Niklas Sulzer, BSc

Preparation of Sulfonyl Chlorides by Oxidative Chlorination of Thiols and Disulfides using $HNO_3/HCl/O_2$ in a Continuous Flow Reactor

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Christian Oliver Kappe

Institute of Chemistry

University of Graz

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Zusammenfassung

Sulfonylchloride sind starke Elektrophile und nützliche Bausteine in der Synthese von Sulfonen und Sulfonamiden. Diese beiden Motive wiederum spielen eine wichtige Rolle als Fungizide, Herbizide und vor allem als Wirkstoffe in verschiedensten Medikamenten. Die meistgenutzten Ausgangsstoffe für die Synthese von Sulfonylchloriden sind Thiole und Disulfide. Viele dieser Synthesemethoden nutzen entweder gefährliche Reagenzien oder sind stark exotherm, was besonders im Vergrößern des Maßstabes schwierig ist. In solchen Fällen bietet sich der Einsatz von Duchflußchemie an. Unter den vielen bekannten Bedingungen zur oxidativen Chlorierung waren wir besonders an jenen interessiert, die diese Transformation mithilfe atomeffizienter Bulk-Chemikalien erzielen.

Dazu wurde ein kontinuierliches und metallfreies Protokoll zur Synthese von Sulfonylchloriden aus Thiolen und Disulfiden durch den Einsatz von Salpetersäure, Salzsäure und Sauerstoff entwickelt. Der Einfluss verschiedenster Reaktionsparameter wurde sowohl im Batch, als auch im Durchfluss untersucht. Durch ^{19}F NMR Monitoring war es möglich die Reaktion in Echtzeit zu überwachen und verschiedene Parameter in einem einzigen Experiment zu variieren. Nach einer einfachen wässrigen Aufarbeitung konnten verschiedene Sulfonylchloride in hoher Reinheit (>95%) und guter Ausbeute (hauptsächlich 70-81%) isoliert werden. Als Stabilitätstest wurde das System mit dem Modelsubstrat Diphenyl Disulfid für mehr als 6 Stunden erfolgreich mit einem Durchsatz von 3.7 g h^{-1} betrieben. Nachhaltigkeitsparameter des Prozesses wurden beurteilt und mit einem anderen bereits bestehenden kontinuierlichen Prozess zur oxidativen Chlorierung verglichen, welcher 1,3-dichloro-5,5-dimethylhydantoin (DCH) als Reagenz nutzt. Dieser neue Ansatz schneidet hinsichtlich der Prozess-Massenintensität (PMI) besser ab (15), als der DCH-Prozess (20).

Zusätzlich wurde eine Machbarkeitsstudie für ein weiteres kontinuierliches Chlorsulfonylierungsprotokoll durchgeführt. Das Konzept der chemischen Generatoren ermöglichte die sichere Verwendung von Cl_2 zur Synthese von Sulfonylchloriden. Cl_2 wurde aus NaOCl und HCl in-situ erzeugt (90 % Ausbeute) und anschließend mit EtOAc extrahiert. Dann wurde dem Cl_2-Fluss Diphenyldisulfid zugesetzt und Benzolsulfonylchlorid in 98 % Ausbeute bei Raumtemperatur erzeugt.

Abstract

Sulfonyl chlorides are potent electrophiles and useful building blocks in the synthesis of sulfones and sulfonamides. Both of these moieties are frequently found in fungicides, herbicides and most importantly as active pharmaceutical ingredients in various drugs. Thiols and disulfides are among the most common and versatile starting materials in the synthesis of sulfonyl chlorides. However, these transformations can be challenging as they often involve hazardous chemicals and are usually highly exothermic. Consequently, many of these conditions are not scalable in batch. In cases like this, flow chemistry can be implemented as an enabling technology. Among the many different protocols, we were especially interested conditions that achieved oxidative chlorination using atom efficient bulk chemicals.

A continuous flow metal-free protocol for the synthesis of sulfonyl chlorides from thiols and disulfides in the presence of nitric acid, hydrochloric acid and oxygen was developed. The influence of the reaction parameters was investigated under batch and flow conditions. Online ^{19}F NMR was successfully implemented to investigate different reaction conditions within a single experiment. The sulfonyl chlorides were isolated (mostly in 70-81% yield) after performing a simple aqueous washing procedure. In particular, the protocol was successfully operated for >6 hours to convert phenyl disulfide to its corresponding sulfonyl chloride, achieving a throughput of 3.7 g h^{-1}. The environmental impact of the protocol was assessed and compared to an existing continuous flow protocol using 1,3-dichloro-5,5-dimethylhydantoin (DCH) as reagent. The process mass intensity (PMI) for the newly-developed flow protocol (15) compared favorably to the DCH flow process (20).

Additionally, a feasibility study of another chlorosulfonylation protocol in flow was executed. The concept of chemical generators enabled the safe use of Cl_2 for the synthesis of sulfonylchlorides. Cl_2 was generated from NaOCl and HCl in-situ (90% yield) and consequently extracted using EtOAc. Then, diphenyl disulfide was added to the Cl_2 stream and benzen sulfonylchloride was generated in 98% yield at room temperature.

Acknowledgements

I would like to express my profound gratitude to Professor Dr Oliver Kappe for the opportunity to do my thesis as a part of his team. I hold these last months dearly in which I could dive deeply into an area of chemistry that I hardly knew existed before. Thank you and the whole CCFLOW team for this experience.

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Finally, I would like to thank my parents for all they have done and their great and constant support throughout my life and studies. You two have never been anything but supportive and encouraging throughout my life, for which I will be forever grateful.

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List of Abbreviations

AE	Atom Efficiency
API	Active Pharmaceutical Ingredient
BPR	Back Pressure Regulator
CSTR	Continuous Stirred Tank Reactor
DCH	1,3-Dichloro-5,5-Dimethylhydantoin
DCM	Dichloromethane
FDA	Federal Drug Administration
FID	Flame Ionization Detector
GC	Gas Chromatography
HMPA	Hexamethylphosphoramide
HPLC	High-Performance Liquid Chromatography
MFC	Mass Flow Controller
MS	Mass Spectrometer
NCS	*N*-chlorosuccinimide
NMR	Nucleic Magnetic Resonance
OE	Optimum Efficiency
PAT	Process Analytical Technology
PFA	Perfluoro Alkoxy
PMI	Process Mass Intensity
ppm	Parts per Million
PTFE	Polytetrafluoroethylene
RME	Reaction Mass Efficiency
TAPC	1,3,5-Triazo-2,4,6-Triphosphorine-2,2,4,4,6,6-Hexachloride
TCCA	Trichloroisocyanuric Acid
TFA	Trifluoroacetic Acid
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl Chloride

1 Introduction

1.1 Continuous Processing: Flow Chemistry

Most chemists, when asked to picture a chemical reaction, will think of flasks, reflux condensers, magnetic stirrers, and similar tools of laboratory scale batch chemistry. A batch process is a discontinuous technique, in which the starting materials are fed into a vessel and after the reaction or operation is finished, a batch of product can be collected. This process technique is well established and in most laboratories it is the only way reactions are carried out. Historically the same has also been true for the chemical industry, in which small flasks are exchanged for huge kettles as the output is scaled up from milligrams to kilograms and tons. However, for many applications continuous processing has gained an ever-increasing importance. The petrochemical and bulk chemical industry were early developers of this technique and today continuous processing plays a fundamental role in those chemical sectors.

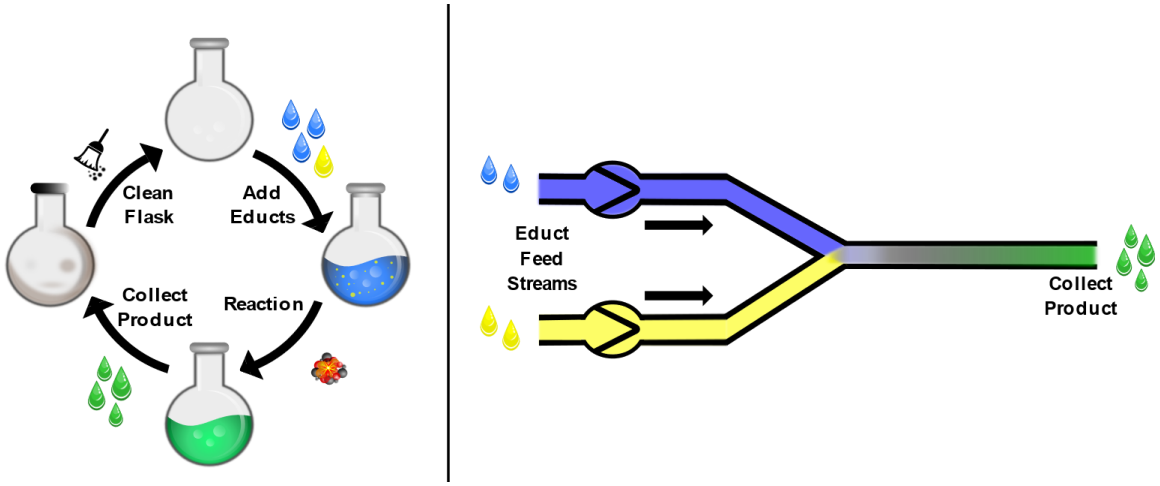


Figure 1. Illustration of a chemical reaction in batch (left) and continuous processing (right)

On the other hand, the pharmaceutical industry still relies mostly on long-established batch processes for the manufacturing and purification of intermediates and active pharmaceutical ingredients (APIs). Pharmaceuticals and fine chemicals are more complex and often require challenging transformations and extensive purification. Consequently, their production in a continuous process has traditionally been a daunting task. Moreover, such a process must severely outperform its batch alternatives, as it requires the establishment of new infrastructure as well as experience and expertise in this field. Despite these obstacles, continuous processing

techniques are utilized more and more in the pharmaceutical industry to facilitate the invention of new production routes and reinvent existing ones.[1–4]

1.1.1 Continuous Processing in the Laboratory

Before any continuous process can be employed in a manufacturing setting it needs to be explored, tested, and optimized on a small scale. The continuous production and treatment of chemicals is a multidisciplinary field that combines chemistry and engineering. To build a robust and successful process both areas must be optimized in a complimentary fashion.

Once a reaction is identified as potentially benefitting from continuous processing, the underlying chemistry is usually first explored in conventional batch experiments.[5] The aim of these experiments is to highlight if and how the reaction could be enhanced, as well as point out potential complications one might encounter. Based on this data a suitable reactor system can then be built and subsequent optimization experiments conducted to finalize the process. There are many different reactor designs, some more general and others more specialized that come with their own strengths and weaknesses. However almost all of them share the same central elements. Common symbols used to the depict these elements in schemes are summed up in scheme 1.

In the vast majority of cases chemicals are introduced and passed through the system via pumps.[6] Commonly used types are syringe, piston, and peristaltic pumps. As a result, chemicals are generally used in a liquid form, so either neat or in solution. Flow systems are also very well suited for reactions that involve gases. Those can be introduced by connecting a gas source, such as an inhouse pipeline or a pressurized gas cylinder, to the reactor via a so-called mass flow controller (MFC).[7] Such a device enables the precise dosing of gases by relating the flow rate to another observable parameter, usually heat transfer or mass inertia. Solids are notoriously difficult to handle in flow and often require specialized solutions or reactor designs.[8,9]

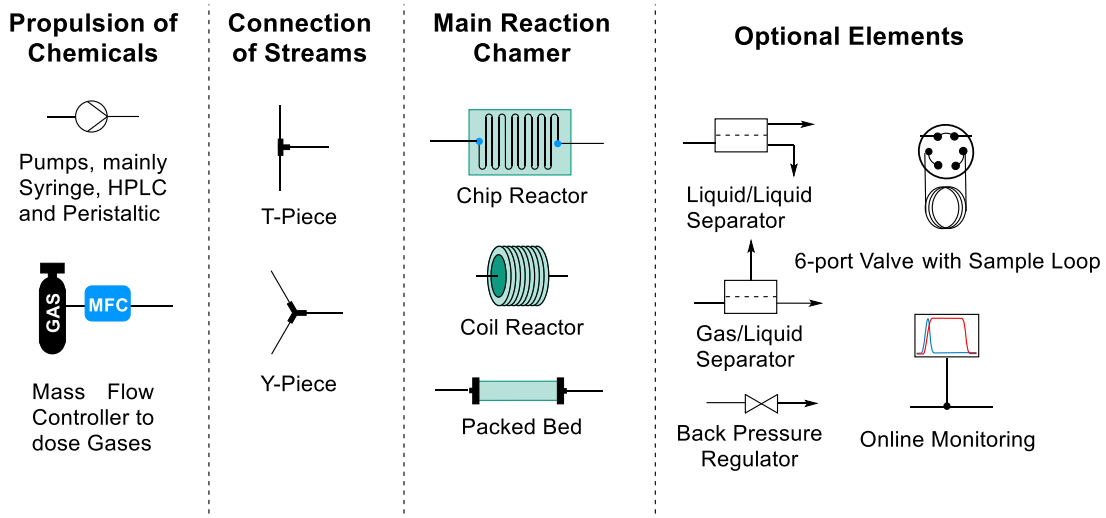
The main reactor chamber can be as simple as a narrow tubing, usually made from chemically resistant polymers, such as perfluoro alkoxy (PFA) or polytetrafluoroethylene (PTFE). Parts of the tubing are often coiled up, to make it more space efficient and easier to handle and are therefore also referred to as coils. This also simplifies heating and cooling, as great temperature control can be achieved by placing coils in tempered oil or water baths.

To be able to mix two reagents from two separate streams, a mixing element can be used. Commonly used examples are Y and T pieces, which both have three narrow channeled openings and are named after their respective geometrical form. Such elements can be tightly connected to the tubing using screw fittings to avoid leakage.

Chemicals can be pumped directly into the reactor from a preprepared stock solution. However, sometimes it can be beneficial to pump a carrier solvent and to use a sample injector to introduce the chemicals. This can be done when dealing with very corrosive chemicals that are suspected to damage the pumping system, but also to reduce the amount of substrate used during reactions. A very common injector element is the 6-port valve as it allows for loading and injection of the reagents without interrupting the flow in the reactor. Other types of valves, such as 3- or 4-port valves, can also be convenient as they can be used to either bypass elements of the system or act as pressure release valves in case of complications.

If a reaction can be enhanced through higher pressure, this can be achieved by using a back pressure regulator (BPR). These devices often work at a defined internal pressure that impedes the flow in the reactor. The reaction mixture can only pass a BPR if the pressure is higher than the internal one, thereby increasing the pressure upstream to the set value. This internal pressure can be achieved through a spring, in which case the set pressure cannot be changed. Adjustable BPRs often utilize a compressed air chamber that can be filled with gas to increase the internal pressure. BPRs are extremely useful when dealing with gas-liquid reactions, as the solubility of a gaseous species is directly proportional to its partial pressure, as described by Henry`s law.

Another powerful device for multiphasic reactions is a phase separator. These utilize different semipermeable membranes to split a heterogenous reaction mixture into two homogenous streams. By using different membranes those can be employed for liquid-liquid, as well as liquid-gas systems. Membrane based phase separators are often employed to telescope multiple reaction steps.[10,11]



Scheme 1. Often used icons to depict the most common flow chemistry elements.

While knowledge of these elements is sufficient to understand most laboratory scale flow systems, this is by no means an exhaustive overview. There are many more other elements as well as variants of the outlined ones. The reader is referred to these reviews for further information[5] and various examples of different flow setups.[12,13] Moreover, flow schemes often include some form of analytical device, as many of them can be directly integrated into the reactor using flow-through measurement cells.

1.1.2 Process Analytical Technology (PAT)

Reaction monitoring is of great importance in any manufacturing process to ensure consistent product quality. The best results are achieved when a suitable analytical technique and monitoring approach are combined. Broadly speaking, there are four different monitoring approaches (see figure 2).[14]

Offline reaction monitoring is most commonly used and performed by manually sampling the reaction mixture throughout the process. Those samples are then transported to an analytical device to be measured. While economical and usually easy to implement, it can take a long time from sampling to results. Divergences of critical process parameters are often caught too late to correct in a time. Furthermore, some chemical transformations can also continue in the sampling vessel, which can distort results. If on the other hand the analytical device is integrated into the process, by continuously and directly analyzing the reaction mixture at some point in the reactor, this is known as inline monitoring. In certain cases, it can be more practical to divert a small part of the reaction mixture to the analytical device, instead of integrating it directly into the production line. This approach also allows for real time analysis and is

termed online monitoring. Atline monitoring can offer a compromise in cases where inline or online monitoring is not economically or technically feasible. The principle behind is similar to offline monitoring, but the analytical device is in close proximity, does not require manual intervention and is often dedicated to the process, reducing the time between measurement and result.

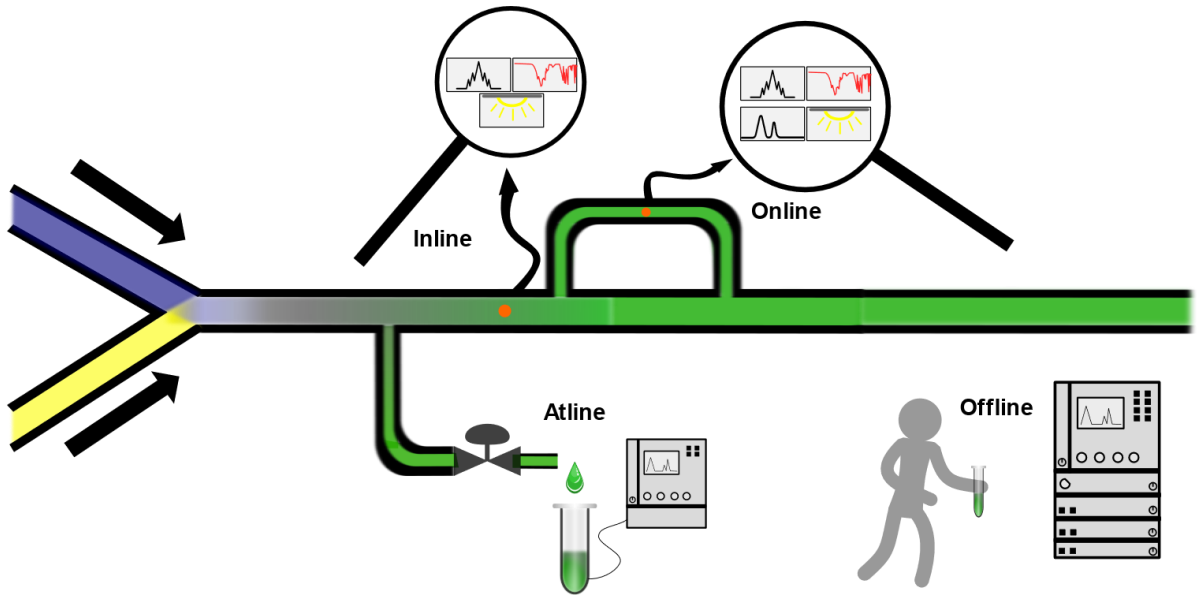


Figure 2. Graphical illustration of the different monitoring regimes.

Inline and online monitoring are generally more challenging to set up. However, once established, such methods are direct windows into the reactor, facilitating flexible decision making. Any deviations of critical process parameters can be identified and acted upon in a timely fashion. The utilization of integrated real time process analysis is therefore one of the cornerstones of process analytical technology (PAT).[15–17] This framework, published by the federal drug administration (FDA), aims to enhance pharmaceutical manufacturing,[18] by reducing process cycle time and minimize rejected product through increased production consistency.

Since there is no need for manual sampling inline and online monitoring are powerful tools in process automation, a field that continuous processing itself is also very well suited for.[19] Critical process parameters can be tracked and kept in an adequate range through automatized feedback loops. Quality control is thereby built into a process, adhering to the quality by design philosophy.[20] Besides the possibility to automize chemical synthesis,[21,22] the very same concept can be employed to optimize and kinetically profile new chemical reactions.[23–25] The prospects of

automation are promising and the field itself is only set to prosper with the rise of artificial intelligence.

1.1.3 Advantages of Flow

Besides the possibilities for online monitoring and automation flow systems can also enhance a process on a chemical level. Based on their kinetics chemical reactions can be grouped into three groups.[26,27] Type A reactions are very fast with a half-life time of less than one second. Such reactions involve very reactive species and are often controlled by the mixing process. The improved heat and mass transfer in flow reactors, especially micro structured ones, can be a huge benefit when dealing with type A reactions. Furthermore, the precise control over the residence time can increase yield by avoiding side reactions. Microreactors can therefore be used to run extremely fast reactions, that would otherwise be impossible to realize in batch with similar efficiency. Due to the fast nature of these reactions, this field has accordingly been coined flash chemistry.[28]

Type B reactions need several seconds up to 10 minutes. Mixing is less crucial for such reactions, but due to their rather fast reaction rate, they might benefit from the improved heat transfer of a flow reactor. This is especially true if temperature dependent side reactions are possible or if the reaction is just very exothermic.

Type C reactions are much slower and examples can also include potentially hazardous chemistry. Based on their kinetics they would be good candidates for a batch process but can be made safer using flow technology. The main reasons for this are the increased thermal control as well as the reduced reaction volume. Autocatalytic reactions that hold a significant risk of thermal runaway belong in this category.

Sometimes this list is expanded by type D reactions.[29] All reactions that do not belong in the other categories, but can still benefit from a flow regime, are summarized in this category. An example would be very slow reactions that can benefit from process intensification, as high temperatures and pressures are easier to achieve in flow. Mixing and heat transfer is crucial for type A reactions and so those benefit the most from the small dimensions of a microreactor. For type B reactions it depends on the reaction and type C and D reactions can usually just as well be run in millireactors.

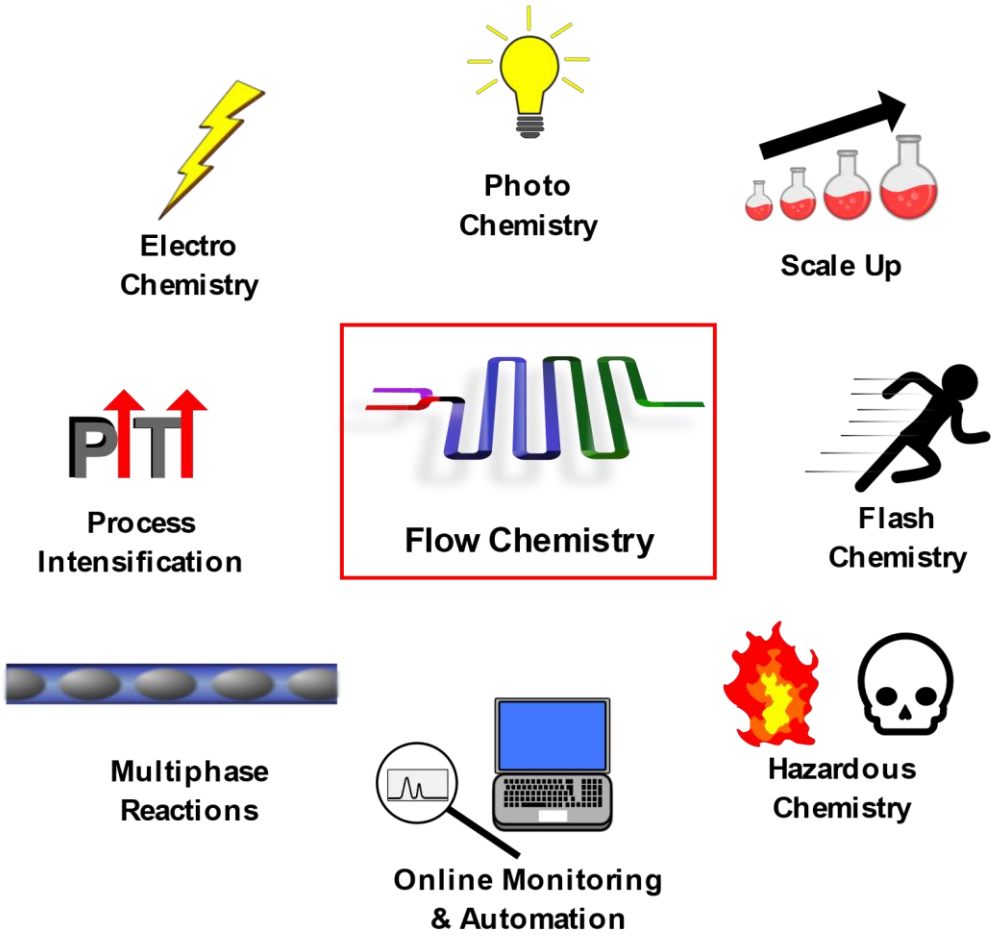


Figure 3. Areas of application for flow chemistry.

On a laboratory scale sufficient cooling is usually not a problem, but it can be a serious challenge during scale up. As a reaction tank becomes larger, its volume is increased to the power of three, while the surface, crucial for heat exchange, is only increased to the power of two. However, the productivity of a flow reactor, the product output per time, can not only be increased by sizing up the tubing`s diameter. A more productive system can also be achieved by increasing the length, or simply running multiple reactors in parallel. Through this approach of smart dimensioning the productivity of a continuous process can be increased while preserving the necessary mixing and heat transfer attributes. [30]

Hazardous chemistry can often be made more accessible using continuous processing.[31] Although substantial quantities of product can be manufactured over time, at any given moment, only a relatively modest amount of chemicals is present in the reactor. Reactions that would otherwise be deemed too dangerous due to drastic conditions or hazardous chemicals can thereby be made more feasible. The exposure to hazardous reaction intermediates can be further minimized by telescoping a

reaction, so that these intermediates only ever exist inside of the reactor. Similarly, powerful but hazardous reagents can be generated in situ from benign chemicals, then used for a reaction and quenched before they can leave the reactor. This concept, of the so-called chemical generator, has been implemented for the on-demand generation of diazomethane, Br_2, HCN, an many other highly reactive species.[32]

Multiphasic reactions are great candidates for continuous processing, as the flow pattern within such a reactor leads to an increased interface between phases. This is especially true for gas-liquid reactions, as there is no headspace, in which the gas could dwell without contact with the liquid components. Additionally, the pressure can be easily increased by employing a BPR resulting in higher gas solubility and therefore more interaction between the phases.

Moreover, the small dimensions of a flow reactor can be beneficial for photo-[33] and electrochemistry.[34] Photochemical reactions involve the absorption of photons and therefore require irradiation of the reaction mixture. Scale up in batch is often difficult due to the rather short penetration depth of light, especially at higher concentrations. A similar problem arises in electrochemical reactions in which an electrical current is used to facilitate redox reactions. A large distance between the electrodes can be problematic as it leads to a high cell resistance and often inhomogeneous electric fields. Furthermore, in case of heat evolution at the electrodes the continuously moving reaction mixture functions as a heat transfer fluid.

Despite all the praise, flow chemistry is not the universal remedy to all chemical problems but should rather be seen as a potent and still underutilized addition to the chemical toolbox. Reactions that involve solids or very viscous reaction mixture can often not even be realized in flow. In the end, if a batch process gives sufficient yield and the scale up is not problematic, there is no reason to invest considerable capital in the development of a new process. For further information on the advantages and disadvantages, as well as all things flow chemistry the reader is referred to this review.[6]

1.2 Sustainable chemistry

The most well-known report on this topic was already published back in 1998 by Paul Anastas and John Warner.[35] In it the authors singled out the 12 most important concepts to make chemistry a more sustainable field, known as the twelve principles of green chemistry. As continuous processing is inherently multidisciplinary those points are best complemented with a similar piece of work, called the twelve principles of green engineering.[36] Several features of flow chemistry are in alignment with what is demanded in the green principles and is therefore often seen a green technology.

There are, as listed in the last chapter, several situations in which flow chemistry can be employed to make a process more efficient, which in turn means, that less material or energy is needed to produce the same amount of product. The reduction of waste is one of the most important objectives to make a chemical process more sustainable. Both sets of principles also advise against the use of hazardous chemicals to make the processes inherently saver. However, while this is desirable, often one encounters chemicals that are toxic or dangerous, but also these reagents can perform very well and be very efficient in certain transformations. Swapping such reagents for more benign alternatives would potentially decrease yield and selectivity. Thereby the green principles can be at odds with each other. In cases where no satisfactory benign alternative exists, it is important to make the process around the reaction as safe as possible, which can be aided by flow chemistry.[37–39]

Table 1. Principles of green chemistry and engineering.

	Green Chemistry Principles	Green Engineering Principles
1	Waste Prevention	Inherently non-hazardous Processes
2	High Atom Economy	Waste Prevention instead of Treatment
3	Less Hazardous Synthesis	Design for Separation
4	Design Safer Chemicals	Maximize Efficiency
5	Safer Solvents and Auxiliaries	Output Pulled vs Input Pushed
6	Design for Energy Efficiency	Converse Complexity
7	Use of Renewable Feedstocks	Durability Rather than Immortality
8	Reduce Derivatives	Meet Need, Minimize Excess
9	Employ Catalysis	Minimize Material Diversity
10	Design for Degradation	Intergrade Material and Energy Flows
11	Real Time Analysis for Pollution Prevention	Design for Commercial “Afterlife”
12	Inherently Saver Chemistry to Prevent Accidents	Renewable Rather than Depleting

Measurable metrics are needed to compare the sustainability of different processes.[40,41] This can often be challenging as metrics have to be complex enough to be meaningful, but also simple enough to be easily used by people of many different backgrounds. Over time waste prevention has crystallized as one of the most important factors to build a green process. The most common metrics to assess how well a reaction is doing in these regards are yield, selectivity, atom efficiency (AE), E-factor and especially process mass intensity (PMI). AE focuses on the reagents as it displays how much of the starting materials are found within the product. The E-factor is the sum of all the waste, divided by the mass of the produced product. It therefore provides a more wholistic picture of a process as especially solvents often make up most of the used mass. E-factor can be reduced by solvent recovery and recycling, however the energy needed for these processes are not reflected within the E-factor. There are other metrics, such as the E+-factor that capture the energy involved, but this comes

with an increase in complexity. For these and other reasons the PMI, the ratio of all the mass used in the process to the mass of the produced product, has established itself as the key mass-based benchmark in the pharmaceutical industry.[42]

$$Atom\ efficiency\ (AE) = \frac{MW\ (Product)}{\sum MW\ (Reagents)} * 100 \qquad (Eq\ 1)$$

$$Reaction\ mass\ efficiency\ (RME) = \frac{mass\ of\ isolated\ product}{\sum mass\ reactants} * 100 \qquad (Eq\ 2)$$

$$Optimum\ efficiency\ (OE) = \frac{RME}{AR} * 100 \qquad (Eq\ 3)$$

$$Process\ mass\ intensity = \frac{\sum mass\ used\ in\ this\ process\ or\ process\ step}{mass\ of\ isolated\ product} \qquad (Eq\ 4)$$

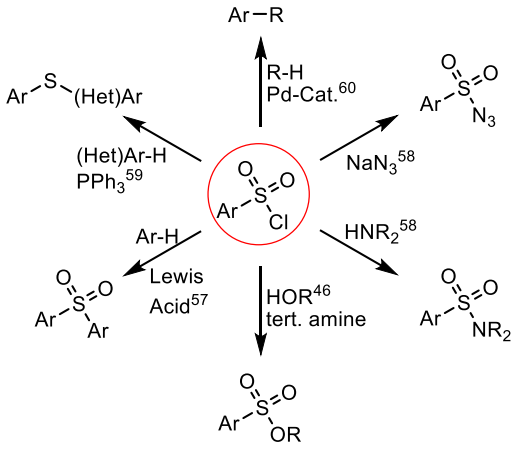
Not only the amount, but also the type of waste and used solvent plays a big role in accessing the sustainability of a reaction. Historically many powerful but hazardous solvents, such as carbon tetrachloride and hexamethylphosphoramide (HMPA, also referred to as liquid cancer), have been replaced by less hazardous alternatives. However, toxic and suspectedly cancerous chemicals, such as hexane and dichloromethane (DCM), are still the go-to solvents and used in vast quantities in many synthetic labs. While feasibly in laboratory scale there is an increasing push away from chlorinated and hazardous solvents towards saver and more sustainable ones. To this avail many different selection guides exist that rate solvents based on metrics like safety, environmental impact, and sustainability.[43,44] One downside with many of the preferable solvents is their low boiling point. Using flow chemistry one can easily increase the pressure within the system, which allows the use of solvents above their respective boiling point. The ability to use a solvent way above its boiling point is generally very useful as it is more energy efficient than refluxing.

