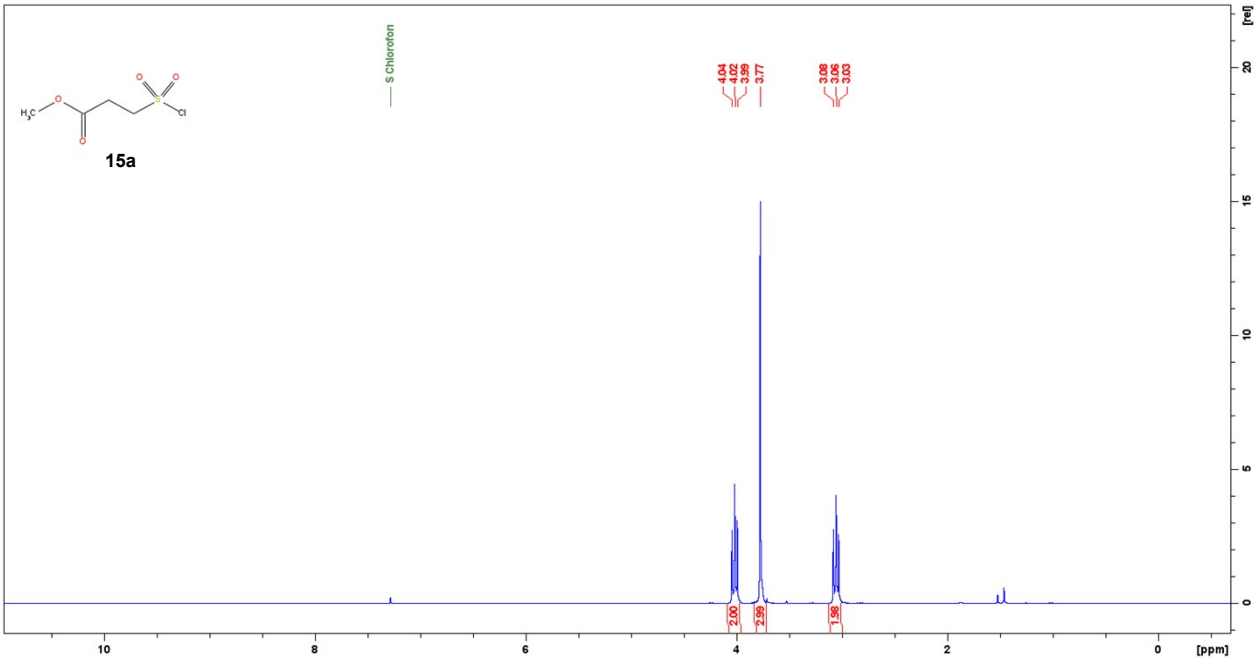

17a
146.88
141.67
130.27
127.04
S Chloroform
S Chloroform
S Chloroform
21.83
[rel]
[ppm]