1.3 Chemical Background

1.3.1 Sulfonyl Chlorides

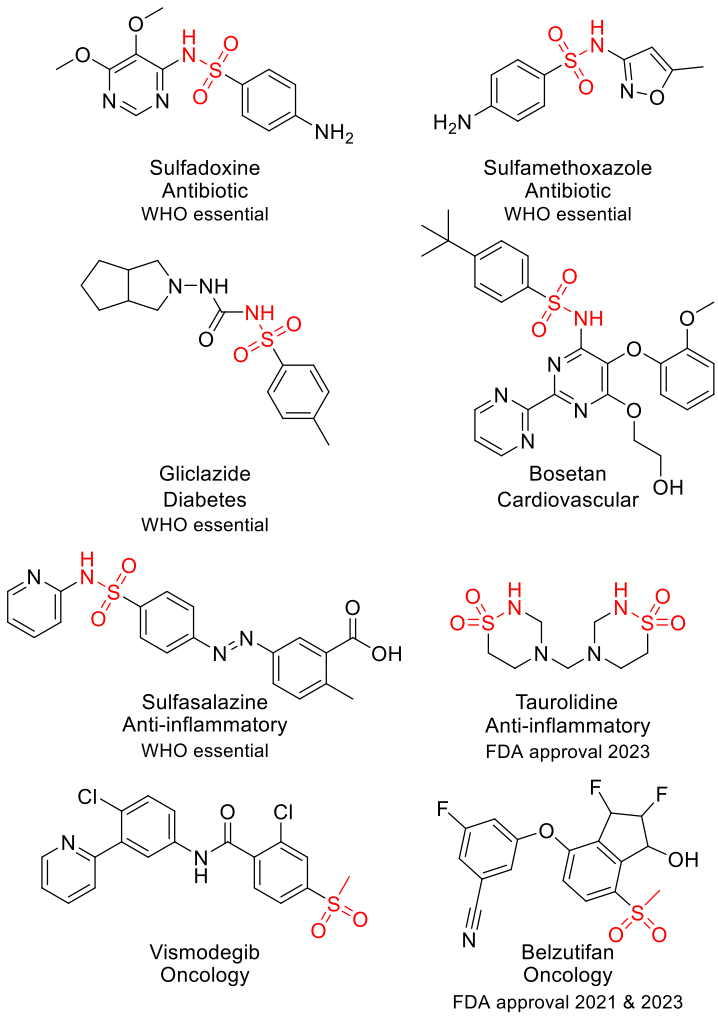
Sulfonyl chlorides are excellent electrophiles and especially arylsulfonyl chlories find a broad range of applications. In organic synthesis they are common protection groups for alcohols and amines[45,46], have been employed as linker resins for the synthesis of heterocycles[47] and as precursors for C-C bond formation through

desulfonylation[48,49]. Furthermore, sulfonyl chlorides provide an easy access to many different sulfides and sulfoxides through cross coupling reactions[50,51] and modified Friedel Crafts reactions[52]. Especially sulfones are of great interest, as they are widely used in synthesis[53] and in functional materials, such as polyethersulfone based high performance polymers[54] and the bisphenol A alternative, bisphenol S[55]. Together with sulfonamides, which are readily available through the reaction of sulfonyl chlorides with an amine, sulfones play an important role as agrochemicals[56], such as fungicides, insecticides, and herbicides.



Scheme 2. Important transformations of sulfonyl chlorides to give sulfones[57], sulfonates[46], sulfonamides[58], sulfonazides[58], sulfides[59] and C-C bonds through desulfonylation[60].

Due to the potent antimicrobial effects of these two moieties[61,62], sulfones and sulfonamides play an important role as versatile APIs in various drugs.[63] The sulfone amide motif is very common and drugs which contain it are also referred to as sulfa drugs. These are especially important as antibiotics, anti-inflammatory and anti-infective drugs. Moreover, sulfones and sulfonamides are used in drugs that act upon the nervous system, cardiovascular diseases and many more.[63] Sulfonamides are also explored as anti-cancer agents[64–67], among recent oncological drugs are Vismodegib and Belzutifan [68,69], as HIV protease inhibitors[70,71], glucocoticoide receptor modulators[72] and to battle diseases such as tuberculosis[73] and hepatitis C[74].



Scheme 3. Six Sulfonamide and two Sulfone based APIs with the respective motives highlighted.

1.3.2 Synthesis of Sulfonyl Chlorides

Thiols and disulfides are some of the main precursors to sulfonyl chlorides. The conversion of thiols and disulfides to sulfonyl chlorides is achieved via oxidative chlorination. Older reported protocols use chlorine (Cl_2) gas in the presence of an acid.[75] These protocols generally provide good yields under relatively mild reaction conditions, and the use of Cl_2 is considered atom efficient.[76] However, it requires careful handling of a highly reactive and toxic gas and the exact dosing of gas into the liquid phase can be difficult to achieved.[77] Thus, protocols with procedures using aqueous Cl_2 have also been developed to mitigate the challenges of gas handling.[78] Some of the hazards associated with handling Cl_2 have also been minimized with the ex-situ generation of Cl_2 from simple to handle starting materials, for example from NaOCl and HCl.[79] A benefit of ex-situ generation is that the conditions for Cl_2 generation do not need to be compatible with the organic reaction. Interestingly, a continuous flow method for the formation of Cl_2 from HCl and NaOCl has been

developed, with NaCl and H_2O generated as byproducts. The Cl_2 was formed in an aqueous phase, extracted into an organic phase, and then the two phases separated with a membrane. Subsequently the Cl_2 was used in organic transformations.[80,81] We also explored the use of such a system in the oxidative chlorination of thiols and disulfides, which is described in the appendix.

More recent approaches were developed that use a combination of chlorinating and oxidizing reagents for the conversion of thiols and disulfides to their corresponding sulfonyl chlorides, including $SOCl_2$-H_2O_2,[82] PCl_3-H_2O_2,[83,84] $ZrCl_4$-H_2O_2,[85] Oxone-PPh_3-$SOCl_2$,[86] SO_2Cl_2-KNO_3,[87] and TMSCl-KNO_3.[88] These reactions can display some limitation in functional group tolerance, and the reactions are typically exothermic and multiphasic, with can make them challenge to handle, especially at a larger scale.

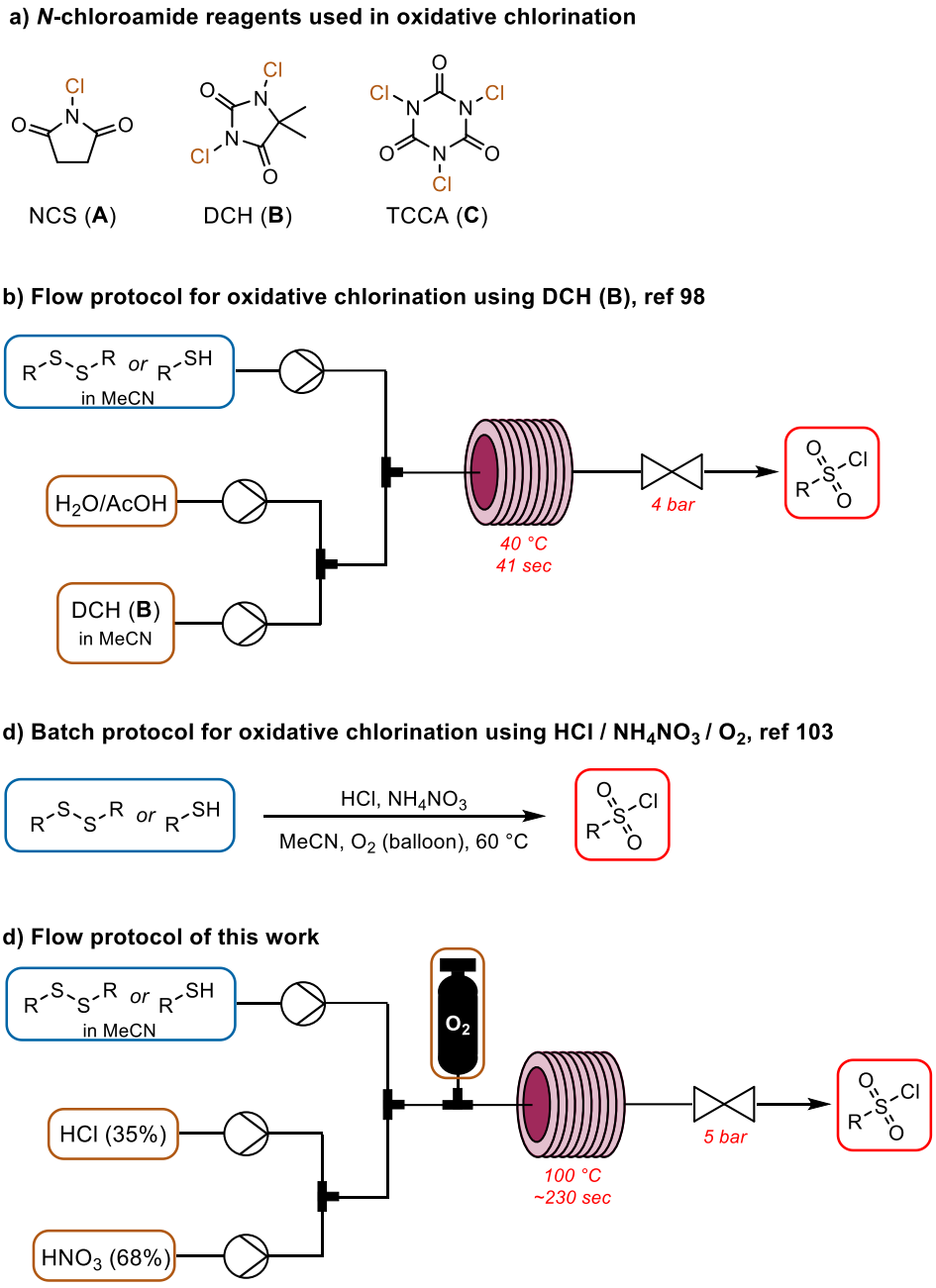
Another strategy for the formation of sulfonyl chlorides from thiols and disulfides is through the use of dual-function reagents that perform both the chlorination and oxidation. Aqueous sodium hypochloride (NaOCl) solution, usually known as bleach, is both an atom efficient and cost-efficient dual function reagent used to prepare sulfonyl chlorides.[89] Recently, Okada et al developed a protocol that implemented sodium hypochlorite pentahydrate ($NaOCl \cdot 5H_2O$) as a solid and stable source of NaOCl.[90][91]

N-Chloroamines or *N*-chloroamides are widely utilized as dual-functional reagents, owing to the mild conditions and their compatibility with different functional groups, relative to hypochlorite-based strategies. The oxychlorination of different thiols and disulfides has been demonstrated with *N*-chloroamides, such as: *N*-chlorosuccinimide (NCS) (**A**),[92] 1,3-dichloro-5,5-dimethylhydantoin (DCH) (**B**),[93] and trichloroisocyanuric acid (TCCA) (**C**) (Scheme 4a).[94,95] The main downside of the *N*-chloroamides approaches is the poor atom economy and reagent cost. For instance, the chlorine content in NCS is 51%, in DCH is 78%, and in TCCA is 92%, thus TCCA has the highest amount of active chlorine.[96] The price of NCS is 172 € per kg, DCH is 117 € per kg, and TCCA is 95 € per kg.[97]

Previous studies reported a large exotherm being released during the oxidative chlorination of disulfides and thiols, which makes it challenging to perform on larger scale.[98] Flow chemistry is established as an enabling technique for handling chemistries that are typically difficult to handle in batch, especially at larger scales.[6][99] The mass and heat transfer are enhanced within the small channels. Furthermore, only a small inventory of material reacting at any-one-time, thus improving safety. The

formation of sulfonyl chlorides has also reported using continuous flow reactors.[98,100–102] For instance, Yu *et al.* developed a multistep continuous flow process involving a magnesium halogen exchange, chlorosulfonylation using sulfuryl chloride ($SOCl_2$), and subsequent reaction with *tert*-butylamine for the preparation of an aryl sulfonamide API intermediate.[100] Malet-Sanz *et al.* reported a flow protocol for the in situ generation of diazonium salts from aniline starting materials which was followed by chlorosulfonylation and then amination.[101] Recently, Roper and co-workers developed an automated continuous process for the generation of aryl sulfonyl chlorides at 0.5 kg scale using chlorosulfuric acid ($ClSO_3H$) as reagent within a continuous stirred tank reactor (CSTR) cascade system.[102] We recently reported a tubular continuous flow chlorosulfonylation procedure using DCH (**B**) as reagent (Scheme 4b).[98] A small reactor volume (639 µL) and short residence time (41 s) provided a high space-time yield for the conversion of thiols and disulfides. However, we were interested in exploring options using more atom efficient reagents to achieve this transformation.

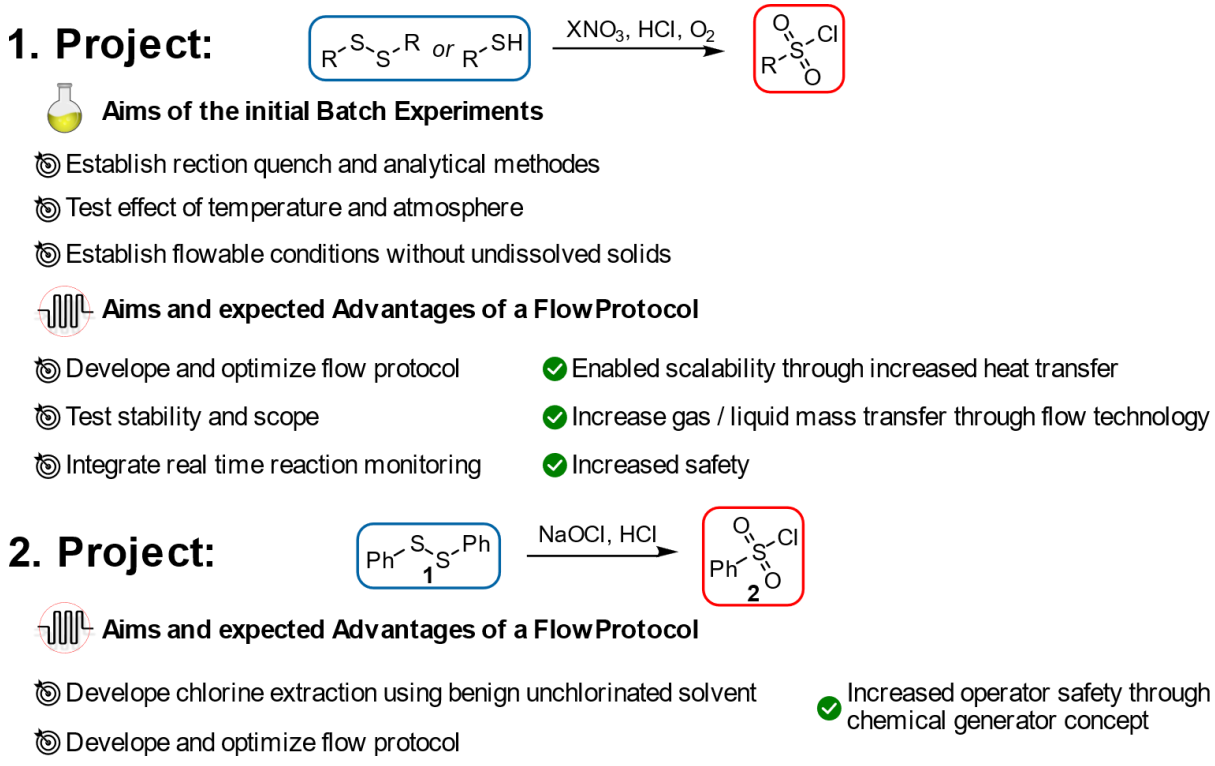
We were inspired by a report by Jereb and Hribernik disclosing the use of ammonium nitrate, HCl and O_2 for chlorosulfonylation in batch (Scheme 4c).[103] The reaction protocol is metal-free and uses only bulk chemicals as reagents. However, the reaction limited in its potential for implementation due to its exothermic and multiphasic nature (combination of gaseous O_2, liquid disulfide/thiol solution, liquid HCl, and solid NH_4NO_3). The safe and efficient operation can be ensured by employing properly designed continuous-flow reactors even upon using O_2 in the presence of flammable organic solvents at elevated temperatures and pressure.[7,31,104–106] We shared this perspective in a Concept Article.[107] Moreover, the mass transfer between the different phases can be enhanced within continuous flow systems.



Scheme 4. Comparison of chlorosulfonylation protocols: a) *N*-chloroamides as reagents; b) Chlorosulfonylation using 1,3-dichloro-5,5-dimethylhydantoin (DCH) within a continuous flow system[98]; c) NH_4NO_3/HCl/O_2 chlorosulfonylation developed by Jereb and Hribernik[103]; d) This work: chlorosulfonylation flow protocol using HNO_3/HCl/O_2.

2 Aims of this thesis

In the spirit of improving sustainability and processability, we were interested in developing a continuous protocol that was atom efficient and potentially scalable. Thus, we explored the further development of the ammonium nitrate, HCl and O_2 reaction system pioneered by Jereb and Hribernik.[103] Due to the strongly exothermic reaction and the chemicals involved (ammonium nitrate under oxygen atmosphere) a scale up in batch would not be possible. Continuous processing would enable scale up and increase the overall safety of the process. Furthermore, a flow protocol would also help to enhance the mass transfer in the liquid gas system, through improved mixing and a higher pressure. Online or inline analysis should be integrated into the system to potentially monitor kinetics and detect irregularities in real time. Robustness and applicability of the flow protocol would be evaluated by performing a long run and exploring the scope of the reaction with different substrates. Furthermore, we were interested in employing the chemical generator principle to safely use Cl_2 for the oxidative chlorination of thiols and disulfides.

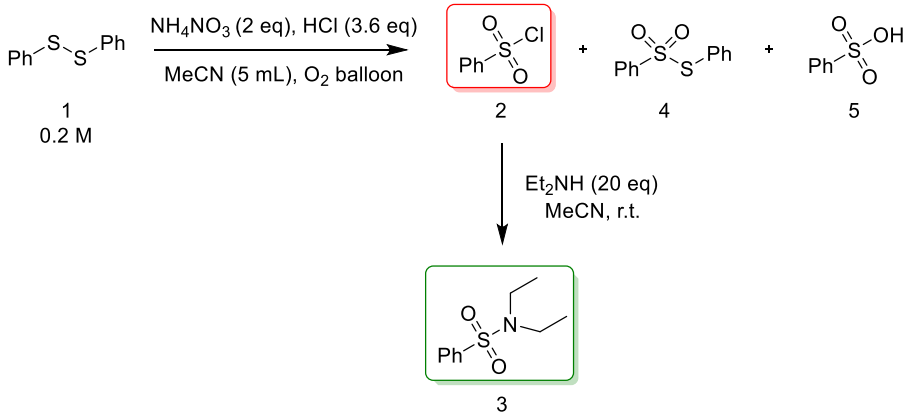


Scheme 5. Overview of the aims of this work and the expected advantages of the 2 flow protocols.

3 Results and Discussion

3.1 Initial Batch Experiments

The aim of our initial experiments was to investigate the influence of different parameters on the conversion and product distribution. We were interested to identify conditions that would be amenable to a gas-liquid continuous flow tubular reactor setup. Table 2 shows the influence of different nitrate sources, available oxygen and temperature on the reaction outcome. Initially, small scale batch experiments were performed using 1 mmol of diphenyl disulfide **1** as model substrate, based on modifying the batch procedure reported by Jereb and Hribernik.[103] We performed the reaction using 5 mL acetonitrile (MeCN) as a solvent, by attaching an O_2-filled balloon to the reaction vessel, and by using 2 and 3.6 eq of nitrate source and aqueous HCl (35%), respectively. These conditions are illustrated in the first part of Scheme 6. At time intervals, an aliquot of reaction was taken and quenched with a large excess of diethyl amine. Diethyl amine and benzenesulfonyl chloride **2** reacted to give *N,N*-diethylbenzenesulfonamide **3** as product.



Scheme 6. Oxychlorination reaction using NH_4NO_3, HCl and O_2 as reagents followed by a quench with amine to form the sulfonamide.

The reaction reached nearly full conversion (94%) at 30 °C after two hours, however the main product was not the desired sulfonyl chloride **2** (Table 2, entry 1). Furthermore, at the beginning of the reaction the profile showed very slow substrate consumption and no product formation (Fig. 4a). After 60 min an increase in desired product **3** was observed. This slow initial rate could have been caused by the low solubility of NH_4NO_3 in MeCN, or due to a delay in the formation of the reactive species.[108] One further peak was observed by HPLC-UV at 254 nm. GC-MS analysis confirmed that this was the reaction intermediate, *S*-phenyl benzenesulfonothioate **4**

(m/z = 250). Disulfide reacts with the in situ formed HOCl to give PhS(O)-S(O)Ph, which rapidly rearranges into $PhSO_2$-SPh, the observed intermediate **4**.[98,103,109] $PhSO_2$-SPh is then cleaved by HCl into $PhSO_2Cl$ and PhSH. Even when considering the intermediate, there was still significant missing mass balance that was unaccounted for by the HPLC analysis. We hypothesized that phenyl sulfonic acid was forming via the hydrolysis of sulfonyl chloride in the presence of the acidic medium. The acid **5** was confirmed by comparison to a commercially available reference sample. We found that **5** could be better observed at a different wavelength by HPLC-UV (215 nm). The formation of the acid was not reported by Jereb and Hribernik.[103]

For quantitative analysis both the quenched product **3** and intermediate **4** were calibrated using isolated compounds, while reference samples were used for calibration of the starting material **1** and the sulfonic acid **5**. Gratifyingly, increased conversion and selectivity towards the desired product were observed at higher reaction temperatures (Table 2, entries 1-3). Fig. 4c shows the reaction progress at 60 °C, with the desired yield reaching 76%. In order to potentially obtain a pumpable homogeneous liquid feed, the ammonium nitrate was dissolved into the reaction medium through the addition of 1.1 mL of water. Adding water resulted in the immediate observation of product formation. However, the addition of water decreased the desired selectivity further, with elevated formation of benzenesulfonic acid **5** (Table 2, entry 4 and Fig. 4d).

Subsequently, the dependency of the reaction on O_2 was examined. When using air instead of pure O_2, the reaction profile started very similar, however, after approximately half of the starting material was consumed the conversion rate slowed down significantly. However, at 40 °C the reaction still reached almost full conversion after two hours and gave an even higher yield than when pure O_2 was supplied (Table 2, entry 5). A similar initial reaction profile could also be observed under argon, but this time the reaction rate was even slower, to a point where the reaction almost stopped completely, as can be seen in Fig. 4e (and Table 2, entry 6). While the presence of O_2 seems to be a requirement for the reaction to proceed, significant conversion occurs even under inert conditions, demonstrating that the reaction is not dependent on the exogenous addition of O_2. Interestingly, the analogous oxidative bromination using NH_4NO_3 and HBr does not occur without the exogenous addition of oxygen.[103] A postulated mechanism is that the nitrate reagent decomposes in the acidic medium to give NO, and NO reacts with O_2 to form NO_2.[109] NO_2 then reacts with HCl to form

HOCl. The presence of O_2 helps to drive the equilibrium as NO is consumed by O_2. It is possible for HOCl to form under the conditions, even without the addition O_2.

The use of KNO_3 (Table 2, entry 7) as an alternative nitrate source resulted in a slower reaction rate and lower yield when compared to NH_4NO_3. On the other hand, nitric acid (HNO_3) was found to perform better than NH_4NO_3 at 40 °C (Table 2, entry 8), achieving >80% yield. The benefit of using HNO_3 was that product formation occurred shortly after the reaction start, which also resulted in a decrease in reaction time (Fig. 4f). The use of HNO_3 also provides a single homogeneous liquid. A 70% product **3** yield was achieved within 30 min of reaction time, which increased to 83% after 2 hours. HNO_3 was used as the nitrate source for the investigation in continuous flow, both due to the improved yield and handling.

Table 2. Results from batch experiments after two hours of reaction time.[a]

N	XNO_3 source	T (°C)	Gas	Conv. **1** (%)[b]	Yield **3** (%)[b]	Yield **4** (%)[b]	Yield **5** (%)[b]
1	NH_4NO_3	30	O_2	94	**30**	10	56
2	NH_4NO_3	40	O_2	>99	**57**	5	32
3	NH_4NO_3	60	O_2	>99	**76**	1	22
4[c]	NH_4NO_3	40	O_2	>99	**43**	1	59
5	NH_4NO_3	40	Air	99	**64**	6	24
6	NH_4NO_3	40	Ar	68	**52**	7	5
7	KNO_3	40	O_2	99	**42**	14	40
8	HNO_3	40	O_2	>99	**83**	0	19

[a] Conditions: 1 mmol of **1** in 5 mL acetonitrile, 2 eq of NH_4NO_3 or KNO_3 or aqueous HNO_3 (68%), 3.6 eq of aqueous HCl, and O_2-filled balloon. [b] Calibrated HPLC conversion and yields. [c] 1.1 mL of H_2O added to the reaction.

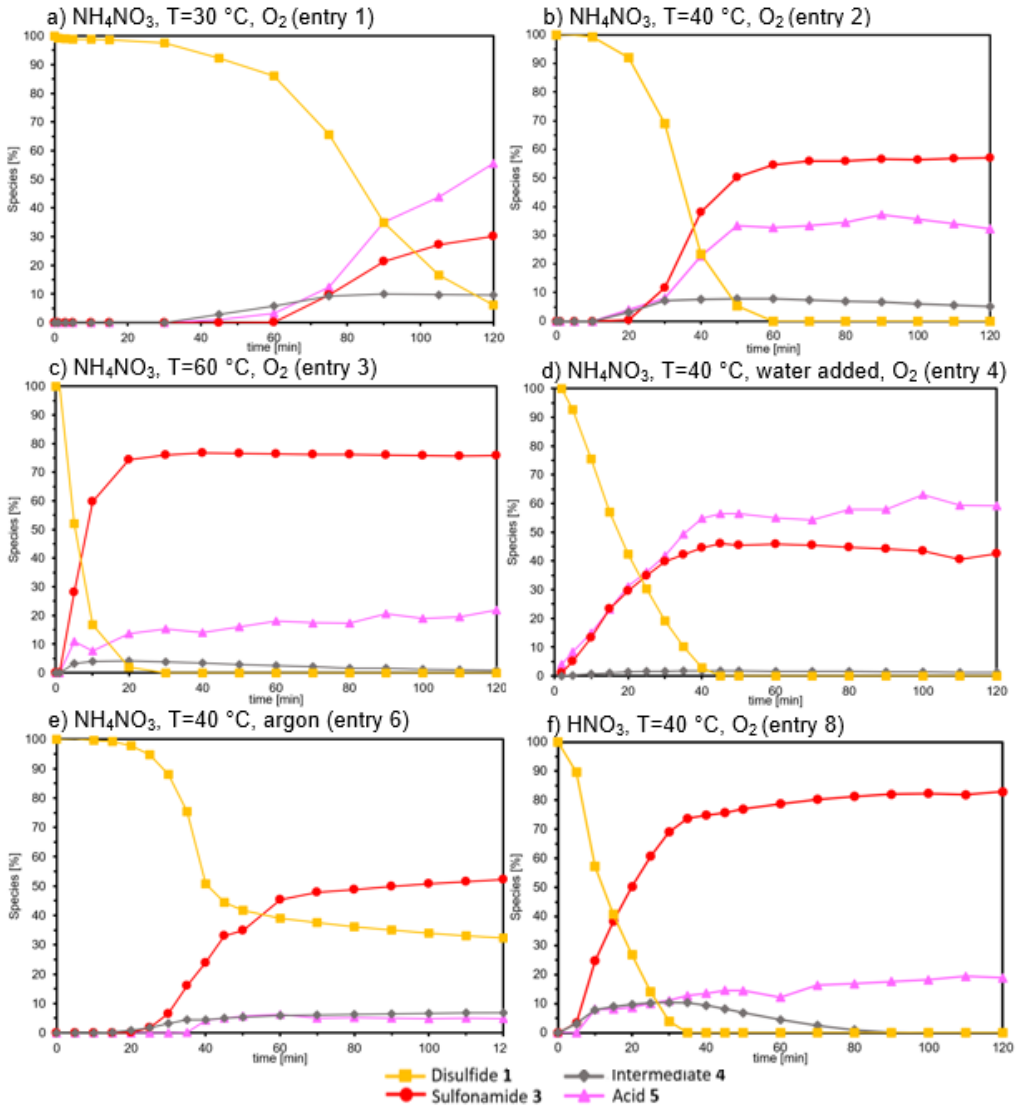
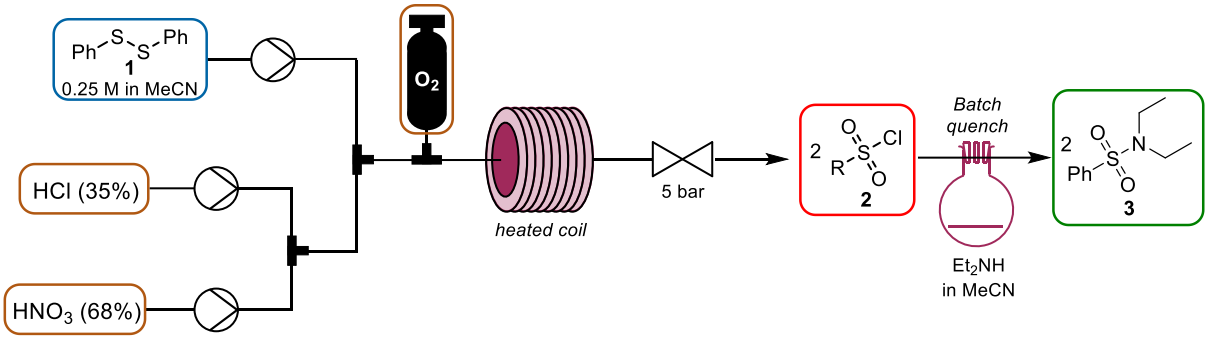


Figure 4. Reaction profiling of selected batch reactions reported in Table 2 (see table for conditions).

3.2 Continuous Flow Experiments

We assembled a continuous flow reactor system for performing the reaction. Syringe pumps were used to introduce the three liquid feeds: 1) diphenyl disulfide **1**and biphenyl as internal standard in MeCN (0.25 M); 2) aqueous HNO_3 (68%); and 3) aqueous HCl (35%). A mass flow controller (MFC, Bronkhorst) was employed to introduce O_2 into the system. Firstly, the two acid streams were mixed in a T-piece. This stream was then mixed with the substrate stream, followed by the O_2 to allow for further investigation of the influence of O_2. The reaction mixture then passed through a heated reactor coil (11 mL, 0.8 mm diameter). The reactor coil was followed by a cooling coil (0.5 mL, 0.8 mm diameter) and a back pressure regulator (BPR, Zaiput),

which provided control over the pressure within the reactor system. At the outlet of the flow system, the reaction mixture was quenched in batch.



Scheme 7. Continuous flow reactor setup for the reaction with HNO_3/HCl/O_2.

Initially, several different reaction conditions were screened within the continuous flow setup. When the reaction was carried out at 50 °C for 112 seconds of residence time (t_{res}), only 21% of the desired product **2** and significant amounts of intermediate **4** were observed (Table 3, entry 1). Increasing the residence time provided an increase in yield to 35%. However, a further increase in residence time provided no improvement in the yield (Table 3, entry 3). The yield of sulfonyl chloride **2** could be increased to 53% by doubling the equivalents of HNO_3 and HCl. However, these high acid equivalents led to the formation of more sulfonic acid **5** (Table 3, entry 4). A benefit of using continuous flow reactors is the ability to pressurize the system, thus enabling easy operation above the boiling point of the solvent. The yield could be increased at 2 eq HNO_3 and 3.6 eq HCl by increasing the temperature. The influence of temperature on yield displayed a linear behavior (see appendix, Fig 21). The best yield was observed at 100 °C, which provided a yield of 75% (Table 4, entry 5). The hydrolysis to the sulfonic acid was less favored at higher temperatures. Above 100 °C resulted in a drop in yield, this is probably due to the decomposition of HOCl at this temperature. At 120 °C, clogging of the reaction system occurred due to poor reaction performance. At 100 °C, the yield of desired product could not be further improved by varying the HCl and HNO_3 equivalents (Table 3, entries 6 and 7).

To study the influence of oxygen, experiments were performed using different oxygen equivalents (Table 4). An increase in conversion and yield was observed with an increase in dosed O_2 (Table 4, entries 1-4). The best result was observed at 1 eq of dosed O_2, which provided complete conversion and 75% desired yield (Table 4, entry 4). This result shows that the addition of exogeneous O_2 helps to drive the reaction

towards completion. A further increase in dosed O_2 did not afford an increase in yield (Table 4, entry 5).

Table 3. Flow optimization of parameters for the oxychlorination of diphenyl disulfide (**1**).[a]

N	T [°C]	HNO_3 [eq]	HCl [eq]	t_{res} [s][b]	Conv **1** (%)[c]	Yield **3** (%)[c]	Yield **4** (%)[c]	Yield **5** (%)[c]
1	50	2	3.6	112	88	**21**	21	29
2	50	2	3.6	268	93	**35**	18	30
3	50	2	3.6	375	96	**34**	20	25
4	50	4	7.2	265	>99	**53**	0	34
5[d]	100	2	3.6	247	>99	**75**	2	22
6	100	2	7.2	240	99	**71**	2	20
7	100	2.1	3.8	286	98	**73**	3	21

[a] Fixed conditions: [**1**] = 0.25 M, 1 eq of O_2. [b] Estimated residence time is based on calculations. (see appendix, equation 5). [c] Calibrated HPLC conversion and yields. [d] Average of 2 flow experiments

Table 4. HPLC yields of further optimization reactions, studying the effect of oxygen.[a]

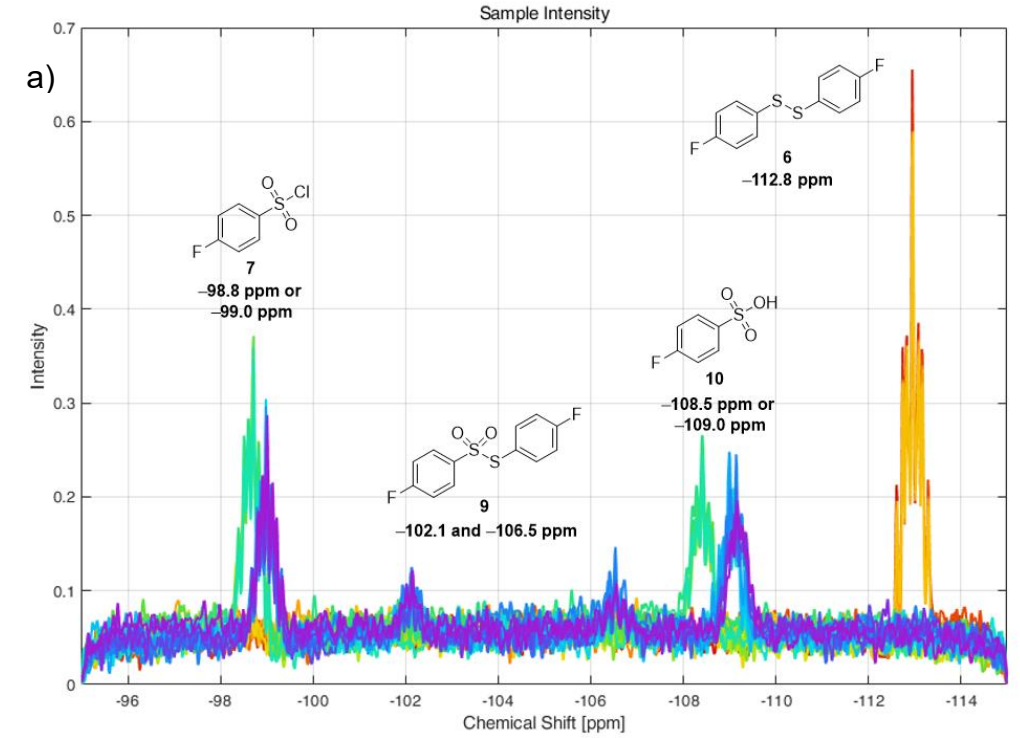
N	O_2 [eq]	t_{res} [s][b]	Conv. **1** (%)[c]	Yield **3** (%)[c]	Yield **4** (%)[c]	Yield **5** (%)[c]
1[d]	0 (Ar)	247	53	**46**	4	4
2	0.5	349	85	**63**	6	16
3[e]	0.75	289	96	**70**	6	17
4[e]	1	247	>99	**75**	2	22
5	1.5	191	>99	**70**	0	25

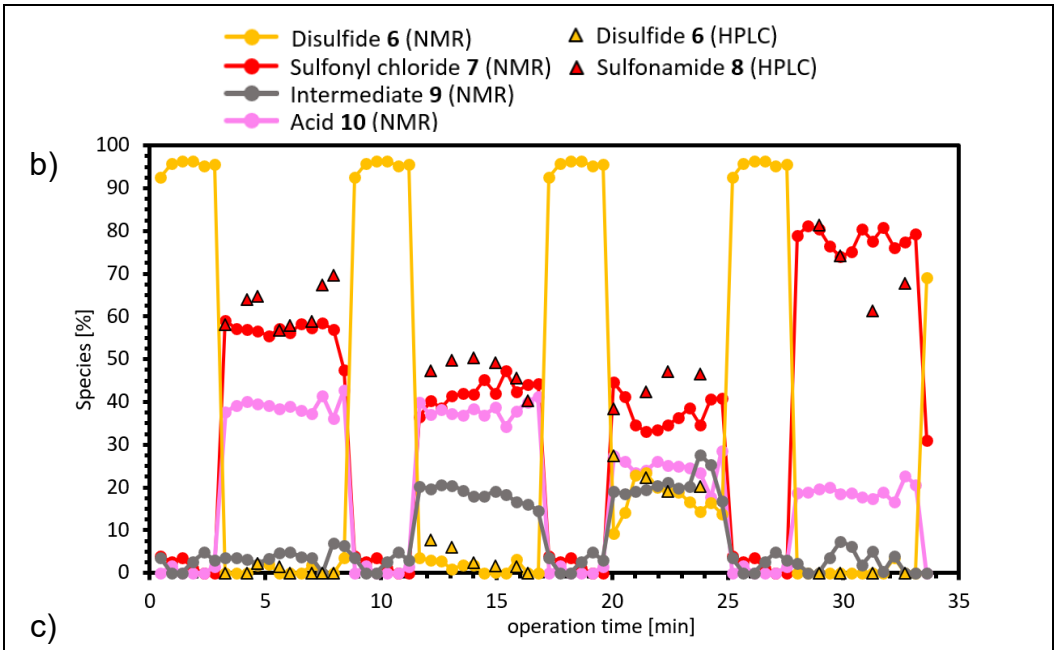
[a] Fixed conditions: [**1**] = 0.25 M, T = 100 °C, 2 eq HNO_3, 3.6 eq HCl. [b] Estimated residence time is based on calculated (see appendix, equation 5). [c] Calibrated HPLC conversion and yields. [d] Experiment was performed using argon (Ar) gas at the same flow rate as for 1 eq of oxygen. [e] Average of 2 flow experiments

3.3 ^{19}F NMR Monitoring

Continuous flow processing has been shown to simplify in situ reaction monitoring of multiphase reactions, which is challenging within pressurized batch systems with a gaseous headspace, especially when hazardous chemicals are involved.[110–113] The utilization of online reaction monitoring was investigated by modifying the flow setup to include a benchtop ^{19}F NMR. The analysis by NMR was initially difficult to achieve in a reliable manner in the presence of undissolved gas within the system. Thus, the system was configured to incorporate a T-piece after the reactor coil so that gas could be removed from the system, prior to pumping the stream by a peristaltic pump through a glass flow-through cell for analysis. The full design of the setup is described in more detail in the appendix. The reaction progress was monitoring in real time through the implementation of process link software and through the use of indirect hard modeling (IHM) for all the components containing fluorine atoms.

1,2-*Bis*(4-fluorophenyl) disulfide **6** was selected as a model substrate. Four different sets of reaction conditions were chosen to explore a wide design space and to see different product distributions (Fig. 5). For each set of reaction conditions, 5 mL of substrate **6** feed (0.25 M in MeCN) were injected via a sample loop at a flow rate of 1 mL/min. Trifluorotoluene was included as an internal standard. In between samples only the substrate feed was introduced into the system. The conversion of **6** and product **7** yield were monitored by the peaks at −112.8 ppm and −99.0 ppm, respectively, and trifluorotoluene (TFT) (−63.7 ppm) was used as an internal standard (Fig. 5a).





c)

T [°C]	50	50	50	100
O_2 [eq]	1	1	0.5	1
HNO_3 [eq]	4	2	2	2.5
HCl [eq]	7.2	3.6	3.6	4.6

Figure 5. Online ^{19}F NMR reaction monitoring for the reaction of 1,2-*bis*(4-fluorophenyl) disulfide (**6**): a) NMR spectra; b) Calibrated percentage component for: online NMR (circles and lines) and offline HPLC (triangle points) for quenched samples; c) Reaction conditions corresponding to the results shown in (b).

The effluent was quenched with diethyl amine to enable analysis by offline HPLC for comparison with the NMR results. In the first experiment,4 eq of HNO_3 and 7.6 eq of HCl and 50 °C were used, this resulted in complete conversion but relatively high (~38%) sulfonic acid formation (−109.0 ppm). In the subsequent experiment, the acid equivalents were halved, high conversion was maintained. Notably, under these reaction conditions, a high amount of the reaction intermediate **9** (−102.1 and −106.5 ppm) could be observed. In the third experiment, halving the oxygen equivalents from 1 to 0.5 eq resulted in a drop in conversion of **6**. In the last experiment, using slightly more reagent excess (2.5 eq of HNO_3 and 4.6 eq of HCl) and a reaction temperature of 100 °C resulted in a higher yield (~80%) of desired product. The measured concentration correlated relatively well with offline HPLC results during the optimization study. Interestingly, when we performed a reaction using 4-fluorobenzenethiol **6'** as starting material, we observed the formation of the disulfide **6**. This result indicated that the reaction pathway from the thiol proceeds via the disulfide as an intermediate. The implementation of an online NMR analysis allowed us to study the reaction of **6** to **7** in an efficient manner and showed that it is possible to circumvent the need to quench and analyze mixtures after each modification of the reaction conditions. Furthermore, the stability of the system over time could be observed.

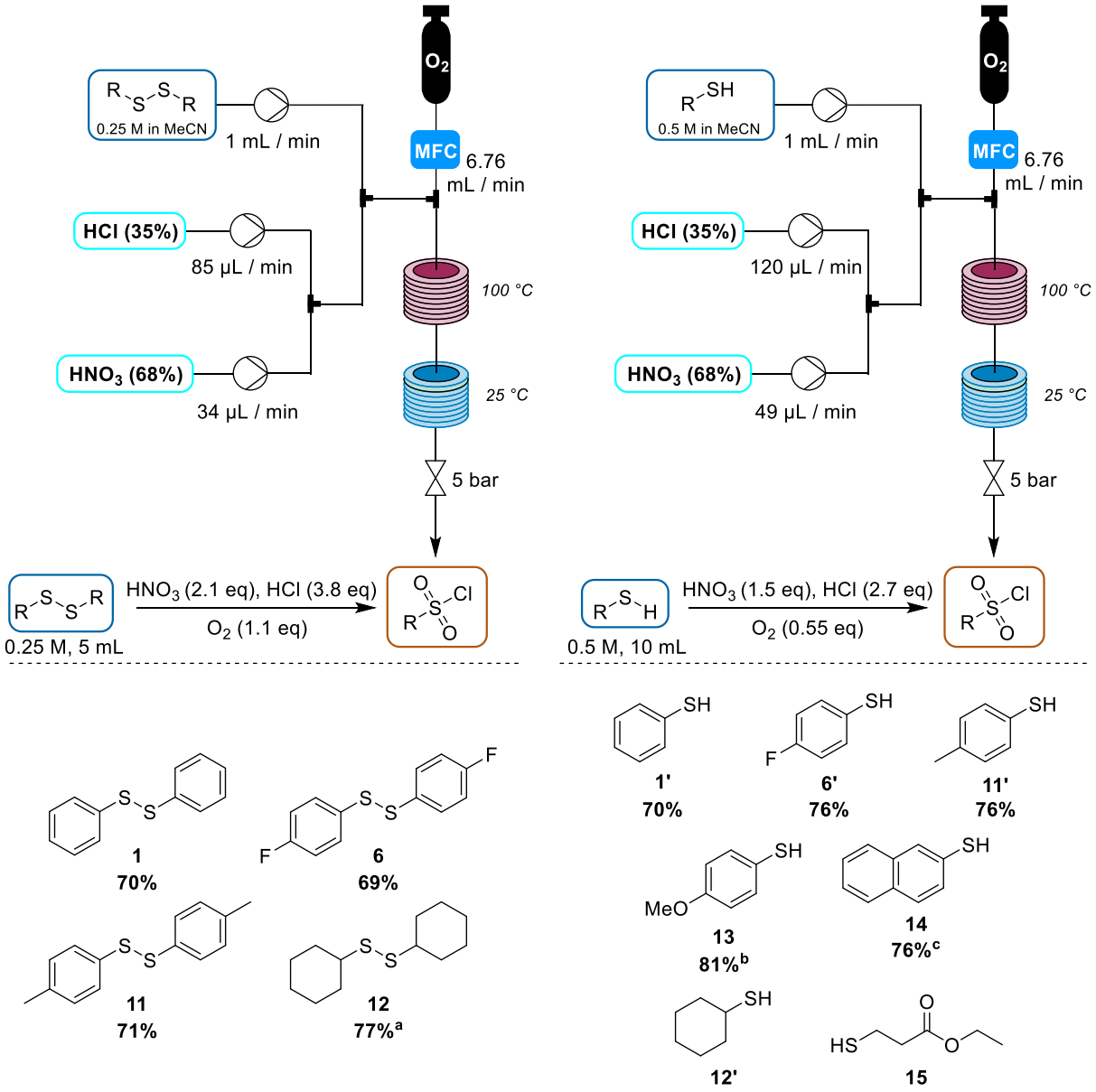
3.4 Scope and Stability Test

Subsequently, we performed a substrate scope using the flow conditions to explore the applicability of different disulfides and thiols on a 1.25 to 5 mmol scale, respectively (Scheme 8). The optimized conditions for the disulfides were selected as 100 °C, 2.1 eq of HNO_3, 3.8 eq of HCl and 1.1 eq of O_2. Based on previous studies for oxidative chlorination, the final conditions for the thiol derivatives were modified: 1.5 eq of HNO_3, 2.7 eq of HCl and 0.55 eq of O_2, whilst keeping the pressure and temperature.[98] To increase the productivity the concentration of the substrate was doubled. These conditions were selected to ensure quantitative conversion of starting material and to avoid the presence of intermediate **4**, thus simplifying post reaction processing. Whilst the sulfonic acid would be formed, this could be removed using a simple aqueous wash.

Overall, the reaction of four disulfides and seven thiols were successful, mostly providing >99% conversion and good isolated yields of 70%-76% and 70-81%,

respectively. Aliphatic **15** could be isolated only in 53% yield due to its high volatility. Gratifyingly, the compounds were isolated in good purity (>95%) after a simple washing step and drying procedure. Thus, column chromatography could be avoided, minimizing solvent use. The reaction of 2,2´-dipyridyl disulfide was also attempted, but did not yield the desired sulfonyl chloride, but rather 2-chloropyridine. 2-Chloropyridine was formed from the desulfonylation of the desired product. It was necessary to lower the concentration of 4-methoxybenzenethiol (**13**) to 0.32 M and 2-naphthalenethiol (**14**) to 0.25 M due to their limited solubility at the general conditions. Toluene (PhMe) was added as co-solvent for the feed solution for 1,2-dicyclohexyl disulfide (**12'**) due to its limited solubility at the general conditions.

To test the robustness of the flow protocol, the system was operated at the optimal conditions for >6 hours. The effluent was collected over 12 different fractions, each for 30 minutes. The system operated in a stable manner over this operation time. At 30 min intervals, an additional sample was collected which was quenched for HPLC analysis to monitor stability. 10 of the fractions were then combined to afford 18.7 g of **2** (70% yield) after an aqueous work-up and drying. This corresponds to a throughput of 3.7 g h^{-1} and a space-time yield of 0.32 kg L^{-1} h^{-1}.



Scheme 8. Substrate scope performed in flow to form the corresponding sulfonyl chlorides. All values are isolated yields for the sulfonyl chlorides. [a] 95:5 MeCN:PhMe solvent mixture for feed. [b] Feed concentration was lowered to 0.32 M. [c] Feed concentration was lowered to 0.25 M.

3.5 Green Metric Assessment

The green metrics of the flow protocol were assessed for the HNO_3/HCl/O_2 system and compared to our previously reported flow protocol using DCH (**B**)/H_2O/AcOH using the CHEM21 toolkit developed by Clark and co-workers in 2015.[114] Quantitative green metrics: process mass intensity (PMI), reaction mass efficiency (RME), atom economy (AE), and optimum efficiency (OE) were calculated using equations summarized in the appendix (Equations 6-9). These results are summarized in Table 5. Furthermore, the toolkit grades different aspects of a process with a green, amber or red flag, which corresponds to whether it is preferred, acceptable with some issues or undesirable. This traffic light system facilitates easy discussion between process developers, so that strengths and weaknesses in a process can be considered.

All of the reactions afforded quantitative conversion and most substrates could be isolated in ~75% yield, therefore this category was graded as an amber flag. An isolated yield of 70% was achieved during the long run using diphenyl disulfide; this value was used in subsequent calculations. Although achieving a higher yield, the DCH protocol was similarly graded with an amber flag. A ≥90% yield would be necessary for a green flag. The DCH protocol displayed a very high space-time yield relative to the moderate one achieved for the HNO_3/HCl/O_2 protocol, showing the high efficiency of the DCH. Values for the STY in the range of >100 g L^{-1} day^{-1} (for low-volume and high-value products) up to values >500 g L^{-1} day^{-1} (for high-volume and low-value products) are necessary.[115] A mass-based criterion of high importance in industry is the process mass intensity (PMI), which is the ratio of the mass used in the process step to the mass of the products.[42] The PMI of reaction was lower for the HNO_3/HCl/O_2 protocol (15) than for the DCH protocol (20). Furthermore, it performed better in terms of RME and AE, but not in terms of OE. The use of reagents in excess was graded with a red flag for both flow protocols, only a green would be assigned for a catalytic process. Even though categorized as a red flag for the HNO_3/HCl/O_2 procedure, in reality this is not a major limitation since these reagents are some of the most widely available bulk chemicals in the world, and recycling strategies can be implemented for their recovery. Even in the case of DCH at large scales, the dechlorinated reagent, 5,5-dimethylhydantoin, could be collected within the aqueous phase and could be conveniently converted to DCH by treatment with sodium hypochlorite (NaOCl) and acetic acid.[116] No critical elements were used in either protocol, therefore they are

marked with a green flag for this criterion. Indeed, the reagents are hazardous, but this limitation is reduced through the utilization of continuous flow protocols.

Table 5. Comparison of the quantitative green metrics for the $HNO_3/HCl/O_2$ and DCH flow protocols using diphenyl disulfide **1** as substrate.

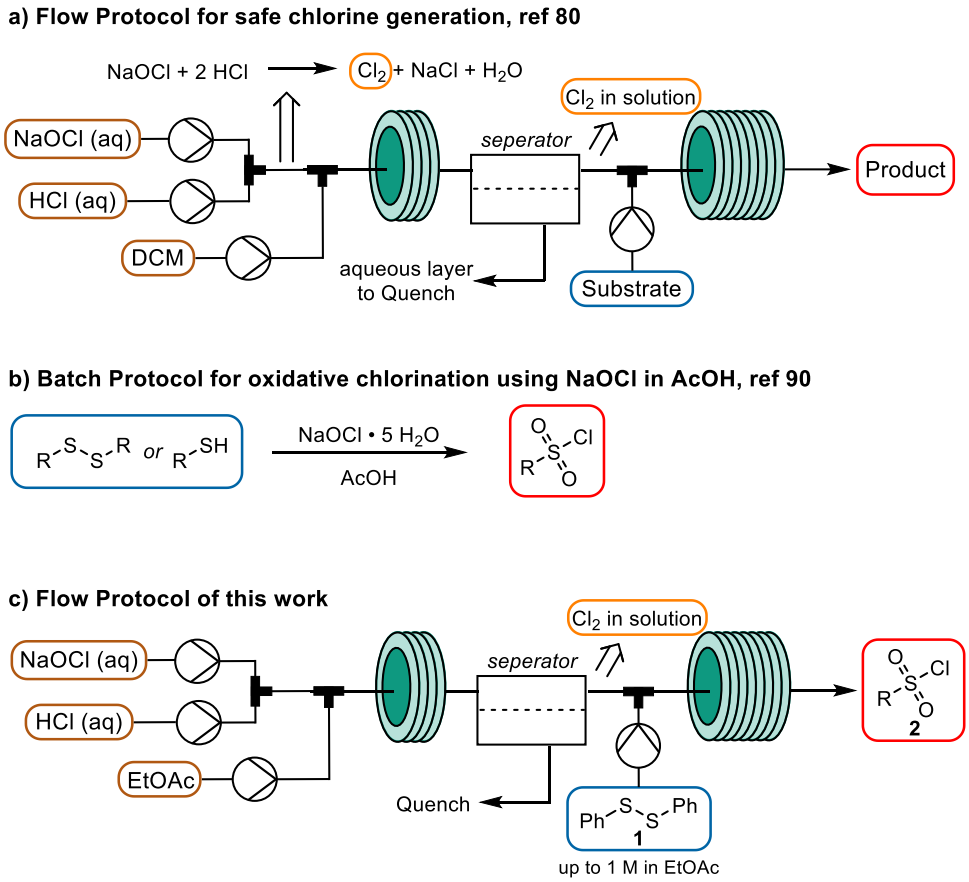
Metric	$HNO_3/HCl/O_2$	DCH[a]
Conv. [%]	>99	>99
Yield [%]	70	82
Space-time yield (kg L^{-1} h^{-1})	0.32	6.7
AE	70	37
RME	48	36
OE	68	97
PMI reactants and reagents	2	3
PMI reaction solvents	13	17
PMI reaction	15	20

[a] Calculations based on DCH flow protocol reported in ref. 33.

The metrics for the reaction solvent would be difficult to improve with the current protocols, since the substrates are unlikely to dissolve at higher concentrations in the established solvent system. The solvent used in both reactions was mostly acetonitrile, there is some water due to the use of aqueous acids, which is given an amber flag. Solvent selection guides from industrial groups provide slightly different perspectives on the use of acetonitrile as a solvent: Sanofi grades it as highly desirable,[43] whereas the GSK guide does not consider it a green solvent.[117] On balance, it is perhaps one of the more sustainable of the dipolar aprotic solvents in common use.[118] The simple post reaction workup was an advantage of this protocol as only an aqueous wash was required. Further steps, could be taken at scale to optimize this to use less solvent. Overall, these results demonstrate that the $HNO_3/HCl/O_2$ flow protocol is superior than the DCH flow in most sustainability metrics, even though the DCH flow protocol was better with respect to yield, OE and space-time yield.

4 The Chlorine Generator Revisited

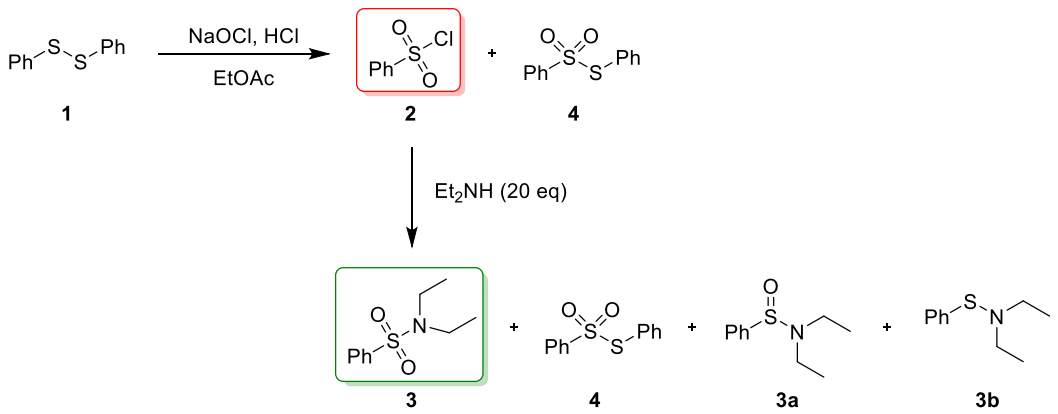
As stated in the introduction Cl_2 is a potent reagent for the oxidative chlorination of thiols and disulfides.[75] The risks as well as the difficulties in dosing associated with gaseous Cl_2 can be reduced through its generation from NaOCl and HCl.[119,120] Flow chemistry facilitates the safety of such a process through on-demand formation of hazardous reagents from benign precursors. [32] Such a system is referred to as a chemical generator[32] and Strauss et al published an in situ Cl_2 generator (Scheme 9**a**) using NaOCl and HCl in 2016.[80] NaOCl · 5 H_2O in AcOH was demonstrated to be a powerful reagent for the oxidative chlorination of thiols and disulfides under mild conditions (Scheme 9**b**).[90] We were interested in combining those two approaches to develop a potent and safe protocol for the oxidative chlorination of disulfides with Cl_2. For this purpose, we developed a modified chlorine generator (Scheme 9**c**) and tested its potential for oxidative chlorination on the model substrate diphenyl disulfide **1**.



Scheme 9. Overview of three different protocols. a) Flow protocol for the on-demand production of Cl_2 from NaOCl and HCl and its extraction into DCM. b) Batch protocol for oxidative chlorination using NaOCl pentahydrate in AcOH. c) Flow protocol for the use of the chlorine generator in the oxidative chlorination of diphenyl disulfide **1**. EtOAc was used instead of DCM for the Cl_2 extraction.

To avoid the use of chlorinated solvents, ethyl acetate was used as an organic solvent. To test the quality of the chlorine extraction from the aqueous phase, the dissolved Cl_2 within the ethyl acetate was determined. For this purpose, a solution of KI and H_2SO_4 in H_2O was prepared and treated with the Cl_2 containing ethyl acetate for either 5 or 10 minutes. Upon addition, Cl_2 and KI rapidly reacted to give I_2, which could be observed as the solution turned first deep purple and then brown. The chlorine content was then determined by titration with an aq. 1 M $Na_2S_2O_3$ solution until discolored. At a flow rate of the NaOCl solution of 100 µL min^{-1}, which at a concentration of 1.75 M corresponds to 0.175 µmol min^{-1}, the Cl_2 yield was determined to be 90%. Tripling the flowrate to 300 µL, the Cl_2 yield was found to be similar at 91%, which is the same yield achieved in the original chlorine generator using DCM as an organic layer. As the solubility of water in ethyl acetate is rather high, the water content after extraction was determined by coulometric Karl Fischer titration. A 1 M solution of diphenyl disulfide **1** in dry ethyl acetate was found to contain 21 ± 12 ppm of water. After mixing with water and subsequent extraction in the phase separator the water content was determined to be 34000 ± 340 ppm, which corresponds to 3.4%.

A small optimization of the system was performed in which temperature, residence time and Cl_2 equivalents were varied. Interestingly, oxidative chlorination under these conditions leads to a different product distribution than the HCl / HNO_3 / O_2 system (Scheme 10). Similarly to the oxidative chlorination with DCH,[98] no sulfonic acid is formed, however two new species (**3a** and **3b**) can be observed. These two species were identified by GC-MS and appear to be reaction intermediates. However, they are more reactive than **4** and unlike **4** can only be observed when quenching the reaction.



Scheme 10. Product Distribution observed in the oxidative chlorination of diphenyl disulfide **1** using NaOCl and HCl. No Sulfonic acid (**5**) is produced, however upon quenching the reaction with diethyl amine species **3a** and **3b** can be observed.

For the purpose of quantification **1**, **3** and **4** were calibrated on the GC-FID, while **3a** and **3b** were assumed to have the same response as **3**. While this assumption seems to be a better fit for **3a** than **3b**. Therefore, experimental runs in which low equivalents of Cl_2 were used (table 6, entries 1), which favored the formation of **3b**, show a slightly worse mass balance (only 94%, compared to otherwise 98-101%). The temperature had very little effect on the product yield. While a little worse at 0 °C, there was hardly any difference when performing the reaction at 25 °C or 50 °C (table 6, entries 2-4). The most influential factor is the amount of Cl_2 (table 6, entries 1, 3, 5-6). At 5.3 eq the yield was high, but there was a big variance between measurements of the same run, leading to a mean yield of 86% (table 6, entry 6). This could be slightly improved upon through an increase in flow rate (table 6, entry 7), but even more so by increasing the residence time, which resulted in > 99% conversion and 98% yield (table 6, entry 8).