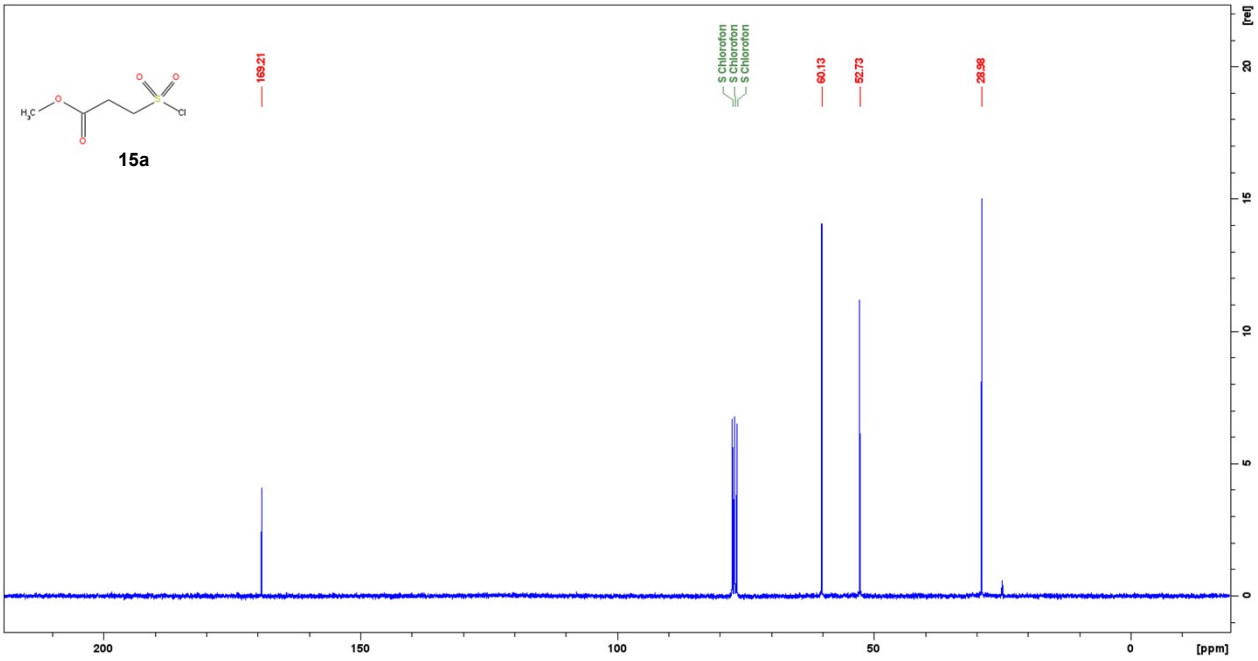

18a
8.61
8.61
8.17
8.14
8.08
8.05
8.03
8.02
8.00
7.97
7.95
7.80
7.79
7.79
7.77
7.77
7.74
7.74
7.73
7.73
7.70
7.68
7.68
S Chloroform
1.00
4.08
2.40
12
10
8
6
4
2
0
[ppm]
[rel]

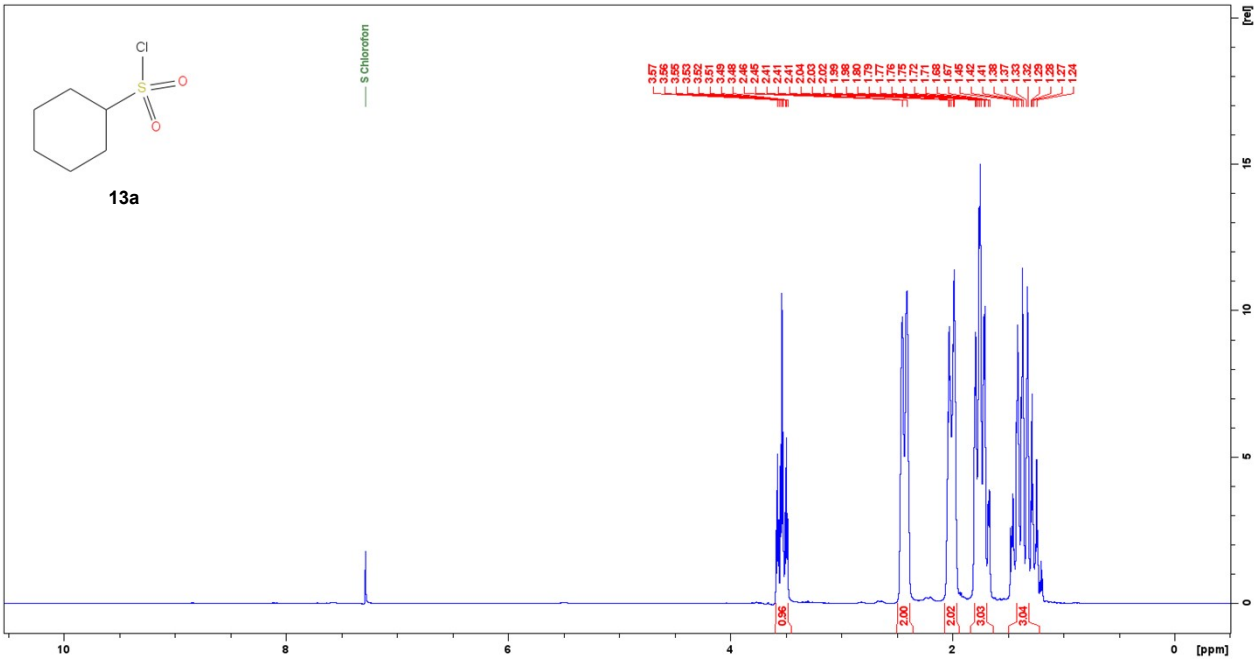

18a
141.09
135.79
131.67
130.42
130.27
129.91
129.56
129.40
128.18
121.29
S Chloroform
S Chloroform
S Chloroform
200
150
100
50
0
[ppm]
[rel]