Table 6. Summarized results of the optimization of the oxidative chlorination of diphenyl disulfide **1** with NaOCl and HCl in flow.

N	T [°C]	Cl_2 [eq][a]	Flow [µL / min]	t_{res} [s]	Conv **1** (%)[b]	Yield **3** (%)[b]	Yield **4** (%)[b]	Yield **3a** (%)[c]	Yield **3b** (%)[c]
1	25	1.3	900	67	67	**5**	22	4	31
2	0	2.6	600	100	97	**17**	55	14	9
3	25	2.6	600	100	95	**23**	54	5	12
4	50	2.6	600	100	95	**23**	53	5	12
5	25	4.2	600	100	98	**62**	22	14	3
6	25	5.3	480	67	>99	**84**	7	4	2
7	25	5.3	1800	67	>99	**91**	4	3	<1
8	25	5.3	480	250	>99	**98**	1	<1	<1

[a] Cl_2 based on Cl_2 yield determined by titration. [b] Calibrated GC-FID yield. [c] GC-FID yield based on the calibrated response of **3**.

Furthermore, this system could successfully be employed in another project. In this work the continuous synthesis of isoxazoles, 5 membered heterocycles of medicinal relevance, was conducted in a 3-step synthetic sequence. The second of which was the chlorination of a previously formed oxime. With the modified chlorine generator, this step could be performed with an excellent assay yield and telescoped with a subsequent cycloaddition.[81]

5 Conclusion & Outlook

The batch procedure for the oxidative chlorination of diphenyl disulfide with ammonium nitrate, hydrogen chloride (35% aq.) and oxygen could be expanded upon by the addition of a diethyl amine quench. This allowed for kinetic profiling of the reaction at different temperatures and atmospheres. An analytical method was developed (HPLC) to quantify conversion and yield of different compounds. Besides the known species, benzenesulfonic acid could be identified as a previously unreported side product of these conditions. Product formation was observed even when no external oxygen was supplied to the reaction, which has been reported to not be the case in the analogous oxidative bromination of p-toluenethiol. As conditions without undissolved solids would be beneficial for material transfer and continuous processing, different conditions and nitrate sources were tested. Nitric acid even outperformed ammonium nitrate at 40 °C in terms of yield and was thus selected as the nitrate source of choice for the development of a flow process.

A continuous flow oxychlorination protocol was developed for the preparation of sulfonyl chlorides from their corresponding disulfides and thiols. The reaction uses HNO_3, HCl and O_2. These are inexpensive, atom–economic, and simple feedstocks. In the initial optimization the yield was found to increase linearly with the reaction temperature, reaching a maximum at 100 °C. Afterwards the yield decreased again, which is likely due to the decomposition of the suspected active species. Formation of sulfonyl chloride was observed without the addition of oxygen, however up to 1 eq of external oxygen has been shown to increase the yield. The optimized flow process operated at 100 °C and 5 bar with a small excess of HCl and HNO_3 and 1 eq of O_2. We modified the system to incorporate online ^{19}F NMR reaction monitoring, which is challenging to achieve in complex multiphasic systems. This setup enabled the investigation of the design space to observe different product distributions within a single experimental run. The continuous flow protocol was operated for more than 6 h run time to produce 18.7 g of phenyl sulfonyl chloride from diphenyl disulfide. Several thiols and disulfides were tested, giving mostly good yields (70 to 81%) after only a simple aqueous washing and drying step. While the protocol gives similar conversion for most tested compounds, its applicability is limited by the low solubility of many disulfides and even thiols in acetonitrile. The environmental impact of the oxychlorination was assessed and compared to an existing flow protocol using 1,3-

dichloro-5,5-dimethylhydantoin (DCH) as reagent. The HNO_3/HCl/O_2 flow protocol represents an improvement in terms of atom economy and process mass intensity, but performs worse in terms of yield and space time yield.

The chemical generator principle was employed to establish a safe protocol for the oxidative chlorination of thiols and disulfides with Cl_2. Ethyl acetate was used as a solvent for the model substrate diphenyl disulfide and as a carrier solvent for the Cl_2. After the extraction step the chlorine yield of the organic phase was determined by iodometry to be 90%. Furthermore, the water content was assessed by Karl Fischer titration to be 3.5%. Interestingly Cl_2 leads to a different product distribution than the HNO_3, HCl, O_2 protocol, as no sulfonic acid, but two new reaction intermediates were observed. Given sufficient residence time, conversion and product distribution depended mostly on the used Cl_2 equivalents, while the effect of temperature was found to be mostly negligible. At 25 °C, using 5.3 eq of Cl_2 and a residence time of 250 s a 98% HPLC yield could be achieved.

Considering the HNO_3, HCl system, it would be interesting to test the performance using pressurized air instead of oxygen. This would further increase the safety of the process and judging from the initial batch experiments might lead to similar yields given enough residence time. Furthermore, the reaction work up could be further optimized to require less reagents and solvents and thereby reduce the overall mass intensity. The ex-situ Cl_2 generation should be further explored in terms of scope and stability of the setup. As there were substantial amounts of water in the ethyl acetate other extraction solvents could be tested to deal with water labile substrates.

6 Materials and Methods

All materials were obtained from commercial suppliers (TCI, Sigma Aldrich, Alfa Aesar or VWR) and used without further purification unless noted otherwise. Numbers in brackets refer to purity reported by the manufacturer. Diphenyl disulfide (**1**) (>99%) was purchased from TCI, benzenethiol (**13**) (97%) from Sigma Aldrich, *bis*(4-fluorophenyl) disulfide (**6**) (98%) from abcr. Aqueous 35% hydrochloric acid (HCl) and aqueous 68% nitric acid were purchased from VWR. HPLC grade acetonitrile was acquired from VWR.

6.1 High Field NMR

Nuclear magnetic resonance (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 either prepared in deuterated $CDCl_3$ or DMSO. The letters s, d, t and m are used to indicate singlet, doublet, triplet, and multiplet, respectively.

6.2 GC-MS

Gas chromatography-mass spectrometry (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.

6.3 HPLC

High performance liquid chromatography (HPLC) analysis was carried out on a C18 reversed-phase analytical column (150 × 4.6 mm, particle size 5 µm) at 37 °C by using mobile phases A [water/acetonitrile 90:10 (v/v) +0.1% TFA] and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear

increase from 30% solution B to 100% B in 13 min, hold at 100% solution B for 4 min. All samples were prepared in HPLC grade acetonitrile and analyzed at 215 and 254 nm.

6.4 GC-FID

GC-FID analysis was performed on a Shimadzu GC FID 230 with a flame ionization detector, using a 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^{-1} 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).

6.5 Flash Column Chromatography

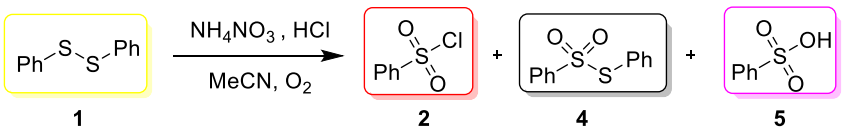
Automated flash column chromatography was performed on a Biotage Isolera system using columns packed with KP-SIL, 60 Å (32-63 µm particle size) silica. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 GF254 plates. Compounds were visualized by means of UV.

6.6 Karl Fisher Analysis

Karl Fisher analysis was performed to determine water content, using an automatic Metrohm Titrando 831 KF coulometric Karl Fisher titration method (EN ISO 12937:2000) in triplicate.

6.7 Compound Identification for the Model Reaction and Example Chromatograms

The chlorosulfonylation of diphenyl disulfide **1** was selected as a model reaction. Scheme 11 shows the species which were observed during the preliminary batch experiments.



Scheme 11. General reaction scheme for the chlorosulfonylation of diphenyl disulfide **1** in batch.

A typical HPLC-UV chromatogram at 254 nm wavelength is shown in Figure 6. From left to right the species (rt = retention time) were identified as: benzenesulfonic acid **5** (rt = 1.35 min), benzenesulfonyl chloride **2** (rt = 6.26 min) as the desired product, *S*-phenyl benzenesulfonothioate **4** (rt = 7.65 min), biphenyl (rt = 9.21 min) as the internal standard, and diphenyl disulfide **1** (rt = 11.25 min) as the starting material.

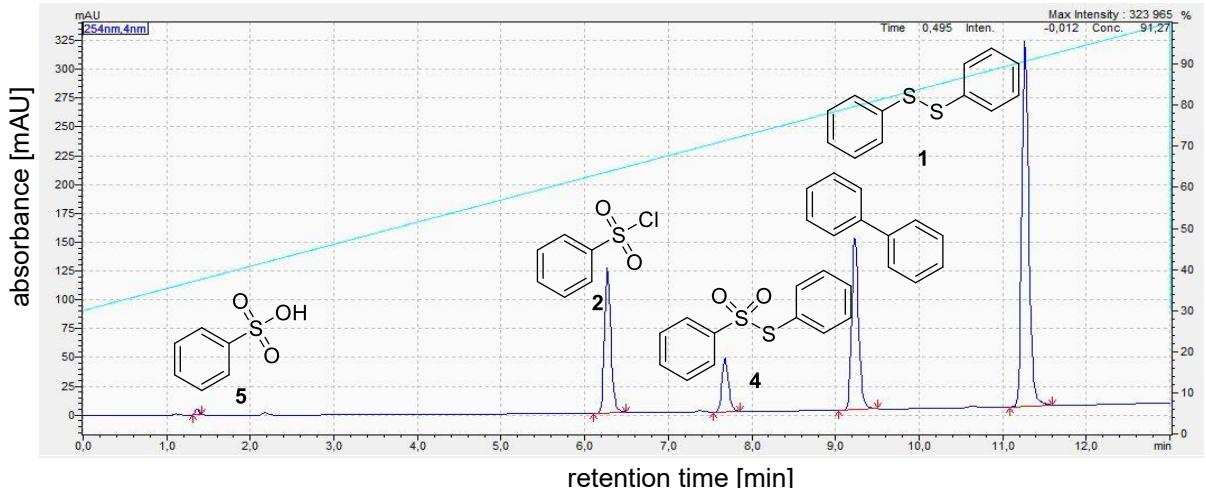


Figure 6. Typical HPLC-UV chromatogram (254 nm) showing the species observed during the chlorosulfonylation of diphenyl disulfide **1**.

Three of the four compounds (and the internal standard) shown on Scheme 11 could also be observed on the GC-MS as can be seen in Figure 7. The mass patterns from the GC-MS analysis for the four peaks are shown in Figures 8-11. Benzenesulfonic acid **5** could not be detected by GC.

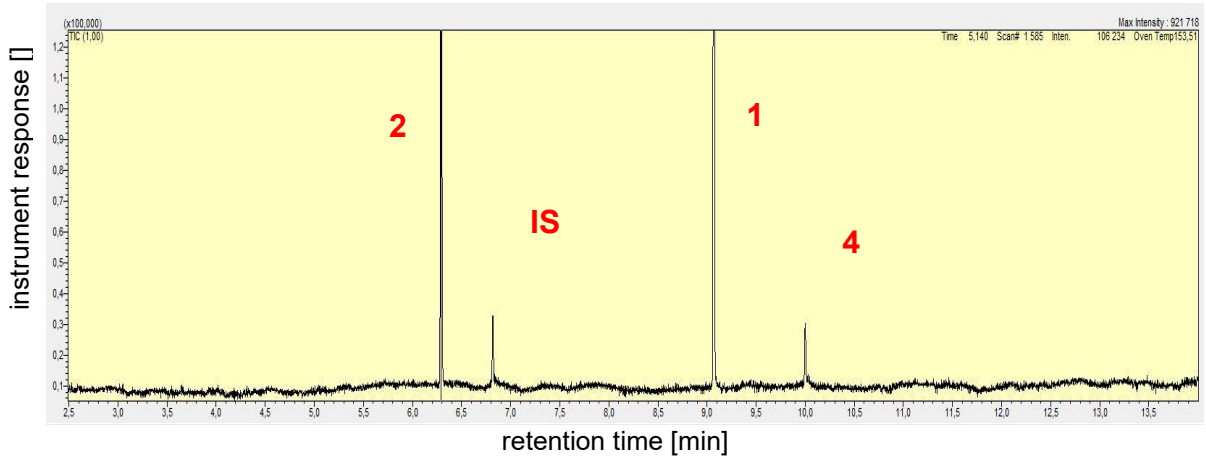


Figure 7. GC chromatogram of the chlorosulfonylation of diphenyl disulfide as shown in Scheme 11. The internal standard biphenyl and three of the four species can be observed by GC: benzenesulfonyl chloride **2**, *S*-phenyl benzenesulfonothioate **4** and diphenyl disulfide **1** were observed by GC. Benzenesulfonic acid **5** could not be detected by GC.

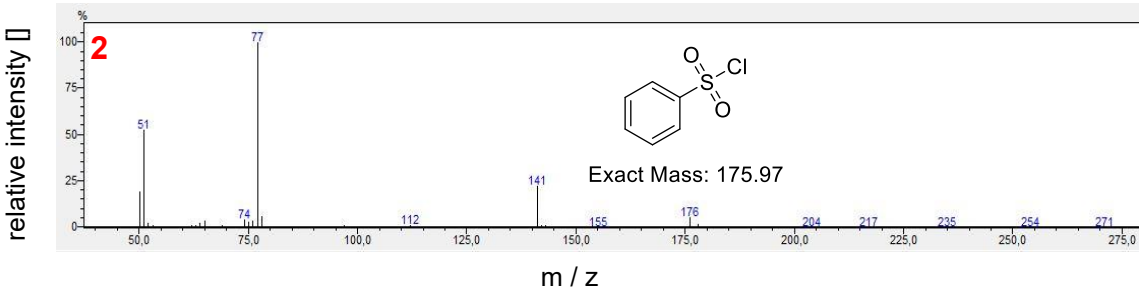


Figure 8. Background subtracted mass pattern of the first peak (rt = 6.29 min) from Figure 7, indicated compound benzenesulfonyl chloride **2**.

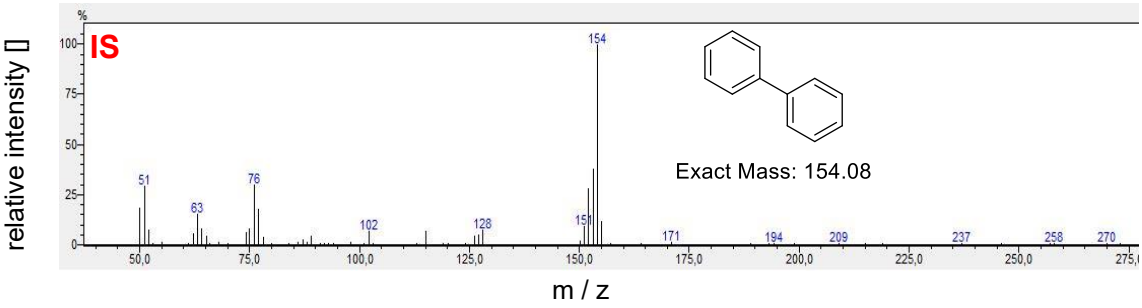


Figure 9. Background subtracted mass pattern of the second peak (rt = 6.82 min) from Figure 7, indicated compound biphenyl.

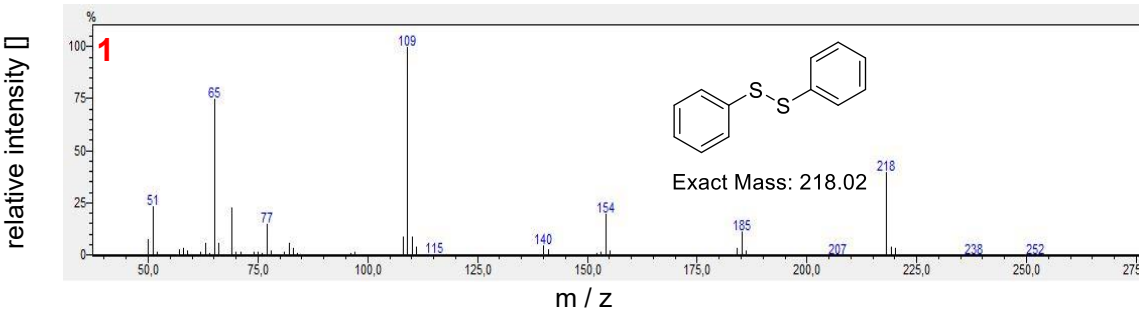


Figure 10. Background subtracted mass pattern of the third peak (rt = 9.08 min) from Figure 7, indicated compound diphenyl disulfide **1**.

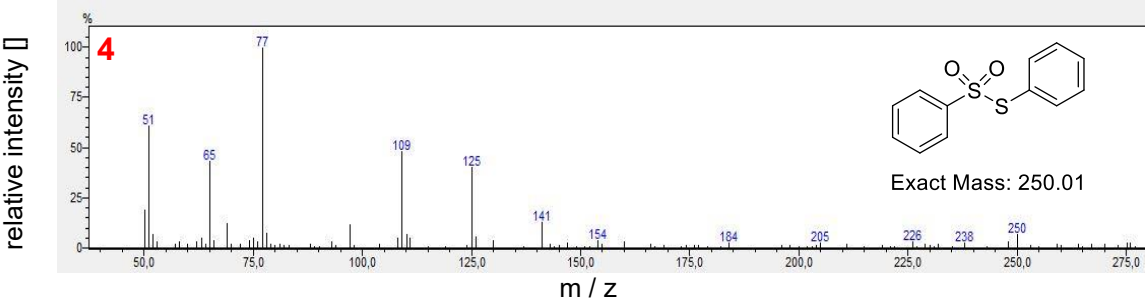


Figure 11. Background subtracted mass pattern of the fourth peak (rt = 10 min) from Figure 7, indicated compound *S*-phenyl benzenesulfonothioate **4**.

After performing a HPLC calibration for species **1**, **3** and **4** to allow quantification after the performed reactions, there was still a substantial missing mass balance for the initial batch experiments. The remaining mass balance stayed close to 100% at low conversion but decreased to between 40% - 80% as the conversion of starting material **1** increased. This missing mass balance could be accounted to benzenesulfonic acid **5** (1.35 min), which was not visible in the GC/GC-MS and showed very low absorption at 254 nm wavelength by HPLC-UV. Benzenesulfonic acid **5** could be better identified at 215 nm wavelength, and confirmed using a reference sample, see Figures 12 and 13.

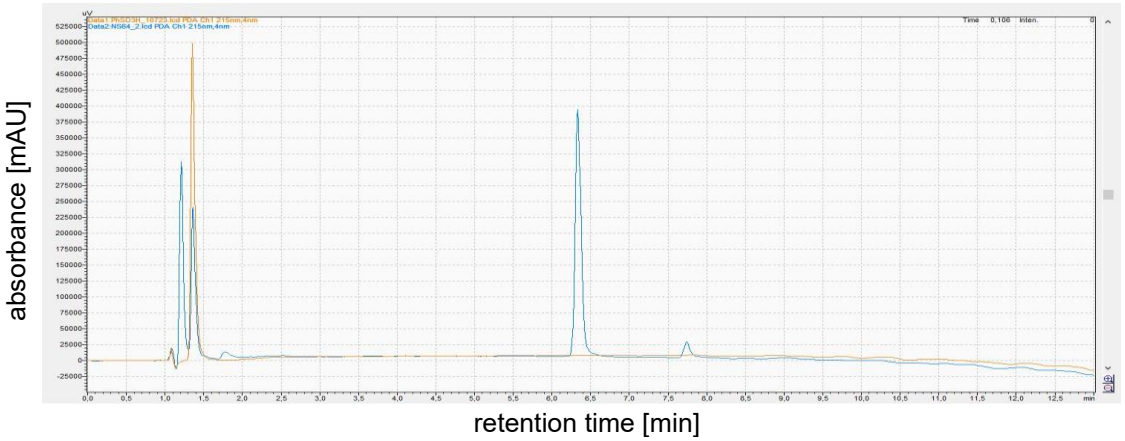


Figure 12. Overlay of the HPLC chromatograms of the reference sample of benzenesulfonic acid **5** (yellow) and a sample of the chlorosulfonylation of diphenyl disulfide (blue) at 215 nm. The blue peak to the left of the benzenesulfonic acid **5** (rt = 1.35 min) is the injection peak.

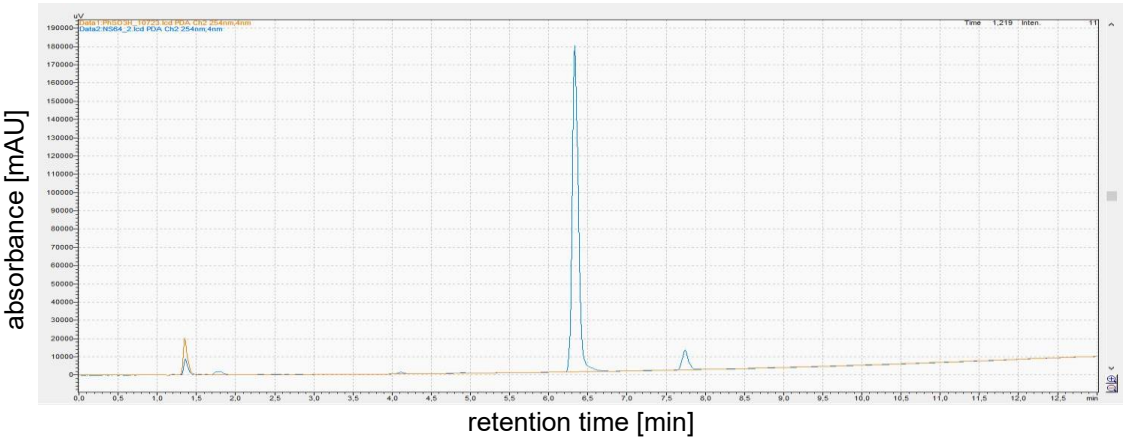
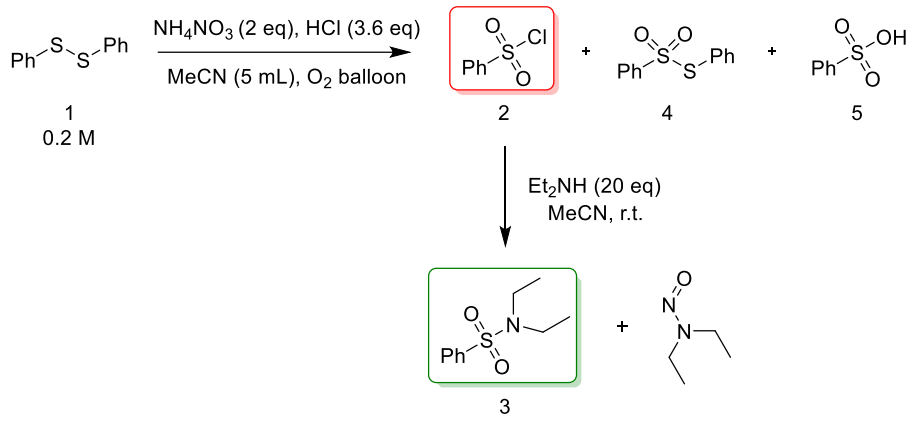


Figure 13. Overlay of the HPLC chromatograms of the reference sample of benzenesulfonic acid **5** (yellow) and a sample of the chlorosulfonylation of diphenyl disulfide (blue) at 254 nm.

To prevent further reaction progress during sample collection for the optimization, the samples were quenched with diethyl amine prior to analysis by HPLC. When this was done the desired product was present as the corresponding sulfonamide, *N,N*-diethylbenzenesulfonamide **3** (rt = 5.73 min). The quenching introduced another peak (rt = 2.15 min), which was attributed to the oxidization of the remaining amine to give *N*-diethyl nitrosamine.



Scheme 12. Chlorosulfonylation of diphenyl disulfide **1** and subsequent quenching with diethyl amine.

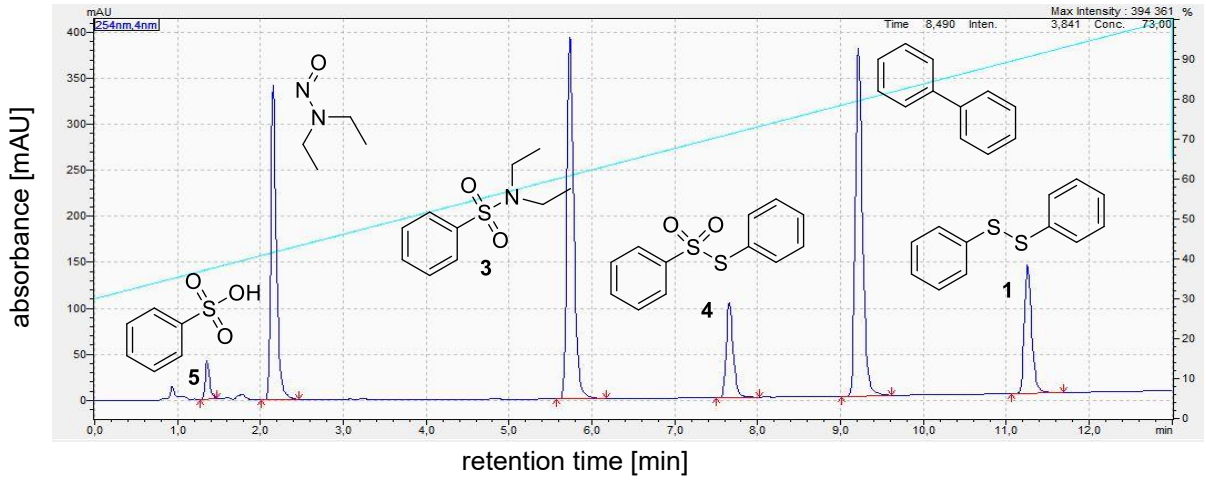


Figure 14. Typical HPLC-UV chromatogram (254 nm) showing the species observed during the chlorosulfonylation of diphenyl disulfide after quenching of the reaction mixture with diethyl amine: benzenesulfonic acid **5** (rt = 1.35 min), *N*-diethyl nitrosamine (rt = 2.15 min), *N,N*-diethylbenzenesulfonamide **3** (rt = 5.73 min), *S*-phenyl benzenesulfonothioate **4** (rt = 7.65 min), diphenyl disulfide **1** (rt =11.25 min), as well as biphenyl (9.21 min) as internal standard.

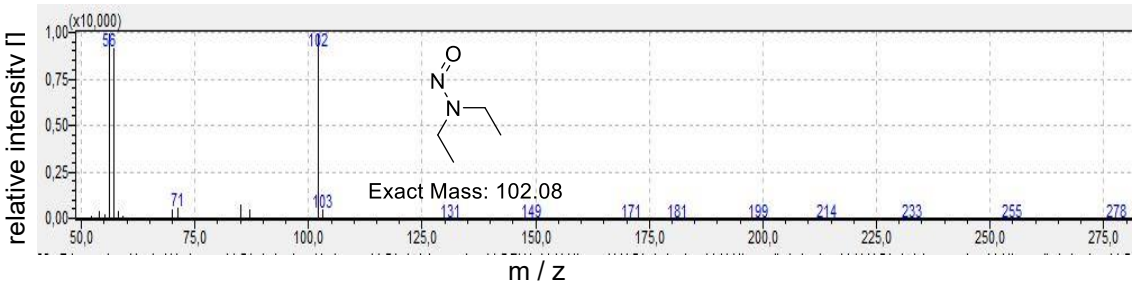


Figure 15. Background subtracted mass pattern observed in a quenched reaction sample, fits for the compound *N*-diethyl nitrosamine.

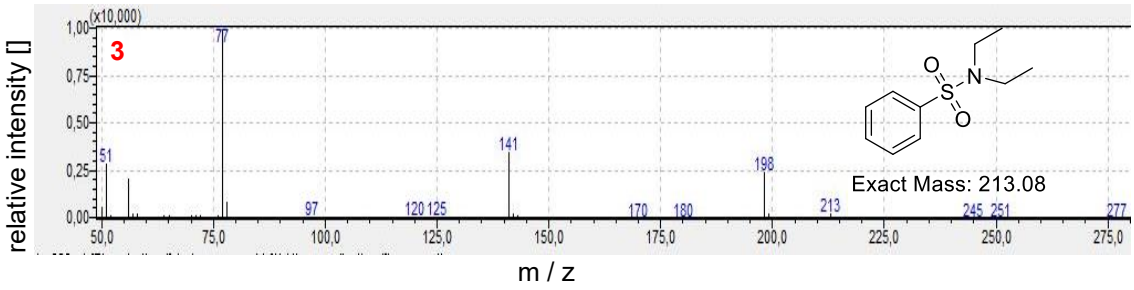


Figure 16. Background subtracted mass pattern observed in a quenched reaction sample, fits for the compound *N,N*-diethylbenzenesulfonamide **3**.

6.8 HPLC Calibrations

The calibration of diphenyl disulfide **1**, *S*-phenyl benzenesulfonothioate **4**, benzenesulfonyl chloride **2** and *N,N*-diethylbenzenesulfonamide **3** were performed at 254 nm. As the absorption of benzenesulfonic acid **5** is much weaker than those of the other compounds at 254 nm, this species was calibrated at 215 nm. The calibrations were performed using biphenyl as an internal standard and are depicted in Figure 17 and 18.

The calibration of diphenyl disulfide **1** and benzenesulfonic acid **5** were performed with reference samples. Benzenesulfonyl chloride **2** and its corresponding amide, *N,N*-diethylbenzenesulfonamide **3,** were obtained from purification of the corresponding compounds after performing the reaction (see Chapter 6.1.3 and 6.1.4). Furthermore, the reaction intermediate, *S*-phenyl benzenesulfonothioate **4**, was obtained by performing the reaction to partial conversion, and then subsequent purification by flash chromatography (see Chapter 6.1.2).

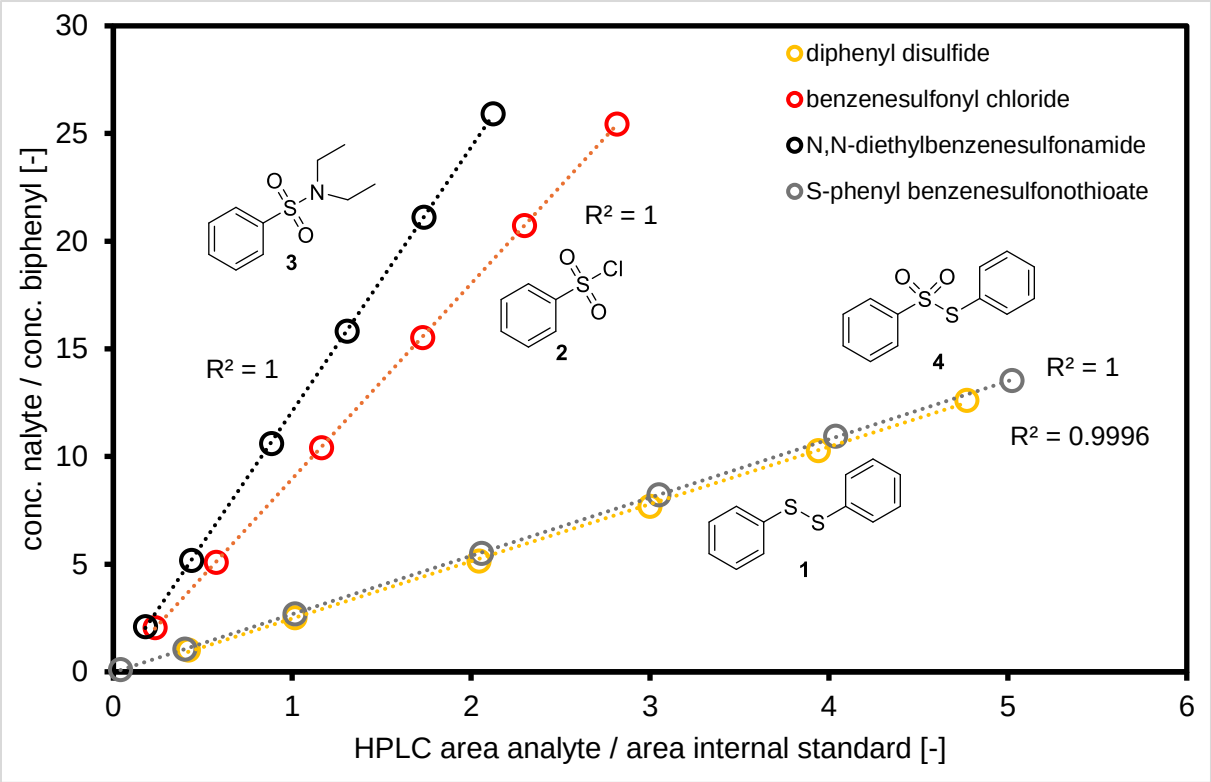


Figure 17. Calibration of diphenyl disulfide **1**, benzenesulfonyl chloride **2**, *N,N*-diethylbenzenesulfonamide **3** and *S*-phenyl benzenesulfonothioate **4** using HPLC analysis at 254 nm against biphenyl as an internal standard.

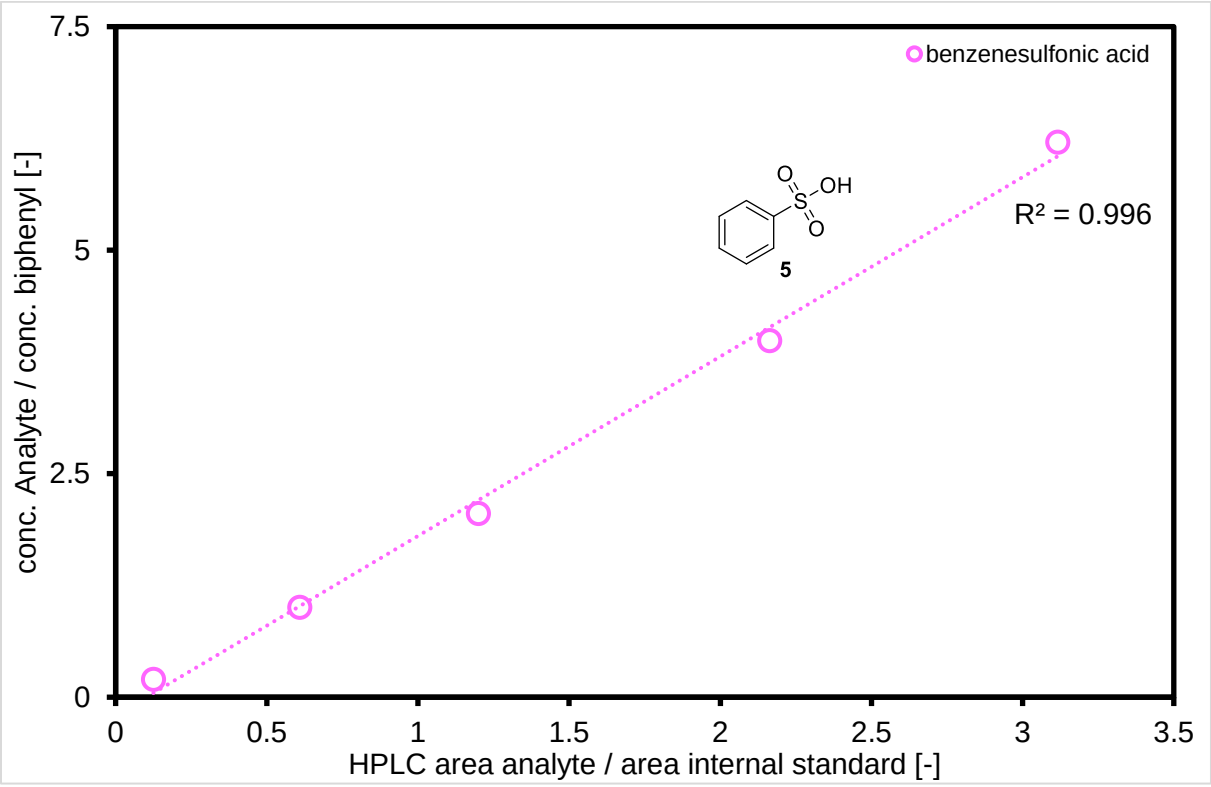


Figure 18. Calibration of benzenesulfonic acid **5** using HPLC analysis at 215 nm against biphenyl as an internal standard.

Furthermore, *bis*(4-fluorophenyl) disulfide **6**, the corresponding quenched product, *N,N*-diethyl-4-fluorobenzenesulfonamide **8**, and 4-fluorobenzenethiol **6'** were calibrated at 254 nm using both biphenyl and trifluorotoluene as internal standards. Figure 19 shows this calibration using trifluorotoluene as an internal standard.

For this purpose, reference samples of *bis*(4-fluorophenyl) disulfide **6** and 4-fluorobenzenethiol **6'** were used, while *N,N*-diethyl-4-fluorobenzenesulfonamide **8** was obtained as a pure compound as described in Chapter 6.1.5.

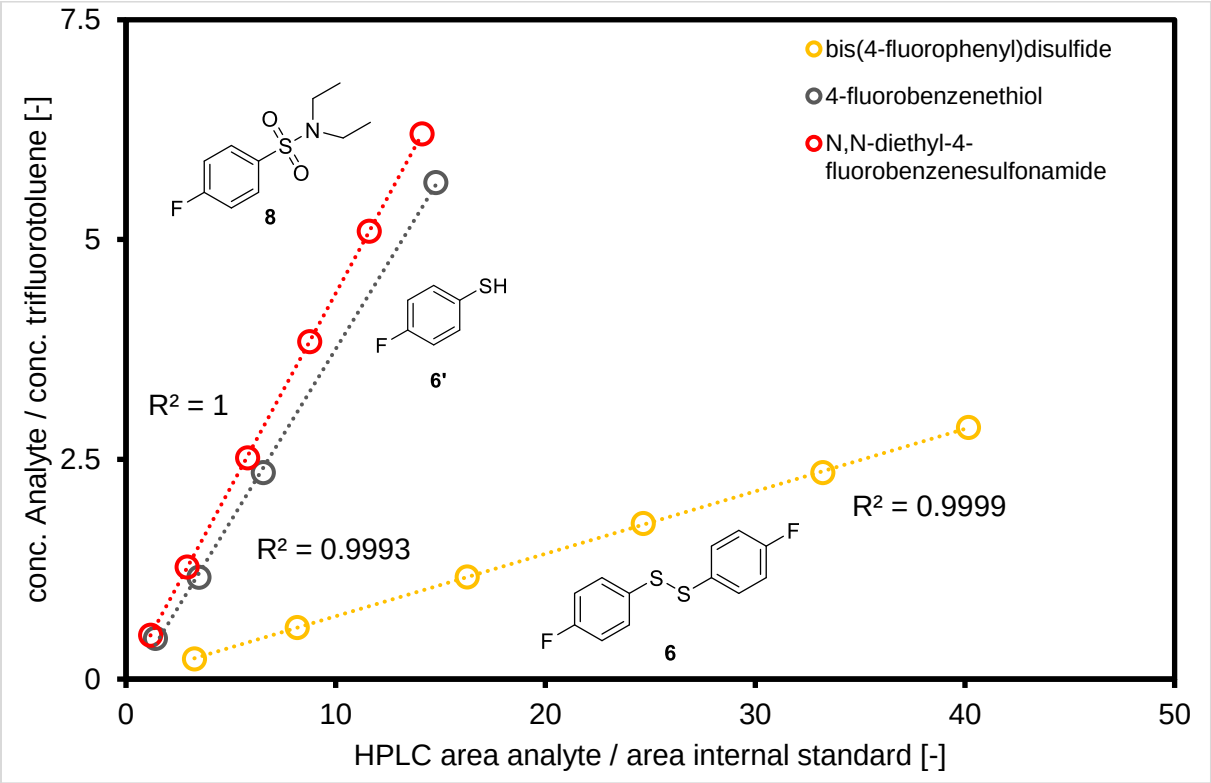


Figure 19. Calibration of bis(4-fluorophenyl) disulfide **6**, 4-fluorobenzenethiol **6'** and *N,N*-diethyl-4-fluorobenzenesulfonamide **8** using HPLC analysis at 254 nm against trifluorotoluene as an internal standard.

7 General Procedures

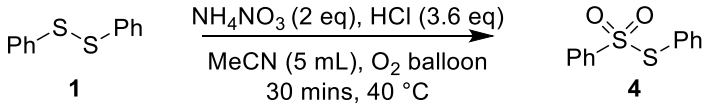
7.1 Batch and Isolation Procedures

7.1.1 General Procedure for the Chlorosulfonylation in Batch

Diphenyl disulfide (**1**) (218 mg, 1 mmol, 1 eq) and biphenyl (internal standard, 15.4 mg, 0.1 mmol, 0.1 eq) were dissolved in acetonitrile (5 mL, 0.2 M) in a 25 mL two necked round bottom flask. The flask was equipped on one neck with a reflux condenser and placed in a water bath heated at the desired temperature. A 10 µL sample of the reaction mixture was taken. Subsequently, NH_4NO_3 (157 mg, 2 mmol, 2 eq) and aqueous HCl (35%, 310 mL, 3.6 mmol, 3.6 eq) were added. After the addition of the reagents the reflux condenser was equipped with a septum with two needles, one carrying a balloon filled with oxygen. The other necked was closed off using a stopper. The reaction was carried out for four hours and periodically sampled by shortly removing the stopper and taking out 10 µL of the reaction mixture using a pipette. All acquired samples were added to 1 mL of a pre-prepared solution of diethyl amine in acetonitrile (40 mM, 20 eq) to quench the reaction. When the reaction was performed to isolate material, no internal standard was added, and it was collected as a single fraction.

Although the batch experiments were carried out at 30 to 60 °C, well below the boiling point of acetonitrile (82 °C), reflux condenser was necessary due to the exothermic nature of the reaction.

7.1.2 Isolation of *S*-Phenyl Benzenesulfonothioate (4)

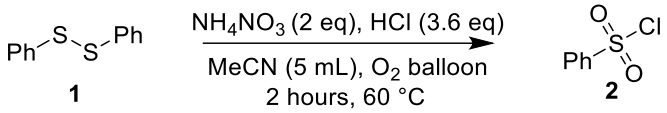


Scheme 13. Synthesis of *S*-phenyl benzenesulfonothioate (**4**).

The reaction was carried out as described in 6.1.1 at 40 °C but was scaled up by a factor of 10. The reaction was terminated after 30 minutes by dilution with cold DCM (50 mL) and putting the flask into an ice bath for 5 minutes. Afterwards the aqueous phase was separated, and the organic phase was washed with saturated $NaHCO_3$ solution (50 mL). The organic phase was then separated, dried over Na_2SO_4,

filtered, and concentrated under reduced pressure. The crude product mixture was then purified by flash chromatography (petroleum ether / ethyl acetate) to yield **4** (94.9 mg, 0.38 mmol, 3.8%) as a yellow liquid.

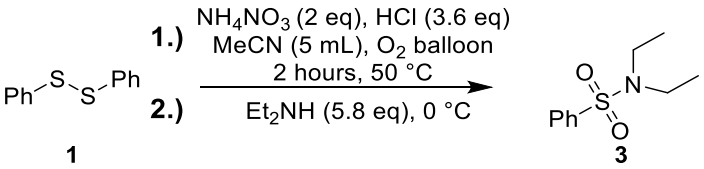
7.1.3 Isolation of Benzenesulfonyl Chloride (2), Batch Conditions



Scheme 14. Synthesis of benzenesulfonyl chloride (**2**).

The reaction was carried out as described in 6.1.1 at 60 °C for two hours. Subsequently, the reaction mixture was diluted with DCM (10 mL) before it was washed with saturated $NaHCO_3$ solution (10 mL). The layers were then separated, the organic layer dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford **2** (142.7, 0.81 mmol, 39%) as a yellow liquid.

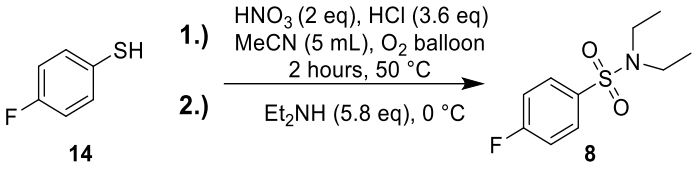
7.1.4 Isolation of *N,N*-Diethylbenzenesulfonamide (3)



Scheme 15. Synthesis of *N, N*-diethylbenzenesulfonamide (**3**)

The reaction was carried out as described in 6.1.1 at 50 °C for two hours. Afterwards the reaction mixture was allowed to cool to room temperature and the flask subsequently put into an ice bath. Then diethyl amine (600 µL) was slowly added to the reaction mixture, and it was stirred for 10 minutes. Afterwards concentrated HCl (35%) was slowly added to the reaction mixture, until its addition produced no more fuming. Then the reaction mixture was diluted with dichloromethane (5 mL) and the phases separated. The organic phase was washed with saturated $NaHCO_3$ (10 mL) solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **3** (167.7 mg, 0.79 mmol, 39%) as a yellow liquid.

7.1.5 Isolation of *N,N*-Diethyl-4-Fluorobenzenesulfonamide (8)



Scheme 16. Synthesis of *N,N*-diethyl-4-fluorobenzenesulfonamide (**8**)

Using 4-fluorobenzenethiol (**14**) as substrate, the reaction was carried out as described in 6.1.1, using HNO_3 instead of NH_4NO_3 and at 50 °C overnight. The initial product **7** was treated as described in 6.1.4 to yield **8** (434 mg, 2.23 mmol, 74%) as a white solid.

7.2 Procedures for Flow Experiments

Before any reactions were carried out, the system was flushed with acetonitrile (1 mL/min), water (120 µL/min) and oxygen (2 mL/min) until the mixture would pass the BPR and the syringe pumps showed a constant pressure. Gas flow rates were measured in units of mL_n/min, where n represents measurement under standard conditions, i.e., T_n=0 °C, P_n=1.01 bar. For some experiments the oxygen was exchanged for argon and dry acetonitrile was used. In such cases the system was flushed for a total of 20 minutes before reactions were carried out.

After reactions were carried out the system was flushed for 15 minutes in a similar manner and after that for 15 more minutes with isopropanol (2 mL/min) and oxygen (0.5 mL/min).

The feed and the acids could be introduced into the system via 6-port valves or pumped directly. When using 6 port valves, the feed solution was introduced using either a 5 mL or 10 mL sample loop, while 1.5 mL and 5 mL sample loops were used for HNO_3 and HCl respectively.

If the system was in operation for an extended period of time feed and acids were introduced directly through the pumps. Otherwise, sample loops were used to reduce the amount of chemical consumption and limit the contact of the syringes, especially important in the case of corrosive chemicals. In both cases the acids were always injected into the system before the feed solution, to prevent clogging. When the acids were pumped directly through the pumps, then the pumps were always exposed to the corresponding weaker acids before and after such experiments to reduce heat

evolution. When starting up the system this was done by pumping water, 9% HCl, 18% HCl and water 17% HNO_3, 34% HNO_3 respectively for 3 minutes each before the introduction of the more concentrated acids. When shutting down the system this order was reversed. Afterwards, the pump heads were removed and the syringes were cleaned manually with water and isopropanol.

7.2.1 Substrate Feed Preparation

Substrate feed solutions were prepared in volumetric flasks. Unless noted otherwise, feeds solutions for the disulfides were prepared as 0.25 M in acetonitrile and thiols at 0.5 M in acetonitrile. If prepared for isolation of the product, then no internal standard was added to the flask. For experiments using argon instead of oxygen the volumetric flask was flushed with argon for 3 minutes, equipped with a septum and an argon balloon, and dry acetonitrile was used.

Example feed preparation: diphenyl disulfide (**1**) (11.04 g, 50 mmol, 1 eq) and biphenyl (internal standard, 0.8 g, 5 mmol, 0.1 eq) were added to a 200 mL volumetric flask. The solids were dissolved in acetonitrile in an ultrasonic bath before the volumetric flask was filled to the fill line with acetonitrile.

7.2.2 Example Procedure Optimization

Three syringe pumps were used to introduce the feed solutions: diphenyl disulfide (**1**) in acetonitrile (0.25 M, 1 mL/min, 0.25 mmol/min, 1 eq), aqueous HCl (35 %, 85 µL/min, 0.95 mmol/min, 3.78 eq) and aqueous HNO_3 (68%, 34 µL/min, 0.53 mmol/min, 2.1 eq) into the system. The feeds were introduced by using 6-port valves and sample loops using either acetonitrile or water as carrier solvents. Oxygen (6.76 mL/min, 0.28 mmol/min, 1.1 eq) was introduced via an MFC. The acids were injected 5 minutes before the feed solution for the substrate.

Two minutes after the reaction mixture reached the outlet, the first sample was collected by sampling for 15 seconds into a 4 mL vial which contained a 1 M solution of diethyl amine in acetonitrile. This was repeated for at least two more times with 30 seconds to 1 minute interval between sampling. The amount of quenching solution used depended on the flow rates of substrate and acids. It was chosen in such a way that there was 2.5 eq of diethyl amine for the combined moles of substrate, HCl and HNO_3. 30 µL of the quenched reaction mixture was then added to 1 mL of acetonitrile and analyzed in the HPLC. HPLC yields are given as mean values with standard deviation.

7.2.3 Stability Test and Long Run

The system was operated as described above, with the feeds introduced directly through the pumps. After the reactor was stable for 10 minutes, the reaction mixture was collected in 12 Duran bottles for 30 minutes each. The system was operated for a total run time of 6 hours and 15 minutes.

All 12 fractions were analyzed by HPLC. 10 of these fractions (5 hours of production, corresponding to a theoretical 100% mass yield of 26.79 g, 0.152 mol) were combined for isolation. The fractions were diluted with ethyl acetate (200 mL) and washed with saturated $NaHCO_3$ solution (200 mL). After the layers had separated, the aqueous layer was reextracted with ethyl acetate (50 mL) and the combined organic layers were dried over Na_2SO_4, before the mixture was filtered and concentrated under reduced pressure to yield benzenesulfonyl chloride **2** (18.66 g, 0.106 mol, 70% yield) as a yellow liquid.

7.2.4 Conditions for Substrate Scope

The reactions for the substrate scope were performed in a similar manner as described above. Different conditions were used for disulfides and thiols, as described in Scheme 8.

The collection of the reaction mixture after the reactor was started 3 minutes after the injection and continued for 10 minutes and 15 minutes for the disulfides and thiols, respectively. The isolation for all substrates was performed as described in 5.2.3 for the long run. However, reagent volumes were adjusted to the reduced amount of starting material. Disulfides/Thiols were diluted with ethyl acetate (10 mL / 20 mL), washed with saturated $NaHCO_3$ (10 mL / 20 mL) and the aqueous layer reextracted with ethyl acetate (5 mL / 10 mL).

8 Appendix

8.1 Additional Optimization Data

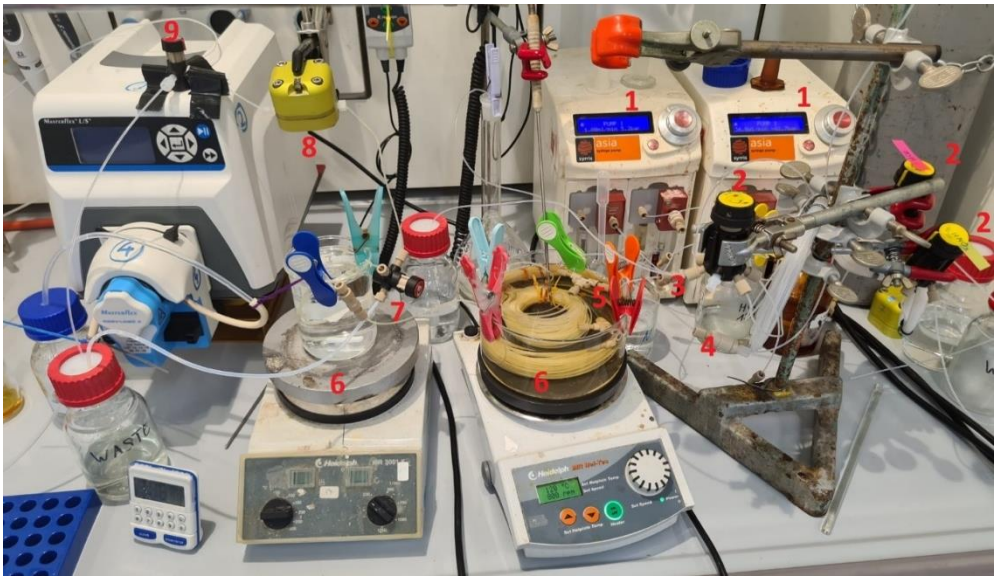


Figure 20. Image of the continuous flow setup: 1. syringe pump, 2. 6-port valve with sample loop to pump the chemicals not directly through the pumps. 3. first T-piece mixed HCl and HNO_3. 4. tube from the MFC with a check valve 5. T-pieces in the oil bath adding the disulfide feed and the oxygen. 6. reaction coil (right) and cooling coil (left). 7. 4-port valve that can be used to release pressure from the coil in case of clogging. 8. BPR set to 5 bar. 9. 4-port valve for sampling the reaction mixture.

Table 7. Results of the chlorosulfonylation of diphenyl disulfide (**1**) at different temperatures. 11.4 mL coil, 5 bar, 2 eq HNO_3, 3.6 eq HCl, 0.75 eq O_2.

Entry	T [°C]	t_{res} [s][a]	**1** [%][b]	**3** [%][b]	**4** [%][b]	**5** [%][b]	Mass balance [%][b]
1	40	315	20.7 ± 2.4	**26.9 ± 1.3**	16.8 ± 0.1	27.2 ± 1.6	91.6
2	50	310	17.4 ± 1.8	**34.4 ± 1.3**	15.7 ± 0.1	28.0 ± 1.4	95.6
3	60	306	15.9 ± 0.2	**40.9 ± 0.4**	12.0 ± 0.5	25.6 ± 1.9	94.4
4	70	302	13.8 ± 1.0	**48.8 ± 1.4**	9.4 ± 0.3	25.2 ± 0.1	97.2
5	80	297	12.6 ± 4.2	**49.9 ± 3.9**	9.5 ± 0.9	23.8 ± 1.6	95.9
6	90	293	11.2 ± 1.7	**56.7 ± 2.8**	8.2 ± 1.3	20.5 ± 0.4	96.6
7	100	289	0.4 ± 0.1	**73.3 ± 0.3**	3.5 ± 0.1	19.4 ± 0.3	97.9
8	110	285	13.4 ± 0.5	**62.3 ± 0.5**	8.0 ± 0.3	15.9 ± 0.3	100.7
9	120			**Clogging**			

[a] Residence time based on Equation 5 using the volume of the heated coil. [b] Calibrated HPLC yields.

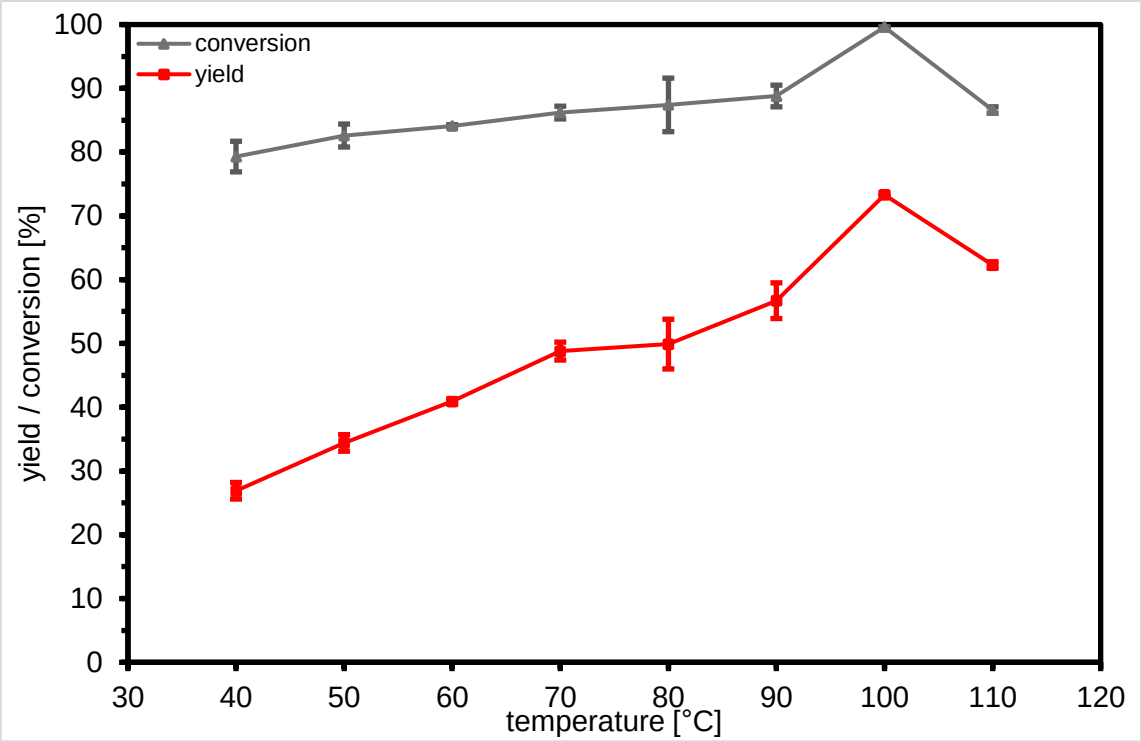


Figure 21. Graphical illustration of the yield at different temperatures as listed in Table 7.

Table 8. Influence of the HCl equivalents, residence time and pressure on reaction performance.

Entry	T [°C]	HNO_3 [eq]	HCl [eq]	O_2 [eq]	t_{res} [s][a]	BPR [bar]	**1** [%][b]	**3** [%][b]	**4** [%][b]	**5** [%][b]	Mass balance [%][b]
1	100	2	7.2	1	240	5	1.1 ± 0.5	**70.5 ± 3.4**	2.4 ± 0.6	20.4 ± 1.1	97.9
2	50	2	3.6	1	375	5	4.1 ± 0.7	**33.8 ± 0.7**	20.2 ± 0.1	25.2 ± 0.1	86.7
3	50	2	3.6	1	268	5	6.8 ± 0.7	**34.7 ± 0.6**	18.2 ± 0.1	30.4 ± 0.9	90.1
4	50	2	3.6	1	112	5	12.0 ± 2.4	**20.7 ± 0.6**	20.7 ± 0.6	29.0 ± 0.9	89.3
5	100	2.1	3.8	1.1	281	7	2.0 ± 2.0	**67.5 ± 5.9**	4.7 ± 3.4	20.7 ± 0.5	94.2

[a] Residence time based on Equation 5 using the volume of the heated coil. [b] Calibrated HPLC yields.

Table 9. Results of different acid equivalents at 50 and 100 °C. 11.4 mL coil, 5 bar.

Entry	T [°C]	HNO_3 [eq]	HCl [eq]	O_2 [eq]	t_{res} [s][a]	**1** [%][b]	**3** [%][b]	**4** [%][b]	**5** [%][b]	Mass balance [%][b]
1	50	2	3.6	0.75	310	17.4 ± 1.8	**34.4 ± 1.3**	15.7 ± 0.1	28.0 ± 1.4	95.6
2	50	2.5	4.5	0.75	306	1.0 ± 0.2	**41.5 ± 0.4**	16.2 ± 0.1	32.0 ± 0.7	93.8
3	50	4	7.2	1	256	0 ± 0.0	**52.5 ± 0.4**	0. ± 0.0	34.3 ± 1.3	86.8
4	100	1.5	2.7	0.75	293	19.0 ± 1.1	**43.3 ± 4.4**	15.6 ± 1.4	20.0 ± 0.4	97.0
5	100	2	3.6	0.75	289	0.4 ± 0.1	**73.3 ± 0.3**	3.5 ± 0.1	19.4 ± 0.3	97.9
6	100	2.5	4.5	0.75	286	1.7 ± 2.4	**72.5 ± 2.5**	2.7 ± 1.2	21.0 ± 0.4	98.7

[a] Residence time based on Equation 5 using the volume of the heated coil. [b] Calibrated HPLC yields.

Table 10. Results of different oxygen equivalents. 11.4 mL coil, 5 bar, 2 eq HNO_3, 3.6 eq HCl, 50 °C.

Entry	Oxygen [eq]	t_{res} [s][a]	**1** [%][b]	**3** [%][b]	**4** [%][b]	**5** [%][b]	Mass balance [%][b]
1	Argon	268	62.3 ± 3.6	**27.2 ± 1.9**	1.0 ± 0.1	10.2 ± 1.1	100.6
2	0.5	369	28.1 ± 1.5	**29.4 ± 1.3**	16.1 ± 0.2	24 ± 0.2	97.7
3	0.75	310	17.4 ± 1.8	**34.4 ± 1.3**	15.7 ± 0.1	28.0 ± 1.4	95.6
4	1	268	6.8 ± 0.7	**34.7 ± 0.6**	18.2 ± 0.1	30.4 ± 0.9	90.1

[a] Residence time based on Equation 5 using the volume of the heated coil. [b] Calibrated HPLC yields.

Table 11. Results of different oxygen equivalents. 11.4 mL coil, 5 bar, 2 eq HNO3, 3.6 eq HCl, 100 °C.