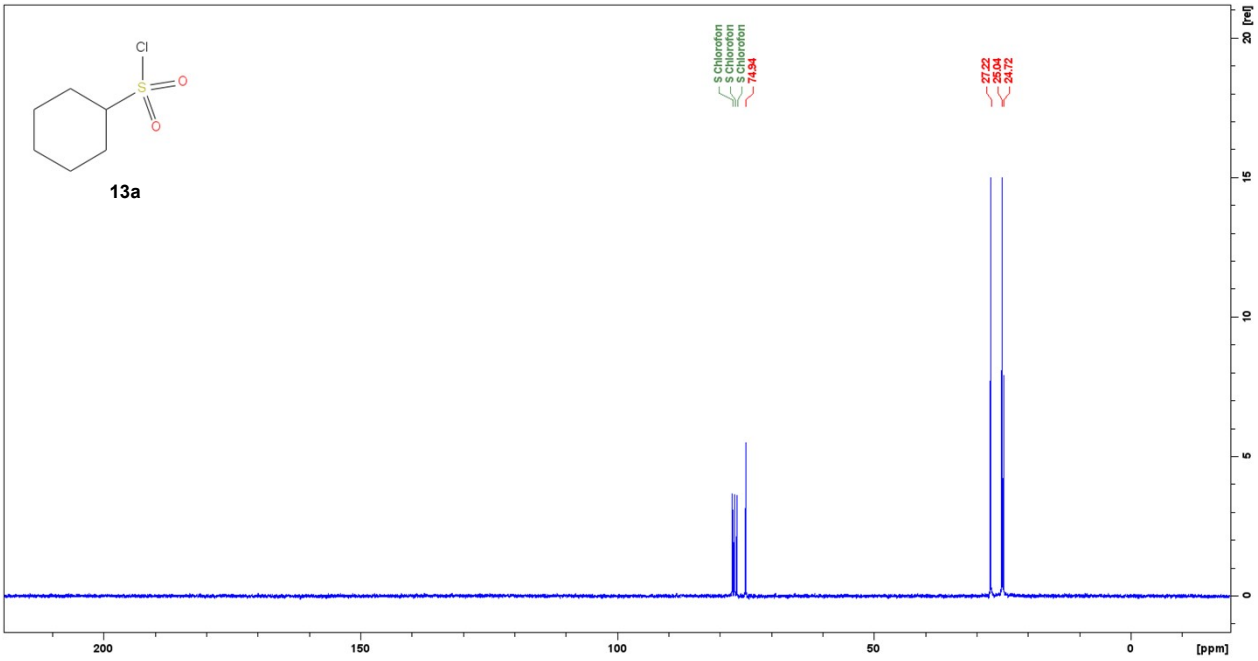

19a
8.20
8.17
7.85
7.84
7.83
7.82
7.82
7.80
7.79
7.77
7.77
7.76
7.75
7.74
7.72
7.71
S Chloroform
4.01
1.00
3.08
3.12
10
8
6
4
2
0
[ppm]
[rel]


19a
166.26
141.65
135.20
132.33
131.49
130.07
129.08
S Chloroform
S Chloroform
S Chloroform
53.40
200
150
100
50
0
[ppm]
[rel]


15a
S Chloroform
4.04
4.02
3.99
3.77
3.08
3.06
3.03
2.00
2.99
1.98
[rel]
[ppm]

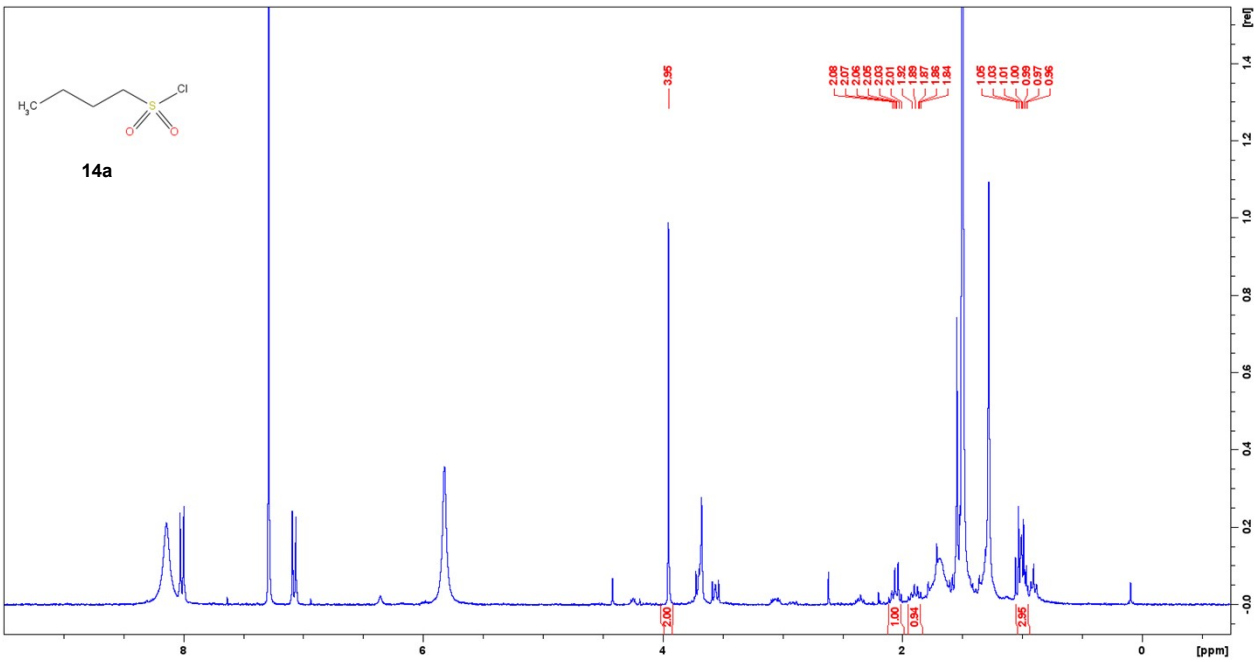

15a
169.21
S Chloroform
S Chloroform
S Chloroform
60.13
52.73
28.98
[rel]
[ppm]


13a
S Chloroform
3.57
3.56
3.55
3.53
3.52
3.51
3.49
3.48
3.46
2.45
2.41
2.41
2.41
2.04
2.03
2.02
1.99
1.98
1.80
1.79
1.77
1.76
1.75
1.72
1.71
1.68
1.67
1.45
1.42
1.41
1.38
1.37
1.33
1.32
1.29
1.28
1.27
1.24
0.96
2.00
2.02
3.03
3.04
[rel]
[ppm]

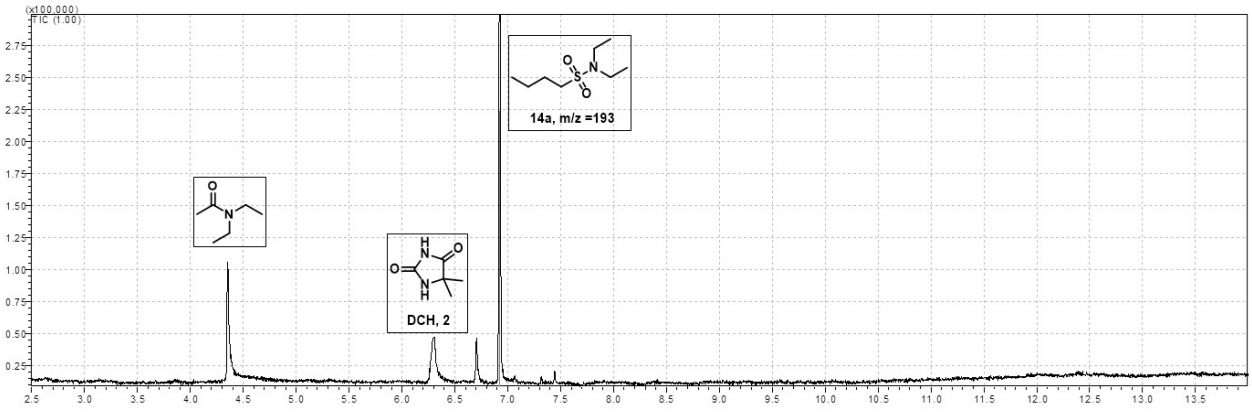

13a
S Chloroform
S Chloroform
S Chloroform
74.94
27.22
25.04
24.72
[rel]
[ppm]

Chlorosulfonylation of 14

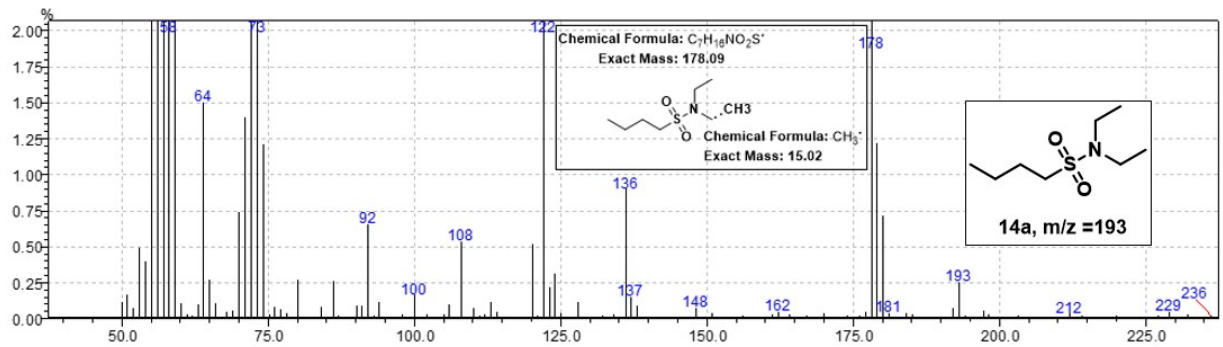
Crude ^{1}H NMR of the reaction mixture:



GC-MS trace of the chlorosulfonylation of 14 after quenching:



Mass spectrum of the peak at 6.9 min:



10 References

1 R. Hunter, M. Caira and N. Stellenboom, *J. Org. Chem.*, 2006, **71**, 8268–8271.