Entry	Oxygen [eq]	t_{res} [s][a]	**1** [%][b]	**3** [%][b]	**4** [%][b]	**5** [%][b]	Mass balance [%][b]
1a	Argon	247	43.3 ± 2.6	**47.9 ± 1.8**	3.5 ± 0.6	5.8 ± 1.3	100.4
1b	Argon	247	50.0 ± 5.6	**43.3 ± 4.5**	3.9 ± 0.5	3.0 ± 0.5	102.1
2	0.5	349	15.0 ± 2.0	**62.8 ± 2.1**	6.3 ± 0.3	15.8 ± 0.6	100.0
3a	0.75	289	8.2 ± 5.0	**66.1 ± 4.4**	6.2 ± 1.0	17.6 ± 1.6	98.1
3b	0.75	289	0.4 ± 0.1	**73.3 ± 0.3**	3.5 ± 0.1	19.4 ± 0.3	97.9
4a	1	247	0 ± 0.0	**72.7 ± 0.2**	1.7 ± 0.4	23.0 ± 1.4	96.4
4b	1	247	0 ± 0.0	**77.1 ± 0.9**	1.8 ± 0.2	20.4 ± 0.6	99.3
5	1.5	191	0 ± 0.0	**70.1 ± 0.6**	0 ± 0.0	25.0 ± 1.0	95.1

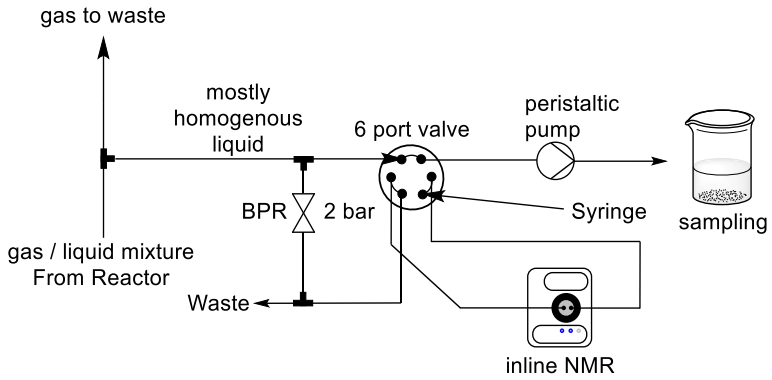
[a] Residence time based on Equation 5 using the volume of the heated coil. [b] Calibrated HPLC yields.

8.2 Additional Information for the Online Monitoring

For the online NMR monitoring a low field 43.795 MHz benchtop NMR device (Magritek, Spinsolve Ultra) with a glass flow through cell was employed. At the start of each day, a “QUICKSHIM: ALL” was performed using an NMR tube filled with deionized water (10%) and deuterated water (90%). Furthermore, shims with neat acetonitrile in the flow cell were performed on a regular base and referenced to 2.1 ppm. The width at 50% was usually below 0.7 Hz, the linewidth at 0.55% below 9.0 and the signal to noise ratio around 35000. The spectra were then collected in the reaction monitoring mode, with a pulse angle of 90°, a repetition time of 3 seconds and 8 scans. During the experiments the reaction progress was monitored in real time using the process link software and indirect hard models for chemical species.

The flow through cell of the benchtop NMR was connected to a 6-port valve, so that the reaction mixture could either flow through the cell or bypass it. This setup enabled the flow cell to be flushed with neat acetonitrile in-between measurements to perform a shim. The tube through which the reaction mixture entered the 6-port valve was equipped with a Y-mixer which also connected the entry stream to the waste stream via a 2 bar cartridge BPR. This BPR serves as an additional safety measure in case of pressure build up in the system due to blockage of the 6-port valve or flow cell. An image and illustration of the NMR 6-port valve is given below in Figure 22 and Scheme 17, respectively.

Figure 22. Image of the 6-port valve that connects the bench top NMR to the flow reactor.



Scheme 17. Graphical illustration of the 6-port valve and NMR after the reactor BPR.

Under most conditions a segmented flow regime of liquid and gas was observed. The evolution of substantial amounts of gas was observed (at 100 °C), even when no gas was introduced as part of the reaction. While the NMR can tolerate minor amounts of undissolved gas, best results for the online monitoring are achieved with a homogenous liquid. An additional T-piece was added after the BPR in order to remove some gas. The upper opening, which represents the top part of the T-piece was drilled open to be wider than the opening in the lower part. It was attached to the stirring plate in such a way, that this wider opening was vertical. The reaction mixture entered the T-piece from the bottom and all of it exited the T-piece through the upper opening from which the gas was directed into a waste collection flask.

To enable the online NMR monitoring a peristaltic pump (Masterflex) was connected to the 6-port valve. This pump was set to a flow rate of 550 µL/min and would constantly suck reaction mixture from the smaller opening of the T-piece into the flow cell of the NMR. Figure 23 shows an image of the whole setup and Scheme 18 as a graphical illustration. If there was not much more gas than liquid in the reaction mixture this system worked very well to separate a homogenous flow of liquid from the reaction mixture and direct it towards the flow cell. Conditions that led to high amounts of gas present, such as high oxygen flow rates at low conversion, therefore proved more challenging to monitor.

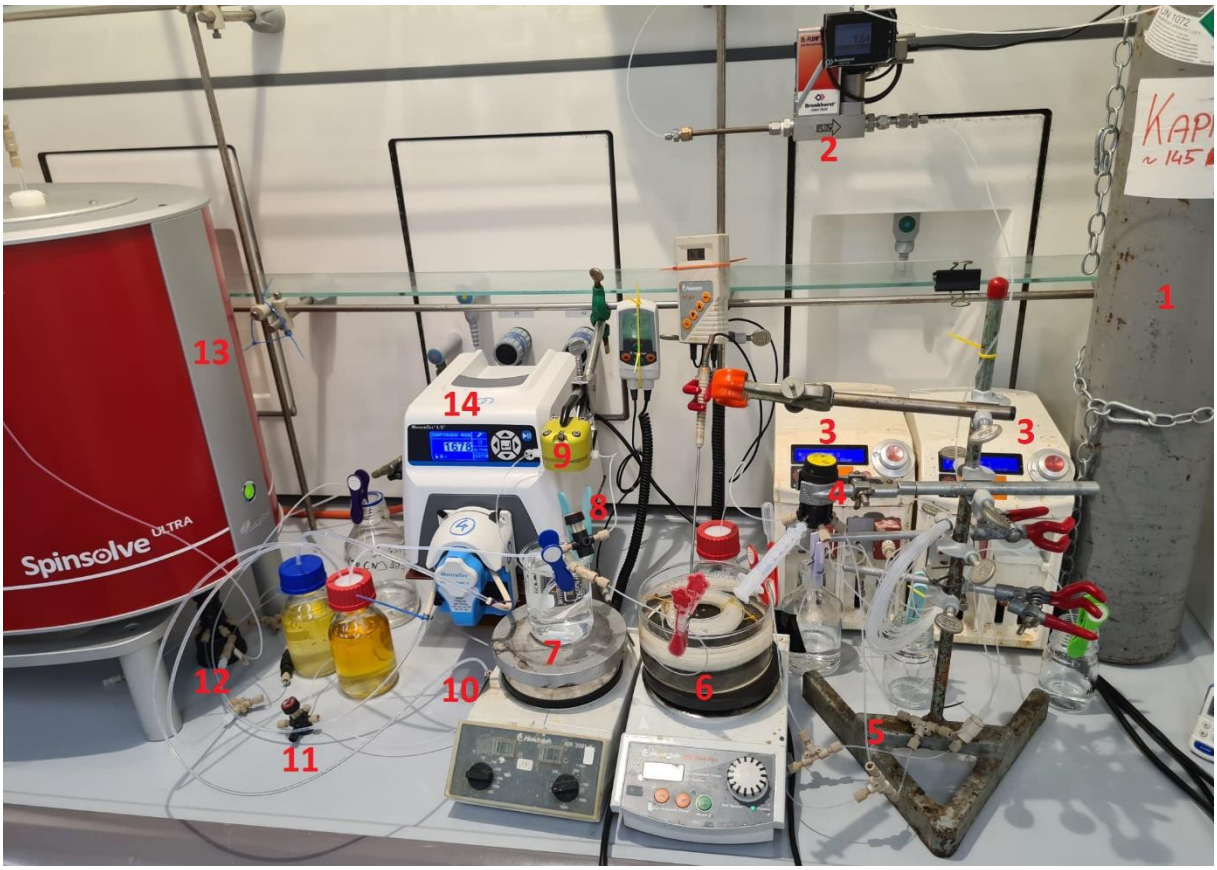
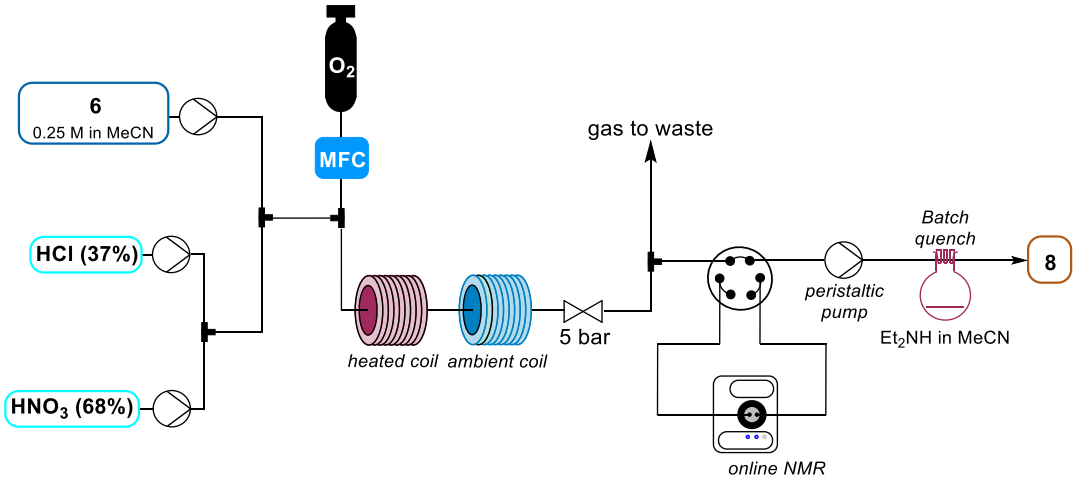


Figure 23. Image of the continuous flow setup for the inclusion of online NMR measurements. 1. oxygen gas cylinder. 2. MFC. 3. syringe pumps. 4. 6-port valve with sample loop. 5. T-pieces. 6. Reactor coil. 7. Cooling coil. 8. 4-port valve for safety pressure release. 9. BPR. 10. T-piece for gas/liquid separation. 11. 4-port valve to flush the flow cell. 12. 6-port valve of the NMR. 13. Benchtop NMR with flow cell. 14. Peristaltic pump.



Scheme 18. Graphical illustration of the reactor setup used for online NMR measurements. The 4-port valves are not included.

8.2.1 Indirect Hard Modelling (IHM) and Quantification

For the indirect hard model of each species, the spectra were subjected to exponential apodization (2 Hz), a straight-line subtraction baseline correction, phase correction of the zeroth order and then referenced to the trifluorotoluene peak at −63.7 ppm. After the spectra of the first experiment were recorded, they were loaded into PEAXACT and hard models for the pure compounds were created by manually fitting 7 to 12 peaks. All compounds could be modeled in the same spectrum, this could be done in the same spectrum as baseline separation was observed for all signals as depicted in Figure 5a.

With these indirect hard models, the PEAXACT software then provided the corresponding areas for each species. As a reference point the area of trifluorotoluene was used, as the corresponding concentration was known. Quantification of the other compounds was then done by comparing their NMR areas to that of trifluorotoluene, with respect to the fluorine atoms contained in each molecule.

Table 12. Conditions and observed NMR and HPLC responses during the experiments during the online ^{19}F NMR measurements.

Entry	T [°C]	Oxygen [eq]	HNO_3 [eq]	HCl [eq]	t_{res} [s][a]	**6** [%][b]	**7** [%][b]	**9** [%][b]	**10** [%][b]	**6** HPLC [%][c]	**8** HPLC [%][c]
1	50	1	4	7.2	257	0.5 ± 0.8	**57.2 ± 1.0**	3.6 ± 1.6	38.7 ± 1.4	0.5 ± 0.8	62.2 ± 4.6
2	50	1	2	3.6	269	1.4 ±1.4	**42.1 ± 2.8**	18.4 ± 1.8	38.0 ± 1.7	3.3 ±2.7	47.1 ± 3.4
3	50	0.5	2	3.6	370	17.1 ± 4.1	**37.5 ± 3.7**	20.7 ± 3.0	24.7 ± 2.7	22.2 ± 3.2	43.7 ± 3.5
4	100	1	2.5	4.6	232	0.3 ± 1.0	**78.2 ± 2.3**	2.6 ± 2.6	19.0 ± 1.5	0 ± 0	71.2 ± 7.5

[a] Residence time based on Equation 5 using the volume of the heated coil. [b] ^{19}F NMR yields. [c] Calibrated HPLC yields.

8.3 Used Formulas and Data

$$flow\,rate_{coil}\left[{mL}/{min}\right] = \frac{p_{ambient}}{T_{ambient}} * \frac{T_{coil}}{p_{coil}} * flow\,rate_{ambient}\left[{mL}/{min}\right] \qquad (Eq\ 5)$$

$$AE = \frac{2 * MW\ (\mathbf{2})}{MW(\mathbf{1}) + 2 * MW(HNO_3) + 2 * MW(HCl) + MW(O_2)} * 100 \qquad (Eq\ 6)$$

$$RME = \frac{m(\mathbf{2})}{m(\mathbf{1}) + m(HNO_3) + m(HCl) + m(O_2)} * 100 \qquad (Eq\ 7)$$

$$Optimum\ efficiency\ (OE) = \frac{RME}{AE} * 100 \qquad (Eq\ 8)$$

$$PMI = \frac{\sum mass\ used\ in\ this\ process\ or\ process\ step}{mass\ of\ isolated\ product} \qquad (Eq\ 9)$$

Table 13. Reagents and solvents used when operating the flow reactor for 5 hours. This resulted in 18.7 g of benzenesulfonyl chloride (**2**). Furthermore, $NaHCO_3$ (18.6 g), $NaSO_4$ (5 g), ethyl acetate (250 mL) and H_2O (200 mL) were used for the workup.

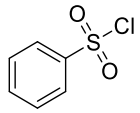
Compound	Flow [mg / min]	Mass after 5 h [g]	MW [g / mol]	Amount of substance after 5 h [mmol]
1	55	16.4	218.36	75
HNO_3	33	9.9	63.01	156
HCl	35	10.4	36.46	286
O_2	9	2.7	32.00	83
Acetonitrile	745	222	41.05	5408
H_2O	63	19	18.02	1054

Table 14. Reagents and solvents used during the reported long run for 4 hours. This resulted in 17.4 g of benzenesulfonyl chloride (**2**).

Compound	Flow [mg / min]	Mass after 4 h [g]	MW [g / mol]	Amount of substance after 4 h [mmol]
1	55	13.1	218.36	59.9
1,3-Dichloro-5,5-dimethylhydantoin	124	29.7	197.02	151
Acetic Acid	39	9.24	60.05	154
H_2O	24	5.88	18.02	326
Acetonitrile	1234	296.1	41.05	7213

8.4 Compound Characterization

8.4.1 Benzenesulfonyl Chloride (2)



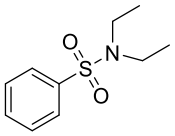
2 was obtained as a yellow liquid: (18.7 g, 70% yield) from diphenyl disulfide (**1**) and (610 mg, 70% yield) from benzenethiol (**1'**) after isolation.

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 8.10 – 8.00 (m, 2H), 7.81 – 7.70 (m, 1H), 7.69 – 7.58 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 144.5, 135.4, 129.8, 127.1.

The analytical data are in agreement with those previously reported in the literature.[98]

8.4.2 *N,N*-Diethylbenzenesulfonamide (3)



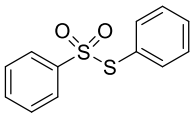
Diphenyl disulfide (**1**) was reacted to afford *N,N*-diethylbenzenesulfonamide (**3**) (167.7 mg, 39% yield) as a yellow oil after isolation.

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 7.80 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.58 – 7.41 (m, 3H), 3.23 (q, *J* = 7.2 Hz, 4H), 1.11 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 140.5, 132.3, 129.1, 127.0, 42.1, 14.2.

The analytical data are in agreement with those previously reported in the literature.[121]

8.4.3 *S*-Phenyl Benzenesulfonothioate (4)



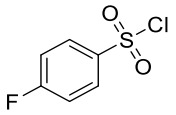
Diphenyl disulfide (**1**) was reacted to afford *S*-phenyl benzenesulfonothioate (**4**) (94.9 mg, 3.8% yield) as a yellow liquid after isolation.

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 7.62 – 7.51 (m, 3H), 7.51 – 7.38 (m, 3H), 7.37 – 7.29 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 143.0, 136.7, 133.8, 131.5, 129.6, 128.9, 127.9, 127.7.

The analytical data are in agreement with those previously reported in the literature.[122]

8.4.4 4-Fluorobenzenesulfonyl Chloride (7)



7 was obtained as a white solid: (343 mg, 69% yield) from 1,2-bis(4-fluorophenyl) disulfide (**6**) and (733 mg, 76% yield) from 4-fluorobenzenethiol (**6'**) after isolation.

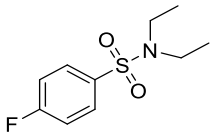
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 8.15 – 8.02 (m, 2H), 7.36 – 7.26 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 166.6 (d, *J* = 259.9 Hz), 140.4 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 10.1 Hz), 117.3 (d, *J* = 23.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ [ppm]: -99.6 (tt, *J* = 8.0, 4.8 Hz).

The analytical data are in agreement with those previously reported in the literature.[123]

8.4.5 *N,N*-Diethyl-4-fluorobenzenesulfonamide (8)



4-fluorobenzenethiol (**6'**) was reacted to afford *N*,*N*-diethyl-4-fluorobenzenesulfonamide (**8**) (434 mg, 74% yield) as a yellow oil after isolation.

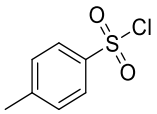
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 7.87 – 7.74 (m, 2H), 7.22 – 7.09 (m, 2H), 3.22 (q, *J* = 7.2 Hz, 4H), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 164.9 (d, *J* = 254.0 Hz), 136.6 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 9.2 Hz), 116.3 (d, *J* = 22.5 Hz), 42.1, 14.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ [ppm]: -106.2 (tt, *J* = 8.3, 5.1 Hz).

The ^{1}H and ^{13}C analytical data are in agreement with those previously reported in the literature.[98,121]

8.4.6 4-Methylbenzenesulfonyl Chloride (11a)



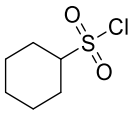
11a was obtained as a white solid: (342 mg, 71% yield) from 1,2-di-*para*-tolyldisulfide (**11**) and (722 mg, 76% yield) from 4-methylbenzenethiol (**11'**) after isolation.

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 7.99 – 7.84 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 2.49 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 147.0, 141.8, 130.4, 127.2, 22.0.

The analytical data are in agreement with those previously reported in the literature.[98]

8.4.7 Cyclohexanesulfonyl Chloride (12a)



When using 1,2-dicyclohexyldisulfide (**12**), toluene (250 µL, 5%) was added to the feed solution to create a homogeneous feed solution.

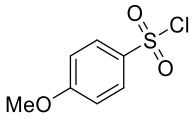
12a was obtained as a yellow liquid: (346 mg, 77% yield) from 1,2-dicyclohexyl disulfide (**12**) and (706 mg, 80% yield) from cyclohexanethiol (**12'**).

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 3.51 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.49 – 2.34 (m, 2H), 2.06 – 1.92 (m, 2H), 1.71 (ddd, *J* = 16.2, 11.6, 5.3 Hz, 3H), 1.46 – 1.20 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 75.0, 27.3, 25.2, 24.9.

The analytical data are in agreement with those previously reported in the literature.[98]

8.4.8 4-Methoxybenzenesulfonyl Chloride (13a)



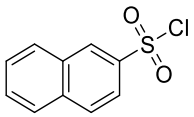
13a (534 mg, 81% yield) was obtained as an orange liquid from 4-methoxybenzenethiol (**13**).

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 8.03 – 7.94 (m, 2H), 7.10 – 6.99 (m, 2H), 3.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 165.0, 136.2, 129.7, 114.8, 56.1.

The analytical data are in agreement with those previously reported in the literature.[124]

8.4.9 Naphthalene-2-sulfonyl Chloride (14a)



The concentration of the feed solution was lowered to 0.25 M.

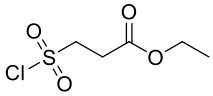
14a (417 mg, 75% yield) was obtained as an orange solid from naphthalene-2-thiol (**14**).

^{1}H NMR (300 MHz, DMSO) δ [ppm]: 8.17 (s, 1H), 8.01 – 7.94 (m, 1H), 7.94 – 7.84 (m, 2H), 7.72 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.56 – 7.47 (m, 2H).

^{13}C NMR (75 MHz, DMSO) δ [ppm]: 145.2, 132.9, 132.2, 128.6, 127.6, 126.7, 126.5, 124.3, 123.9, 39.5.

The analytical data are in agreement with those previously reported in the literature.[103]

8.4.10 Ethyl 3-(Chlorosulfonyl)propanoate (15a)



15a (539 mg, 53% yield) was obtained as an orange liquid from ethyl 3-mercaptopropanoate (**15**).

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 4.25 (q, *J* = 7.1 Hz, 2H), 4.07 – 3.98 (m, 2H), 3.13 – 3.00 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 168.9, 62.1, 60.3, 29.3, 14.2.

The analytical data are in agreement with those previously reported in the literature.[125]

9 References

[1] B. Gutmann, D. Cantillo, C. O. Kappe, *Angew Chem Int Edit,* **2015**, *127*, 6788–6832.

[2] A. S. Burange, S. M. Osman, R. Luque, *iScience*, **2022**, *25*(3), 103892.

[3] R. Porta, M. Benaglia, A. Puglisi, *Org Process Res Dev,* **2016**, *20*, 2–25.

[4] D. L. Hughes, *Org Process Res Dev,* **2020**, *24*, 1850–1860.

[5] C. A. Hone, C. O. Kappe, *Chem Methods,* **2021**, *1*, 454–467.

[6] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem Rev,* **2017**, *117*, 11796–11893.

[7] C. J. Mallia, I. R. Baxendale, *Org Process Res Dev,* **2016**, *20*, 327–360.

[8] U. Wietelmann, J. Klösener, P. Rittmeyer, S. Schnippering, H. Bats, W. Stam, *Org Process Res Dev,* **2022**, *26*, 1422–1431.

[9] R. L. Hartman, *Org Process Res Dev,* **2012**, *16*, 870–887.

[10] P. Sagmeister, R. Lebl, I. Castillo, J. Rehrl, J. Kruisz, M. Sipek, M. Horn, S. Sacher, D. Cantillo, J. D. Williams, C. O. Kappe, *Angew Chem Int Ed*, **2021**, *60(15)*, 8139–8148.

[11] R. Lebl, T. Murray, A. Adamo, D. Cantillo, C. O. Kappe, *ACS Sustain Chem Eng,* **2019**, *7*, 20088–20096.

[12] M. Baumann, I. R. Baxendale, *Beilstein J Org Chem,* **2015**, *11*, 1194–1219.

[13] J. C. Pastre, D. L. Browne, S. V. Ley, *Chem Soc Rev,* **2013**, *42*, 8849–8869.

[14] C. Minnich, S. Hardy, S. Krämer, *Chem Ing Tech,* **2016**, *88*, 694–697.

[15] L. L. Simon, H. Pataki, G. Marosi, F. Meemken, K. Hungerbühler, A. Baiker, S. Tummala, B. Glennon, M. Kuentz, G. Steele, H. J. M. Kramer, J. W. Rydzak, Z. Chen, J. Morris, F. Kjell, R. Singh, R. Gani, K. V. Gernaey, M. Louhi-Kultanen, J. Oreilly, N. Sandler, O. Antikainen, J. Yliruusi, P. Frohberg, J. Ulrich, R. D. Braatz, T. Leyssens, M. Von Stosch, R. Oliveira, R. B. H. Tan, H. Wu, M. Khan, D. Ogrady, A. Pandey, R. Westra, E. Delle-Case, D. Pape, D. Angelosante, Y. Maret, O. Steiger, M. Lenner, K. Abbou-Oucherif, Z. K. Nagy, J. D. Litster, V. K. Kamaraju, M. Sen Chiu, *Org Process Res Dev,* **2015**, *19*, 3–62.

[16] A. S. Rathore, R. Bhambure, V. Ghare, *Anal Bioanal Chem,* **2010**, *398*, 137–154.

[17] W. Chew, P. Sharratt, *Anal Methods,* **2010**, *2*, 1412–1438.

[18] **2004**, Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.

[19] S. V Luis, E. Garcia-Verdugo, *Flow Chemistry: Integrated Approaches for Practical Applications*, The Royal Society of Chemistry, **2019**.

[20] L. X. Yu, G. Amidon, M. A. Khan, S. W. Hoag, J. Polli, G. K. Raju, J. Woodcock, *AAPS Journal,* **2014**, *16*, 771–783.

[21] J. Wu, X. Yang, Y. Pan, T. Zuo, Z. Ning, C. Li, Z. Zhang, *J Flow Chem,* **2023**, *13*, 385–404.

[22] C. A. Shukla, A. A. Kulkarni, *Beilstein J Org Chem,* **2017**, *13*, 960–987.

[23] B. J. Reizman, K. F. Jensen, *Acc Chem Res,* **2016**, *49*, 1786–1796.

[24] R. Labes, Ra. Bourne, TW. Chamberlain, *Chim Oggi – Chem Today,* **2020**, *38(4)*

[25] D. C. Fabry, E. Sugiono, M. Rueping, *React Chem Eng,* **2016**, *1*, 129–133.

[26] D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem Eng Technol,* **2005**, *28*, 318–323.

[27] P. Plouffe, A. Macchi, D. M. Roberge, *Org Process Res Dev,* **2014**, *18*, 1286–1294.

[28] J. I. Yoshida, A. Nagaki, T. Yamada, *Chem Eur J*, **2008**, pp. 7450–7459.

[29] N. Kockmann, M. Gottsponer, D. M. Roberge, *Chem Eng J,* **2011**, *167*, 718–726.

[30] Z. Dong, Z. Wen, F. Zhao, S. Kuhn, T. Noël, *Chem Eng Sci: X,* **2021**, *10*, 100097.

[31] M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem Soc Rev,* **2016**, *45*, 4892–4928.

[32] D. Dallinger, B. Gutmann, C. O. Kappe, *Acc Chem Res,* **2020**, *53*, 1330–1341.

[33] D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem Rev* **2016**, *116*, 10276–10341.

[34] T. Noël, Y. Cao, G. Laudadio, *Acc Chem Res,* **2019**, *52*, 2858–2869.

[35] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**.

[36] P.T. Anastas, J. B. Zimmerman, *Environ. Sci. Technol.,* **2003**, *37*(5), 94A–101A.

[37] L. Rogers, K. F. Jensen, *Green Chem,* **2019**, *21*, 3481–3498.

[38] J. A. Bennett, Z. S. Campbell, M. Abolhasani, *Curr Opin Chem Eng,* **2019**, *26*, 9–19.

[39] S. G. Newman, K. F. Jensen, *Green Chem,* **2013**, *15*, 1456–1472.

[40] R. A. Sheldon, M. L. Bode, S. G. Akakios, *Curr Opin Green Sustain Chem,* **2022**, *33*, 100569.

[41] F. G. Calvo-Flores, *ChemSusChem,* **2009**, *2*, 905–919.

[42] C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley, *Org Process Res Dev,* **2011**, *15*, 912–917.

[43] D. Prat, O. Pardigon, H. W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani, P. Hosek, *Org Process Res Dev,* **2013**, *17*, 1517–1525.

[44] L. J. Diorazio, D. R. J. Hose, N. K. Adlington, *Org Process Res Dev,* **2016**, *20*, 760–773.

[45] J. R. Joshua R. Sacher, S. M. Weinreb, *Org Synth,* **2012**, *89*, 34.

[46] P. G. M. Wuts, T. W. Greene, Greene*'s Protective Groups in Organic Synthesis*, John Wiley & Sons, Hoboken, NJ, USA, **2006**.

[47] M. Mentel, A. M. Schmidt, M. Gorray, P. Eilbracht, R. Breinbauer, *Angew Chem Int Edit,* **2009**, *48*, 5841–5844.

[48] M.-L. Alcaraz, F. K. Griffin, D. E. Paterson, R. J. K. Taylor, *Tetrahedron Lett*,**1998**, *39(44)*, 8183–8186.

[49] H. Modrzejewska, K. Wojciechowski, *Synlett,* **2008**, 2465–2470.

[50] S. Guo, W. He, J. Xiang, Y. Yuan, *Tetrahedron Lett,* **2015**, *56*, 2159–2162.

[51] Y. Chen, F. Xiao, H. Chen, S. Liu, G. J. Deng, *RSC Adv,* **2014**, *4*, 44621–44628.

[52] M. V. Alexander, A. C. Khandekar, S. D. Samant, in *J Mol Catal A Chem*, **2004**, *223*, 75–83.

[53] S. Patai, Z. Rappoport, C. Stirling, *The Chemistry of Sulphones and Sulphoxides*, John Wiley and Sons, Chichester, **1988**.

[54] J. K. Fink, in *High Performance Polymers (Second Edition)* (Ed.: J.K. Fink), William Andrew Publishing, **2014**, 177–208.

[55] C. Liao, F. Liu, K. Kannan, *Environ Sci Technol,* **2012**, *46*, 6515–6522.

[56] P. Devendar, G. F. Yang, *Top Curr Chem,* **2017**, *375*, 82.

[57] B. M. Graybill, *J. Org. Chem,.* **1967**, *32*, 2931–3933.

[58] B. Maleki, S. Hemmati, R. Tayebee, S. Salemi, Y. Farokhzad, M. Baghayeri, F. M. Zonoz, E. Akbarzadeh, R. Moradi, A. Entezari, M. R. Abdi, S. S. Ashrafi, F. Taimazi, M. Hashemi, *Helv Chim Acta,* **2013**, *96*, 2147–2151.

[59] Q. Wu, D. Zhao, X. Qin, J. Lan, J. You, *Chem Commun,* **2011**, *47*, 9188–9190.

[60] S. R. Dubbaka, P. Vogel, *Chem Eur J,* **2005**, *11*, 2633–2641.

[61] P. A. Petkar, J. R. Jagtap, *Int J Pharm Sci Res,* **2021**, *12*, 2535–2547.

[62] A. Ovung, J. Bhattacharyya, *Biophys. Rev.*, **2021**, *13*, 259-272.

[63] C. Zhao, K. P. Rakesh, L. Ravidar, W. Y. Fang, H. L. Qin, *Eur J Med Chem,* **2019**, *162*, 679–734.

[64] B. D. Allison, V. K. Phuong, L. C. McAtee, M. Rosen, M. Morton, C. Prendergas, T. Barrett, G. Lagaud, J. Freedman, N. Li, X. Wu, H. Venkatesan, M. Pippel, C. Woods, M. C. Rizzolio, M. Hack, K. Hoey, X. Deng, C. King, N. P. Shankley, M. H. Rabinowitz, *J Med Chem,* **2006**, *49*, 6371–6390.

[65] D. Guianvarc'h, M. Duca, C. Boukarim, L. Kraus-Berthier, S. Léonce, A. Pierré, B. Pfeiffer, P. Renard, P. B. Arimondo, C. Monneret, D. Dauzonne, *J Med Chem,* **2004**, *47*, 2365–2374.

[66] N. S. Reddy, M. R. Mallireddigari, S. Cosenza, K. Gumireddy, S. C. Bell, E. P. Reddy, M. V. R. Reddy, *Bioorg Med Chem Lett,* **2004**, *14*, 4093–4097.

[67] V. Dudutiene, J. Matuliene, A. Smirnov, D. D. Timm, A. Zubriene, L. Baranauskiene, V. Morkunaite, J. Smirnoviene, V. Michailoviene, V. Juozapaitiene, A. Mickevičiute, J. Kazokaite, S. Bakšyte, A. Kasiliauskaite, J. Jachno, J. Revuckiene, M. Kišonaite, V. Pilipuityte, E. Ivanauskaite, G. Milinavičiute, V. Smirnovas, V. Petrikaite, V. Kairys, V. Petrauskas, P. Norvaišas, D. Linge, P. Gibieža, E. Čapkauskaite, A. Zakšauskas, E. Kazlauskas, E. Manakova, S. Gražulis, J. E. Ladbury, D. Matulis, *J Med Chem,* **2014**, *57*, 9435–9446.

[68] (**2023**, December 14) FDA approves belzutifan for advanced renal cell carcinoma. "https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-advanced-renal-cell-carcinoma,".

[69] (**2022**, February 1) FDA approves belzutifan for cancers associated with von Hippel-Lindau disease. "https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease,".

[70] B. R. Stranix, G. Sauvé, A. Bouzide, A. Coté, G. Sévigny, J. Yelle, V. Perron, *Bioorg Med Chem Lett,* **2004**, *14*, 3971–3974.

[71] B. R. Stranix, J. F. Lavallée, G. Sévigny, J. Yelle, V. Perron, N. LeBerre, D. Herbart, J. J. Wu, *Bioorg Med Chem Lett,* **2006**, *16*, 3459–3462.

[72] D. R. Marshall, G. Rodriguez, D. S. Thomson, R. Nelson, A. Capolina, *Bioorg Med Chem Lett,* **2007**, *17*, 315–319.

[73] J. Smith, H. Wescott, J. Early, S. Mullen, J. Guzman, J. Odingo, J. Lamar, T. Parish, *Medchemcomm,* **2019**, *10*, 934–945.

[74] P. L. Donner, Q. Xie, J. K. Pratt, C. J. Maring, W. Kati, W. Jiang, Y. Liu, G. Koev, S. Masse, D. Montgomery, A. Molla, D. J. Kempf, *Bioorg Med Chem Lett,* **2008**, *18*, 2735–2738.

[75] William Caldwell T, Kornfeld Edmund C, *J Am Chem Soc*, **1942**, *64(7)*, 1695–1696.

[76] C. Wang, C. Hamilton, P. Meister, C. Menning, *Org Process Res Dev,* **2007**, *11*, 52–55.

[77] A. K. Saroha, *J Chem Health Saf,* **2006**, *13*, 5–11.

[78] R. J. Watson, D. Batty, A. D. Baxter, D. R. Hannah, D. A. Owen, J. G. Montana, *Tetrahedron Lett*, **2002**, *43(4)*, 683–685.

[79] G. C. Aguilar, P. A. Lis, D. E. Wise, J. S. Martinez, M. Parasram, *Tetrahedron Lett,* **2023**, *124*, 154591.

[80] F. J. Strauss, D. Cantillo, J. Guerra, C. O. Kappe, *React Chem Eng,* **2016**, *1*, 472–476.

[81] M. Prieschl, N. Sulzer, J. Sedelmeier, D. Kaldre, R. Lebl, K. Püntener, S. Hildbrand, J. D. Williams, C. O. Kappe, *J Flow Chem,* **2023**, *13*, 405–411.

[82] K. Bahrami, M. M. Khodaei, M. Soheilizad, *J Org Chem,* **2009**, *74*, 9287–9291.

[83] K. Bahrami, M. M. Khodaei, J. Abbasi, *Tetrahedron,* **2012**, *68(25)*, 5095–5101.

[84] K. Bahrami, M. M. Khodaei, J. Abbasi, *Synthesis,* **2012**, *2*, 316–322.

[85] K. Bahrami, M. M. Khodaei, M. Soheilizad, *Synlett,* **2009**, *17*, 2773–2776.

[86] L. Kværnø, M. Werder, H. Hauser, E. M. Carreira, *Org Lett,* **2005**, *7*, 1145–1148.

[87] Y. Gareau, J. Pellicelli, S. Laliberté, D. Gauvreau, *Tetrahedron Lett,* **2003**, *44*, 7821–7824.

[88] G. K. S. Prakash, T. Mathew, C. Panja, G. A. Olah, *J Org Chem,* **2007**, *72*, 5847–5850.

[89] S. W. Wright, K. N. Hallstrom, *J Org Chem*, **2006**, *71(3)*, 1080-1084.

[90] T. Okada, H. Matsumuro, T. Iwai, S. Kitagawa, K. Yamazaki, T. Akiyama, T. Asawa, Y. Sugiyama, Y. Kimura, M. Kirihara, *Chem Lett,* **2015**, *44*, 185–187.

[91] M. Kirihara, T. Okada, Y. Sugiyama, M. Akiyoshi, T. Matsunaga, Y. Kimura, *Org Process Res Dev,* **2017**, *21*, 1925–1937.

[92] H. Veisi, R. Ghorbani-Vaghei, S. Hemmati, J. Mahmoodi, *Synlett,* **2011**, *16*, 2315–2320.

[93] Y. M. Pu, A. Christesen, Y. Y. Ku, *Tetrahedron Lett,* **2010**, *51*, 418–421.

[94] A. Reza Massah, S. Sayadi, S. Ebrahimi, *RSC Adv,* **2012**, *2*, 6606–6616.

[95] J. D. Bonk, D. T. Amos, S. J. Olson, *Synth Commun,* **2007**, *37*, 2039–2050.

[96] U. Tilstam, H. Weinmann, *Org Process Res Dev,* **2002**, *6*, 384–393.

[97] J. S. Sharley, G. Gambacorta, A. M. Collado Pérez, E. E. Ferri, A. F. Miranda, I. F. Fernández, J. S. Quesada, I. R. Baxendale, *Tetrahedron Lett,* **2022**, *126*, 133058(1)-133058(14).

[98] D. Polterauer, D. M. Roberge, P. Hanselmann, R. Littich, C. A. Hone, C. O. Kappe, *React Chem Eng,* **2022**, *7*, 2582–2592.

[99] L. Capaldo, Z. Wen, T. Noël, *Chem Sci,* **2023**, *14*, 4230–4247.

[100] M. Yu, N. A. Strotman, S. A. Savage, S. Leung, A. Ramirez, *Org Process Res Dev,* **2019**, *23*, 2088–2095.

[101] L. Malet-Sanz, J. Madrzak, S. V. Ley, I. R. Baxendale, *Org Biomol Chem,* **2010**, *8*, 5324–5332.

[102] M. Glace, C. Armstrong, N. Puryear, C. Bailey, R. S. Moazeni-Pourasil, D. Scott, S. Abdelwahed, T. D. Roper, *Molecules,* **2023**, *28(10)*, 4213.

[103] M. Jereb, L. Hribernik, *Green Chem,* **2017**, *19*, 2286–2295.

[104] N. Kockmann, P. Thenée, C. Fleischer-Trebes, G. Laudadio, T. Noël, *React Chem Eng,* **2017**, *2*, 258–280.

[105] C. A. Hone, C. O. Kappe, *Top Curr Chem,* **2019**, *377(7)*, 2.

[106] A. A. H. Laporte, T. M. Masson, S. D. A. Zondag, T. Noël, *Angew Chem Int Edit*, **2023**, Article: e202316108.

[107] C. A. Hone, D. M. Roberge, C. O. Kappe, *ChemSusChem,* **2017**, *10*, 32–41.

[108] A. García-Domínguez, N. M. West, R. T. Hembre, G. C. Lloyd-Jones, *ACS Catal,* **2023**, *13*, 9487–9494.

[109] S. Madabhushi, R. Jillella, V. Sriramoju, R. Singh, *Green Chem,* **2014**, *16*, 3125–3131.

[110] D. Polterauer, P. Hanselmann, R. Littich, M. Bersier, D. M. Roberge, S. Wagschal, C. A. Hone, C. O. Kappe, *Org Process Res Dev,* **2023**, *27(12)*, 2385–2392

[111] P. Giraudeau, F. X. Felpin, *React Chem Eng,* **2018**, *3*, 399–413.

[112] T. Maschmeyer, P. L. Prieto, S. Grunert, J. E. Hein, *Magn Reson Chem,* **2020**, *58*, 1234–1248.

[113] A. Saib, A. Bara-Estaún, O. J. Harper, D. B. G. Berry, I. A. Thomlinson, R. Broomfield-Tagg, J. P. Lowe, C. L. Lyall, U. Hintermair, *React Chem Eng,* **2021**, *6*, 1548–1573.

[114] C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton, J. H. Clark, *Green Chem,* **2015**, *17*, 3111–3121.

[115] P. De Santis, L. E. Meyer, S. Kara, *React Chem Eng,* **2020**, *5*, 2155–2184.

[116] Z. Yang, J. Xu, *Synthesis,* **2013**, *45*, 1675–1682.

[117] R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem,* **2011**, *13*, 854–862.

[118] F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. Robert McElroy, J. Sherwood, *Sustain Chem Process,* **2016**, *4(7)*, 1-24.

[119] P. Schmittinger, T. Florkiewicz, L. , C. Curlin, B. Lüke, R. Scannell, T. Navin, E. Zelfel, R. Bartsch, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag, Weinheim, **2003**.

[120] *The Chlorine Manual*, 6th Edition, The Chlorine Institute, Inc., Washington, D. C., **2001**

[121] M. Lai, Z. Wu, Y. Wang, Y. Zheng, M. Zhao, *Org Chem Fron,* **2019**, *6*, 506–511.

[122] X. Ren, Q. Liu, Z. Yang, Z. Wang, X. Chen, *Chin Chem Lett,* **2023**, *34(5)*, 107821.

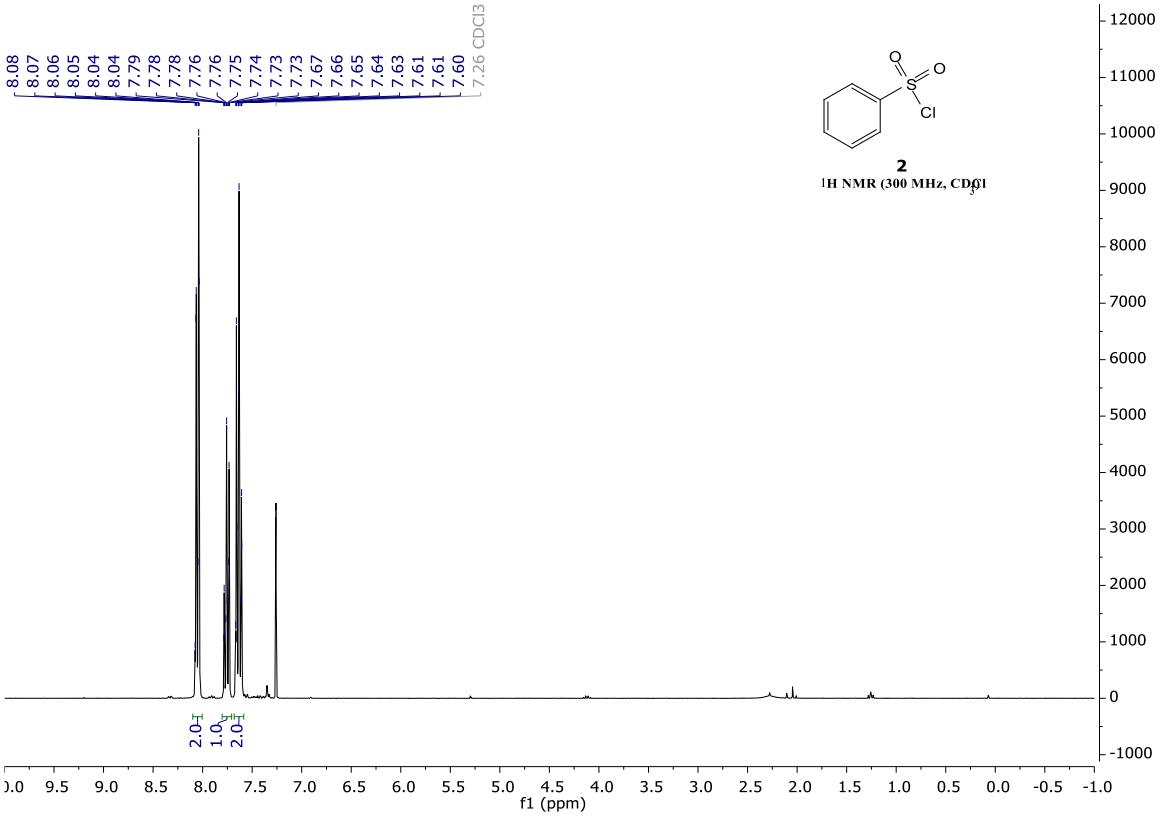
[123] V. Magné, L. T. Ball, *Chem Eur J,* **2019**, *25*, 8903–8910.

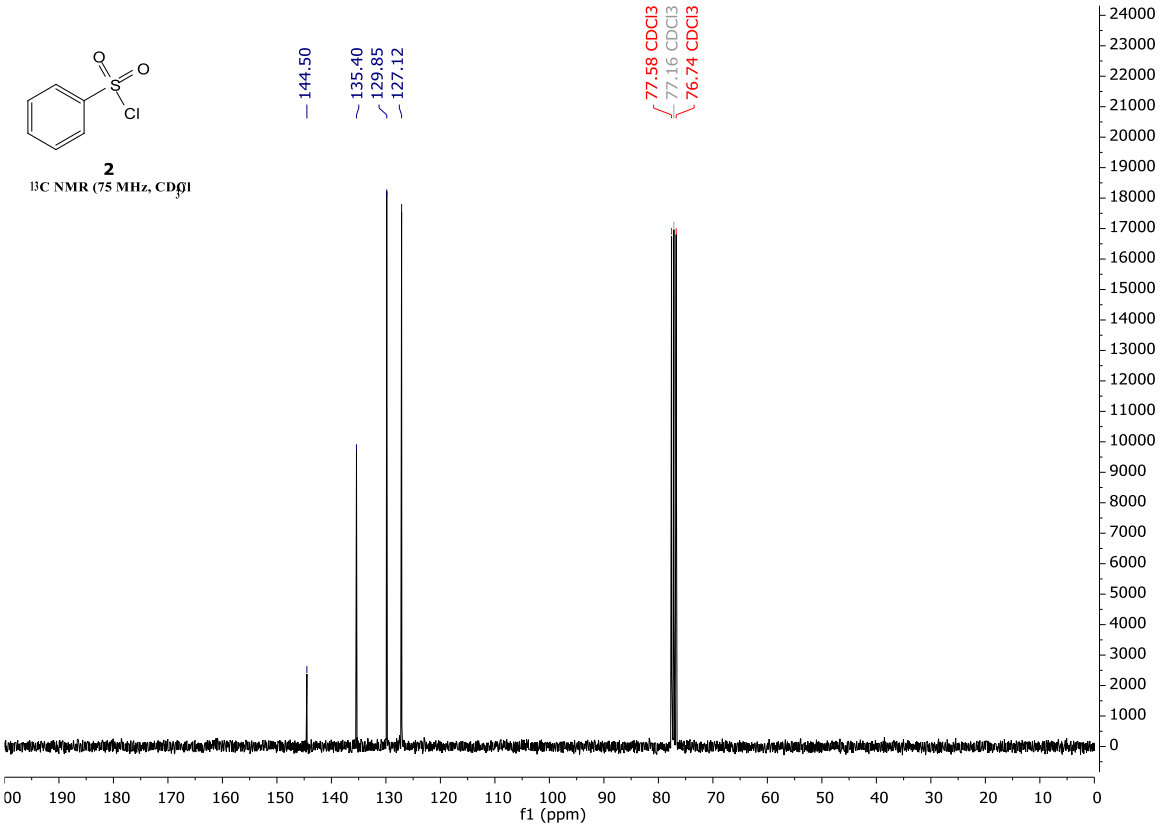
[124] M. Kirihara, S. Naito, Y. Nishimura, Y. Ishizuka, T. Iwai, H. Takeuchi, T. Ogata, H. Hanai, Y. Kinoshita, M. Kishida, K. Yamazaki, T. Noguchi, S. Yamashoji, *Tetrahedron Lett,* **2014**, *70*, 2464–2471.

[125] O. O. Orazi, R. A. Corral, H. Giaccio, *J Chem Soc, Perkin Trans 1,* **1986**, 1977–1982.

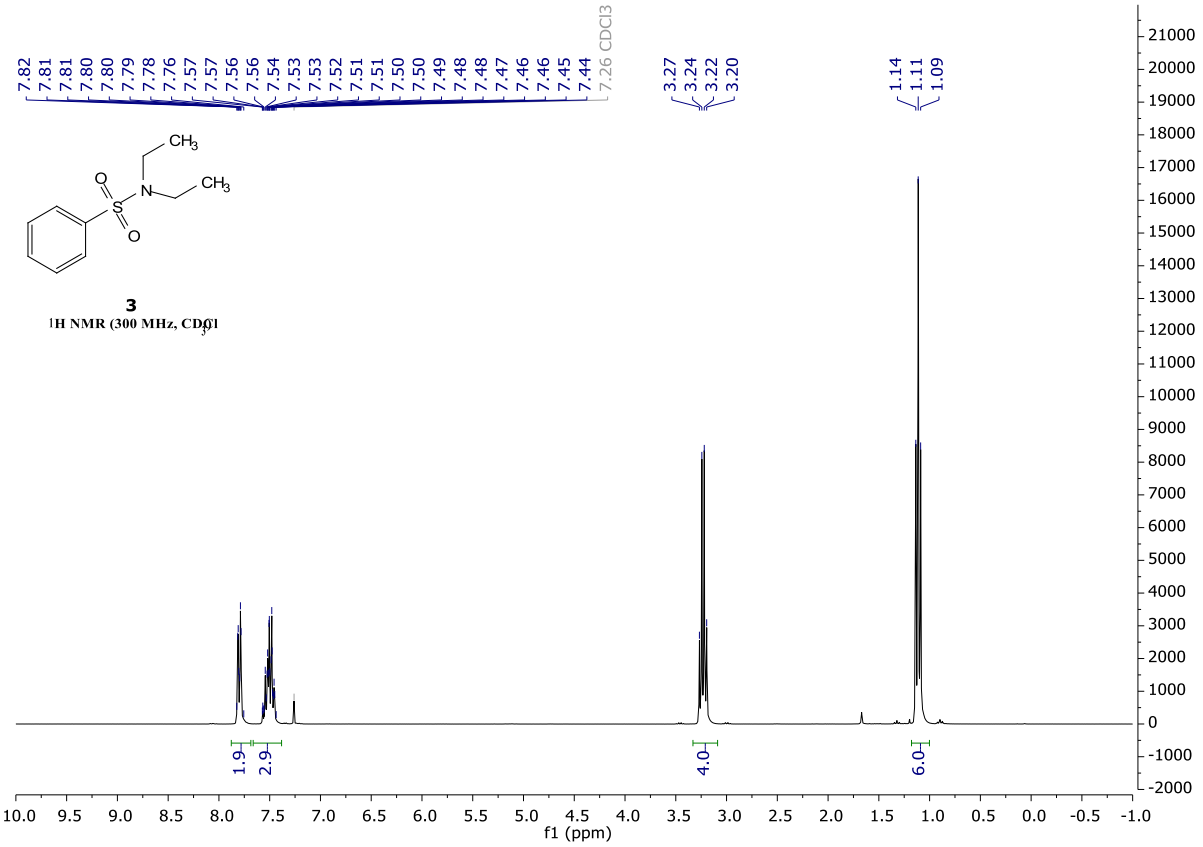
10 NMR Spectra

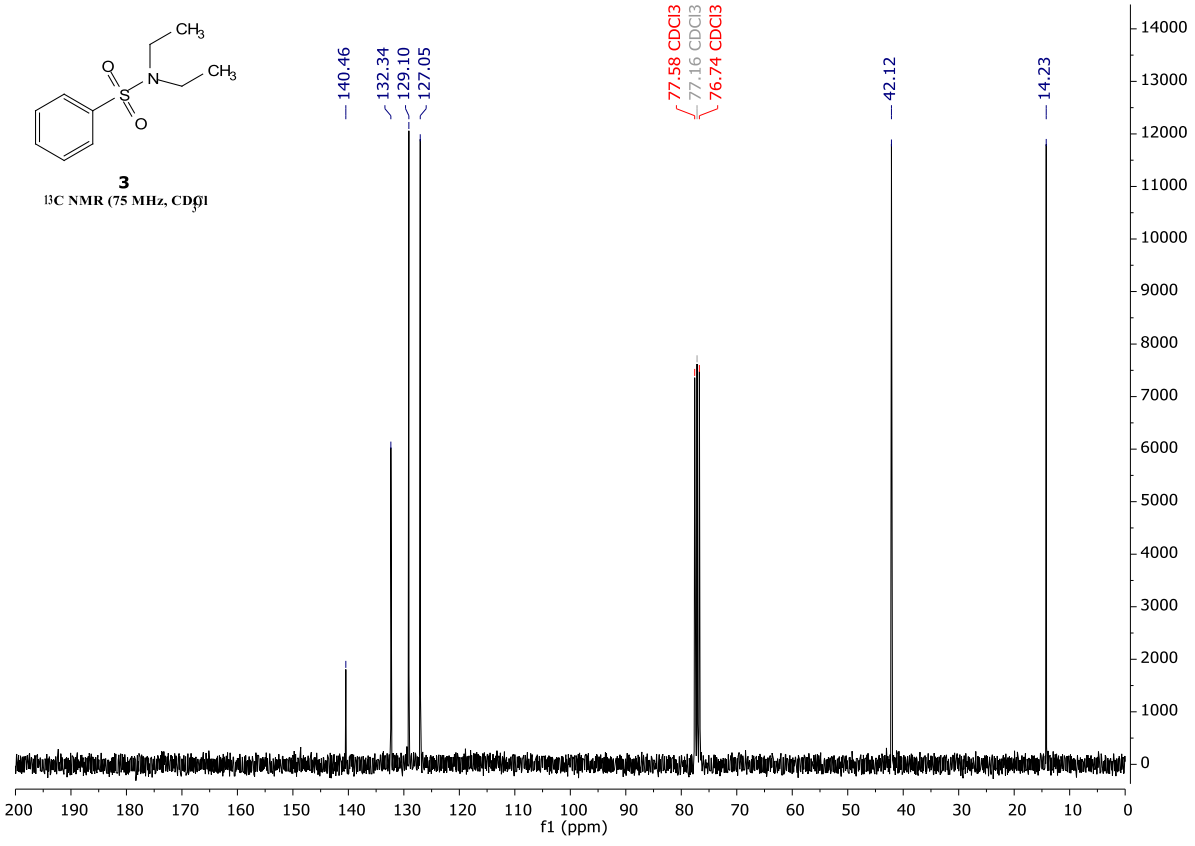
10.1 Benzenesulfonyl Chloride (2)



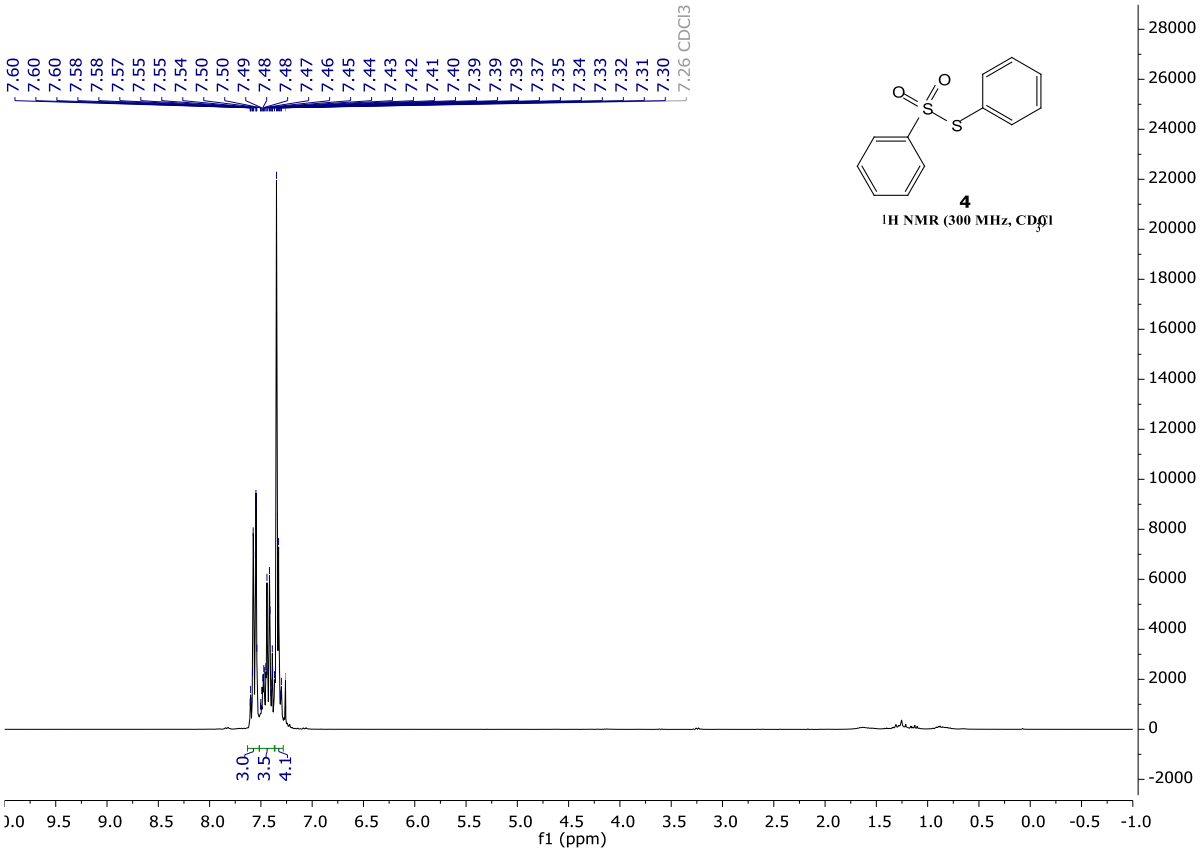


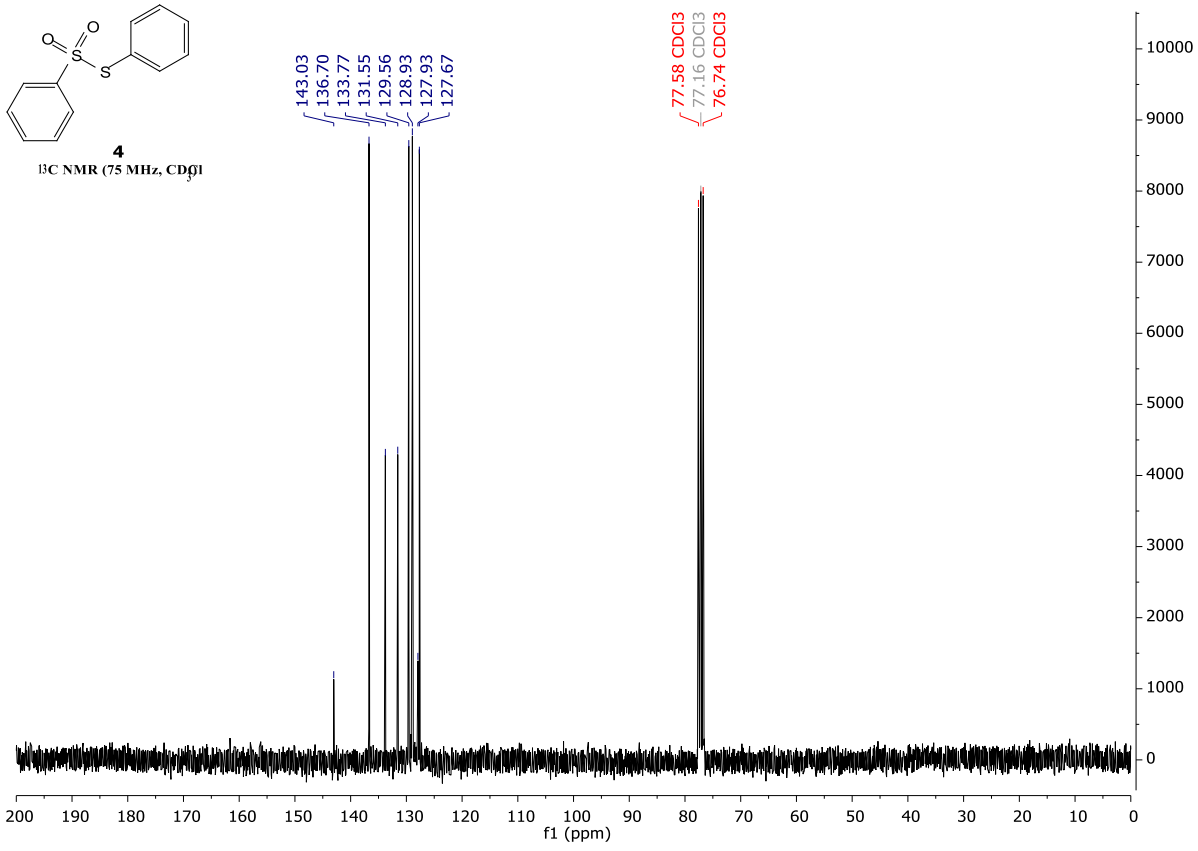
10.2 *N, N*-diethylbenzenesulfonamide (3)



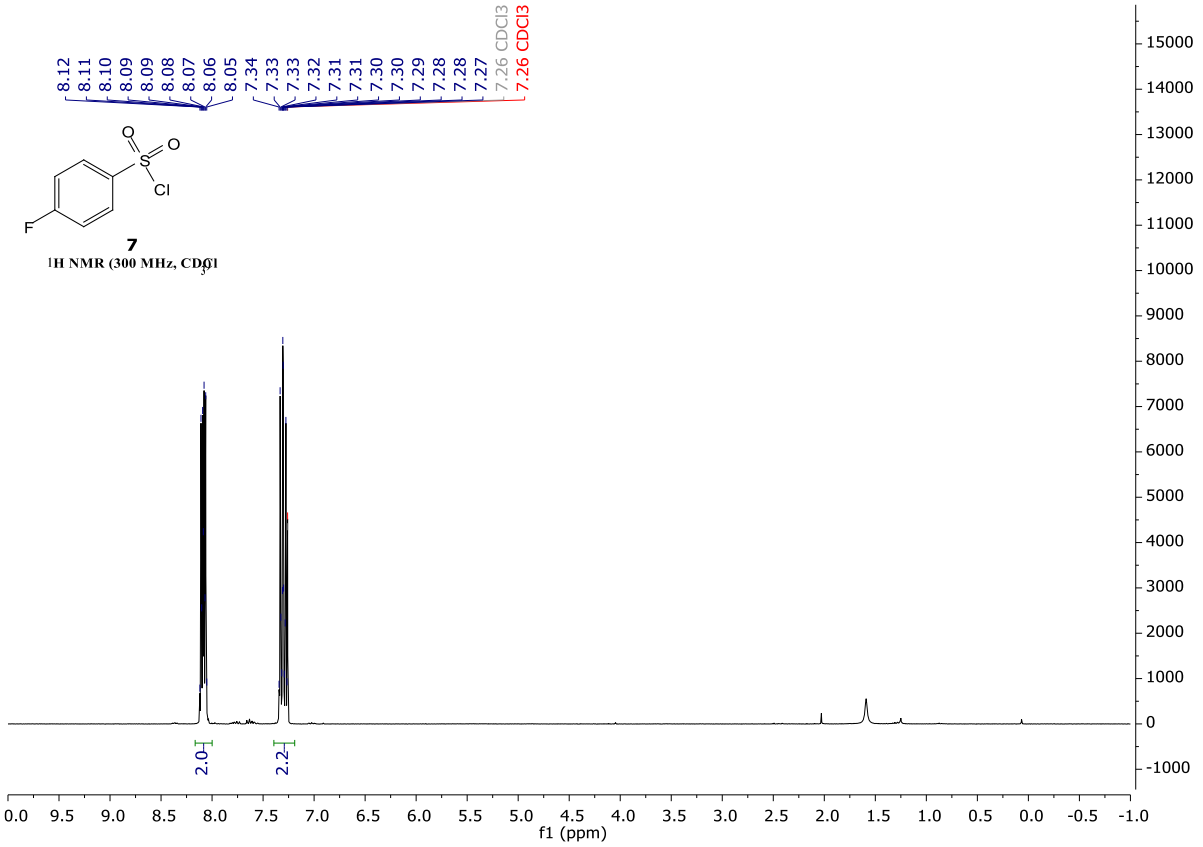


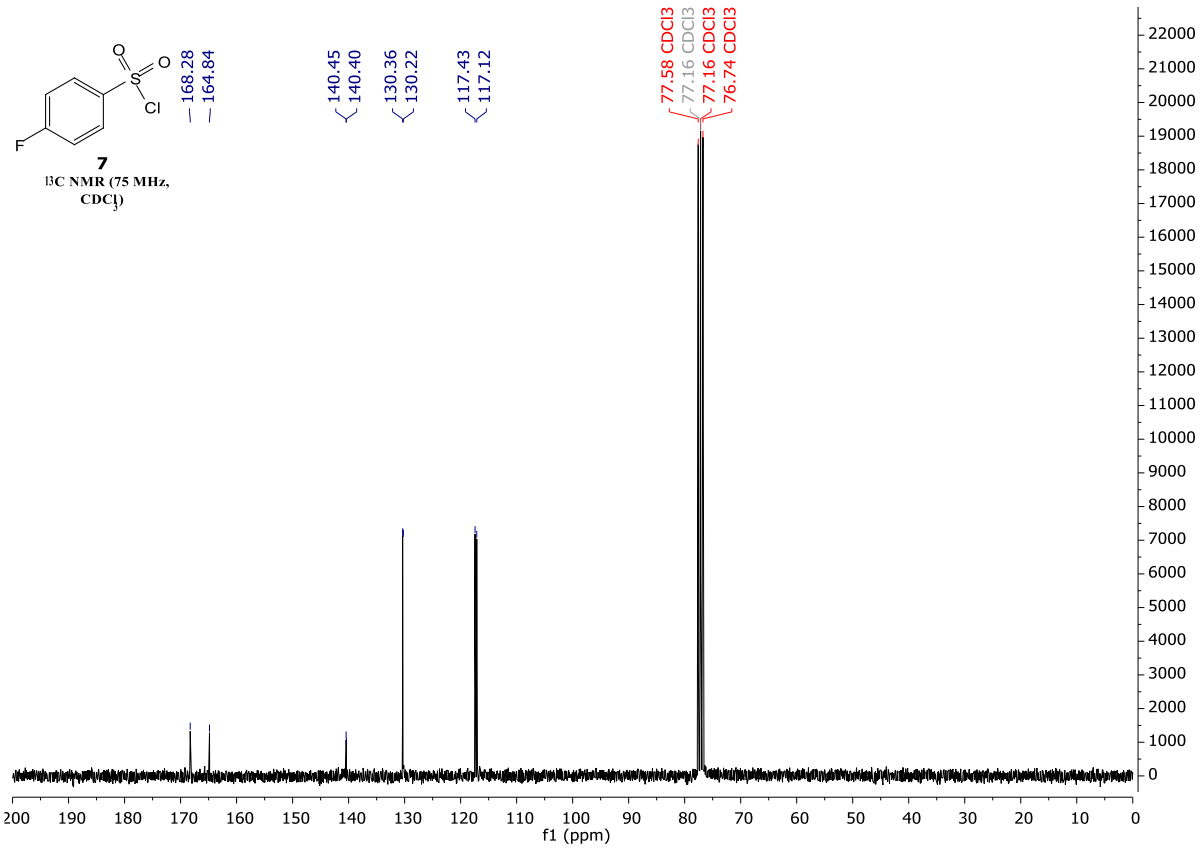
10.3 *S*-phenyl benzenesulfonothioate (4)

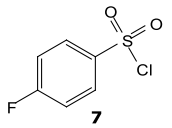




10.44-Fluorobenzenesulfonyl Chloride (7)



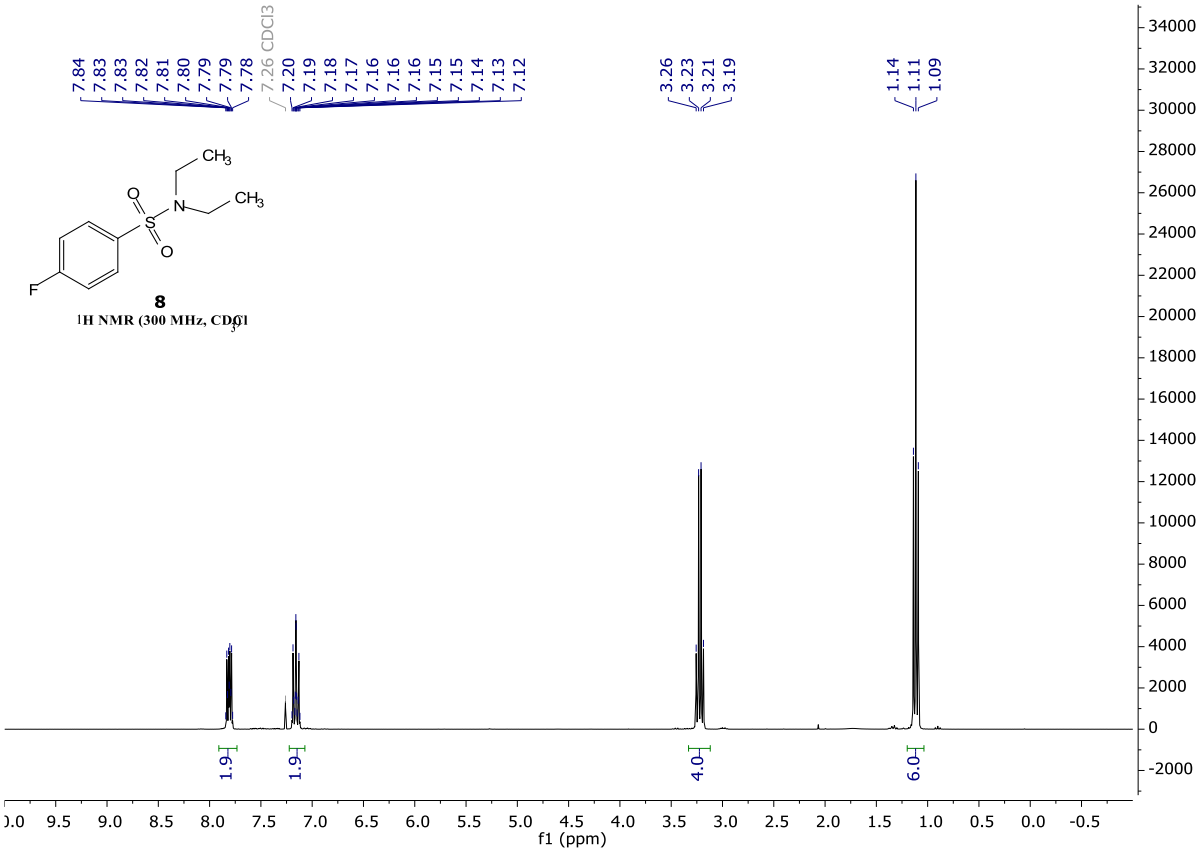


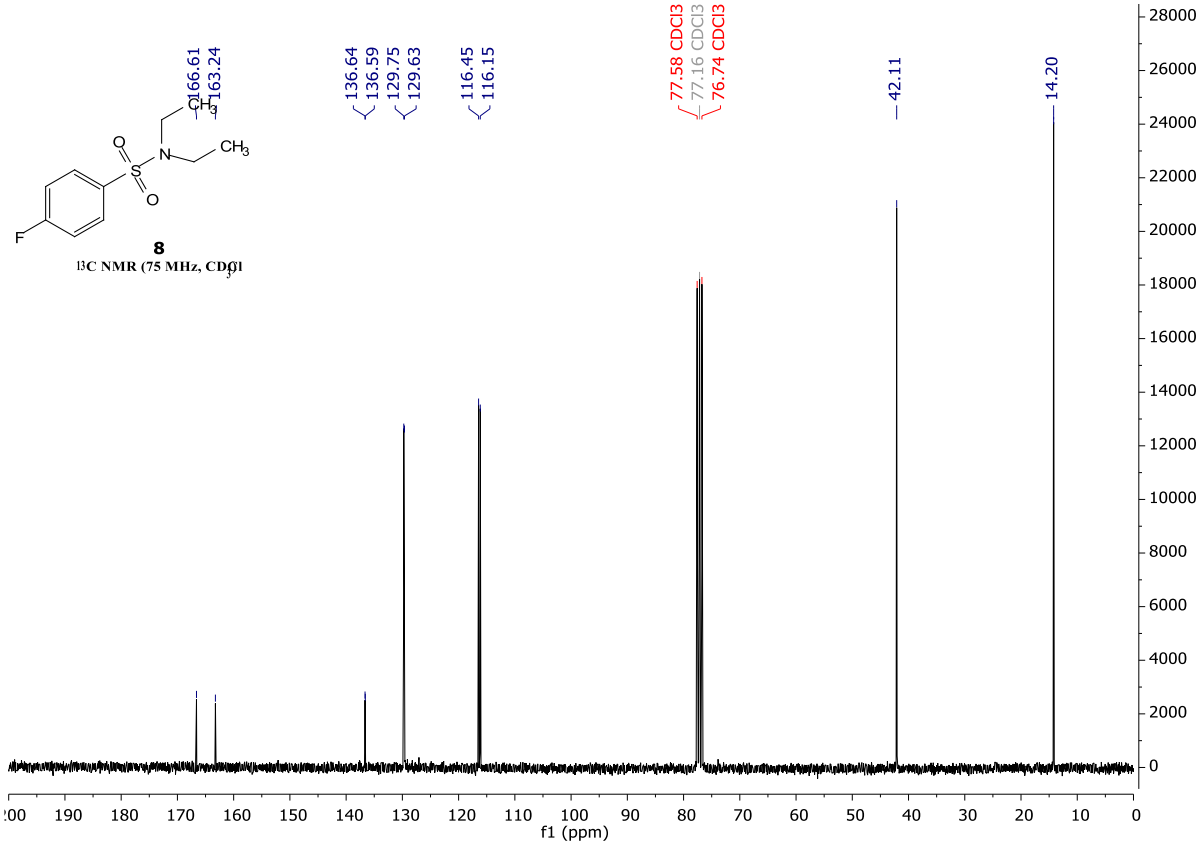


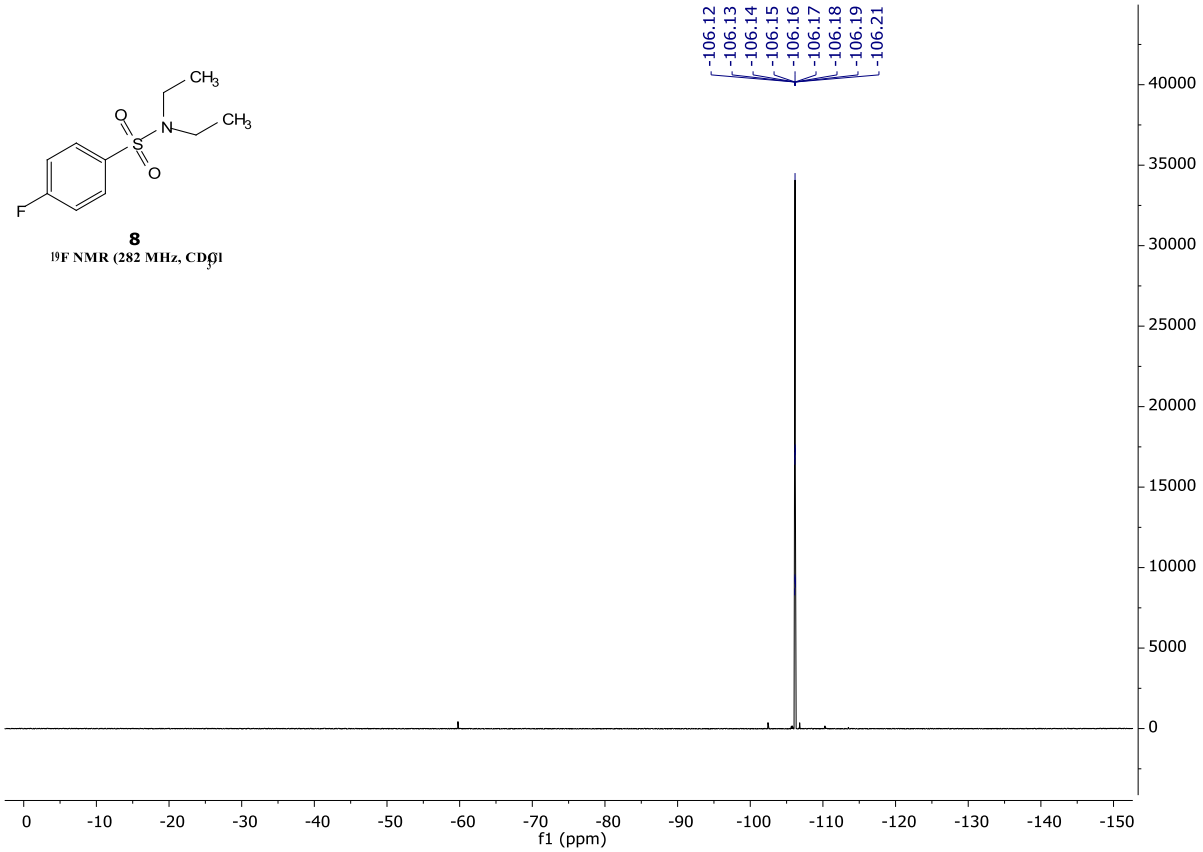
7

^{19}F NMR (282 MHz, $CDCl_3$)

10.5*N, N*-diethyl-4-fluorobenzenesulfonamide (8)



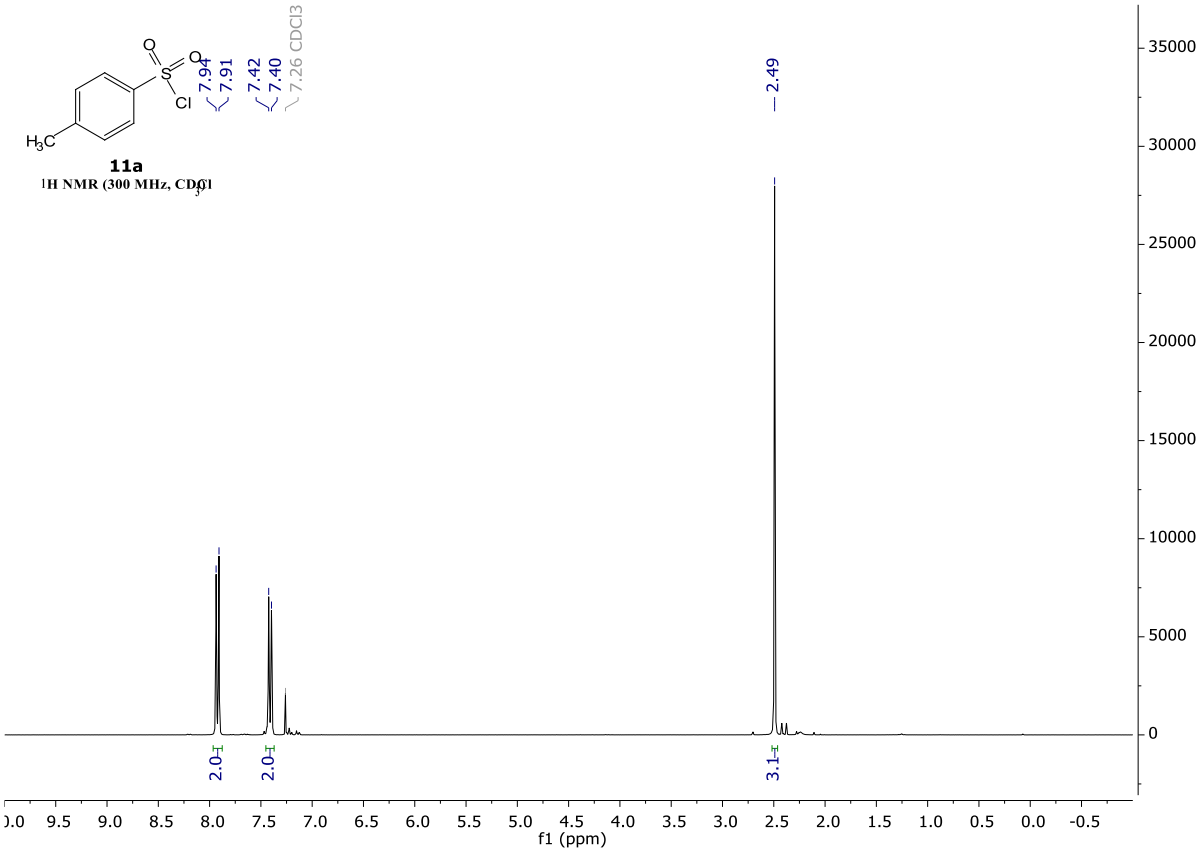


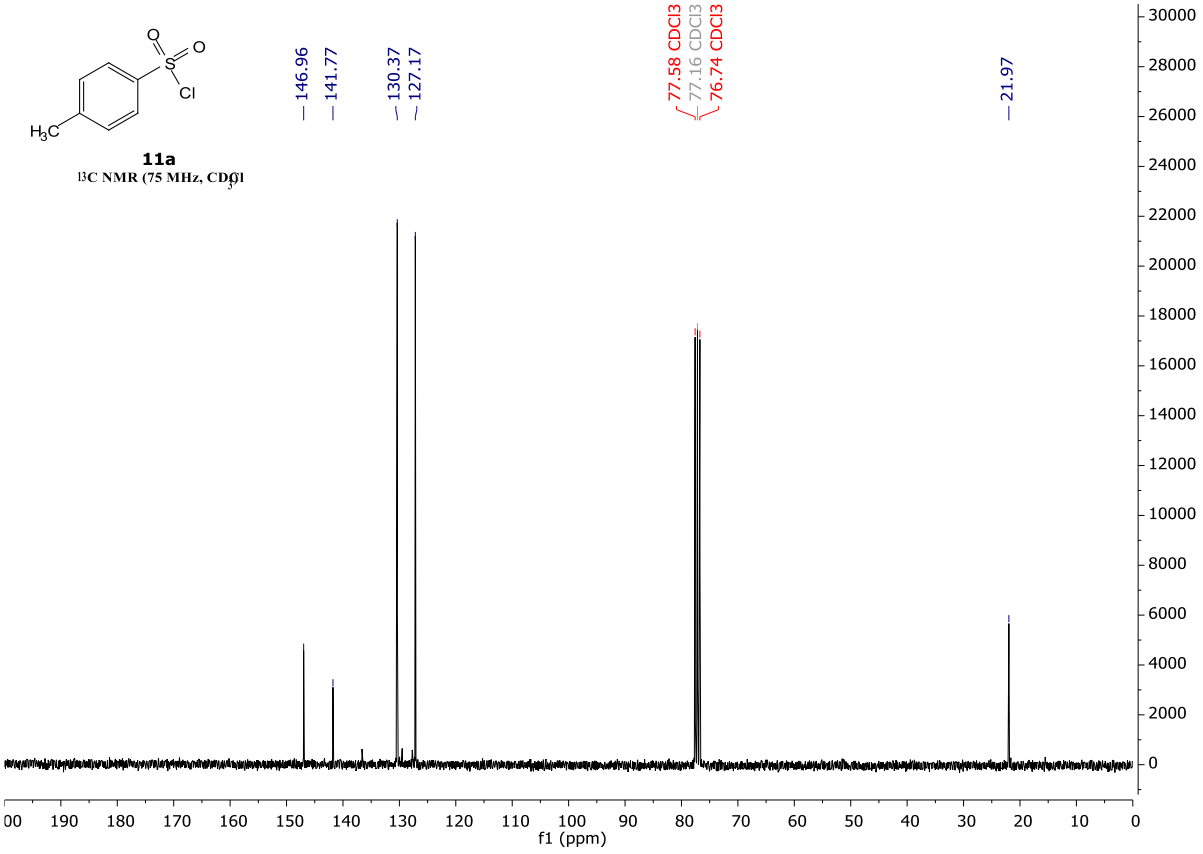


8

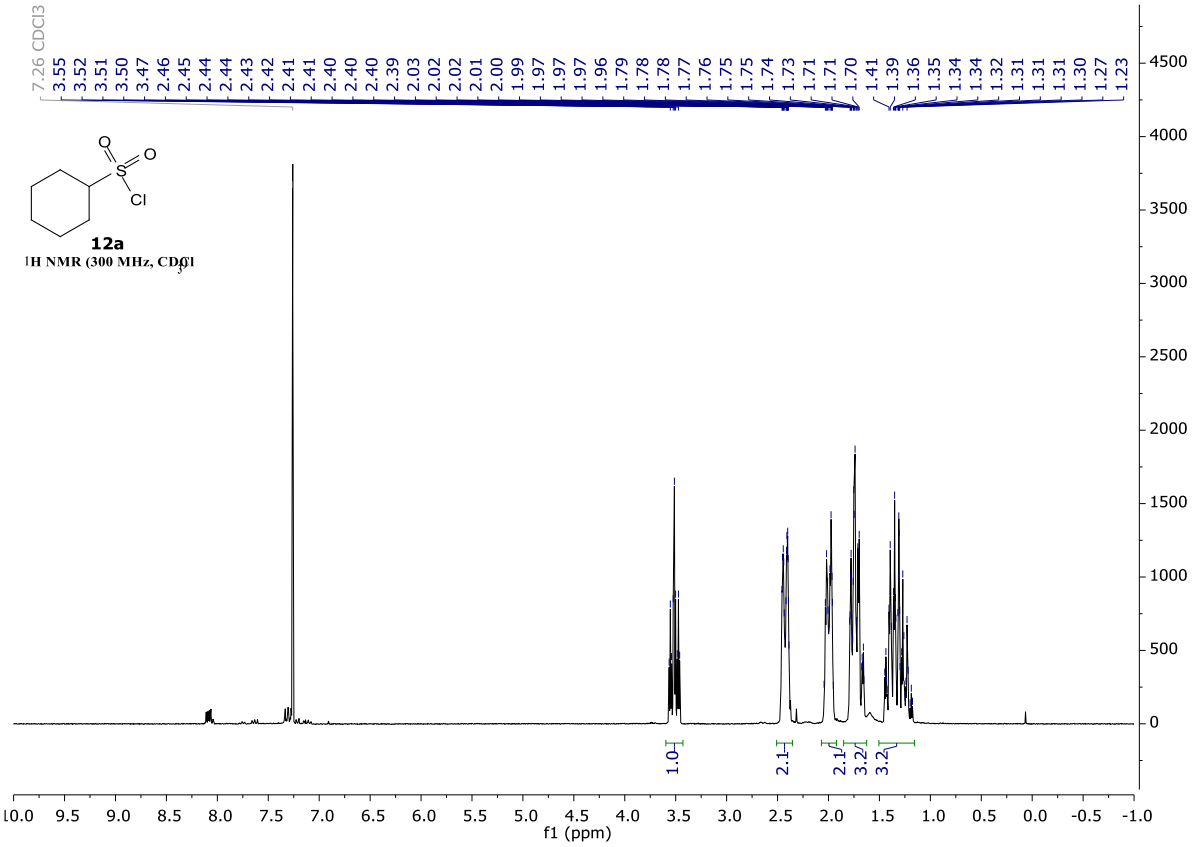
^{19}F NMR (282 MHz, $CDCl_3$)

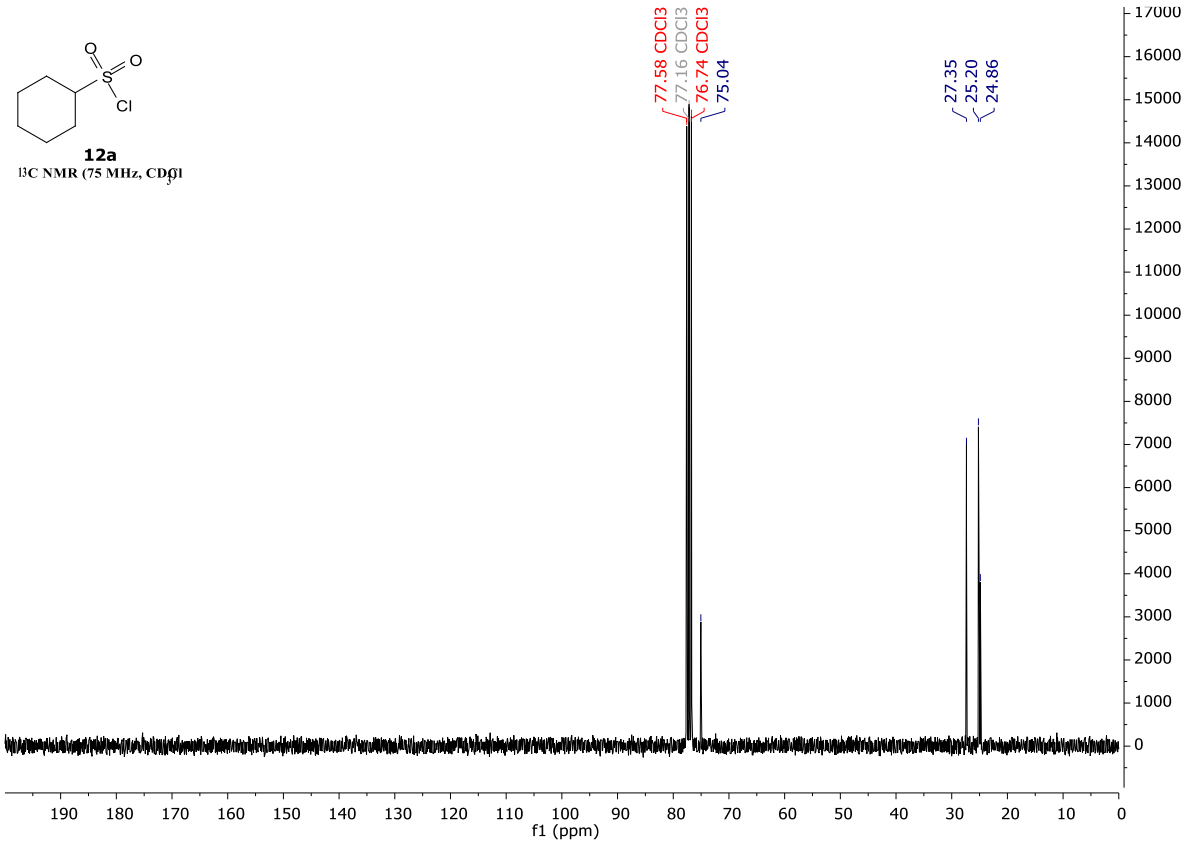
10.64-Methylbenzenesulfonyl Chloride (11a)



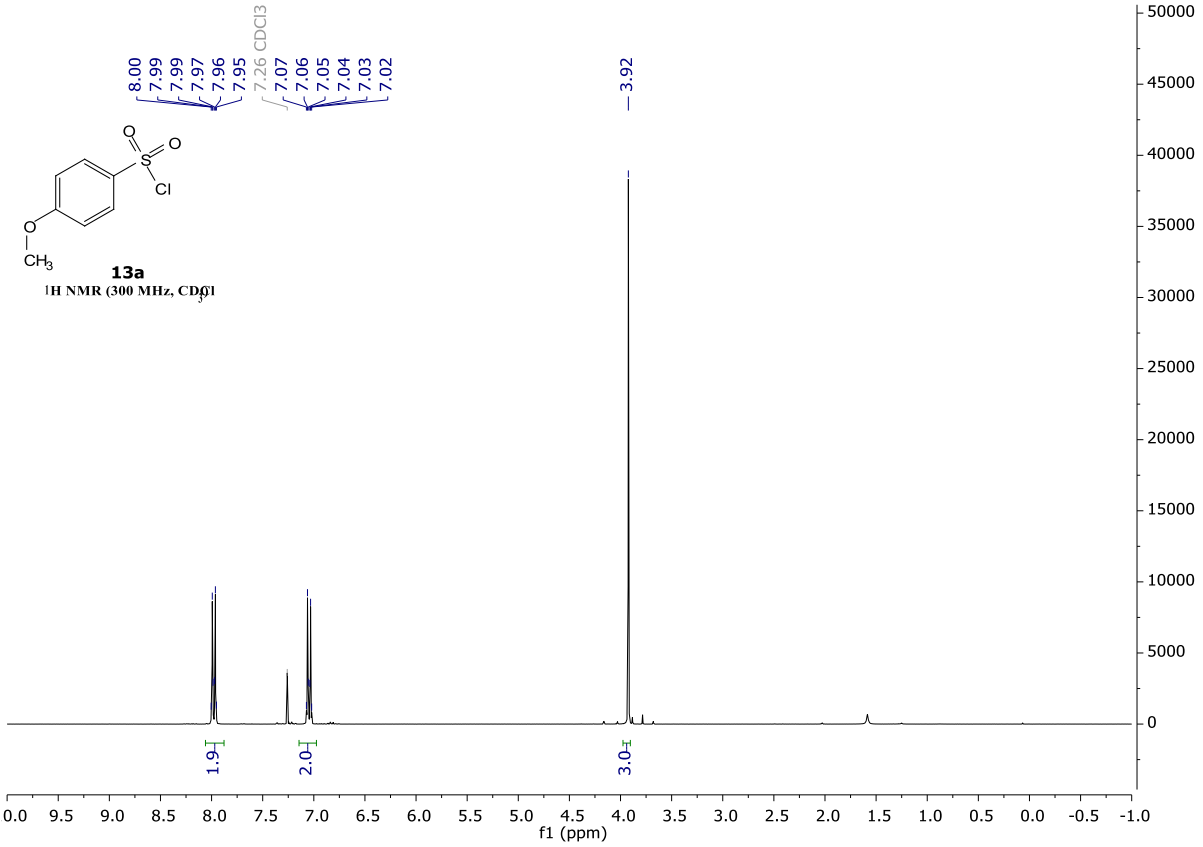


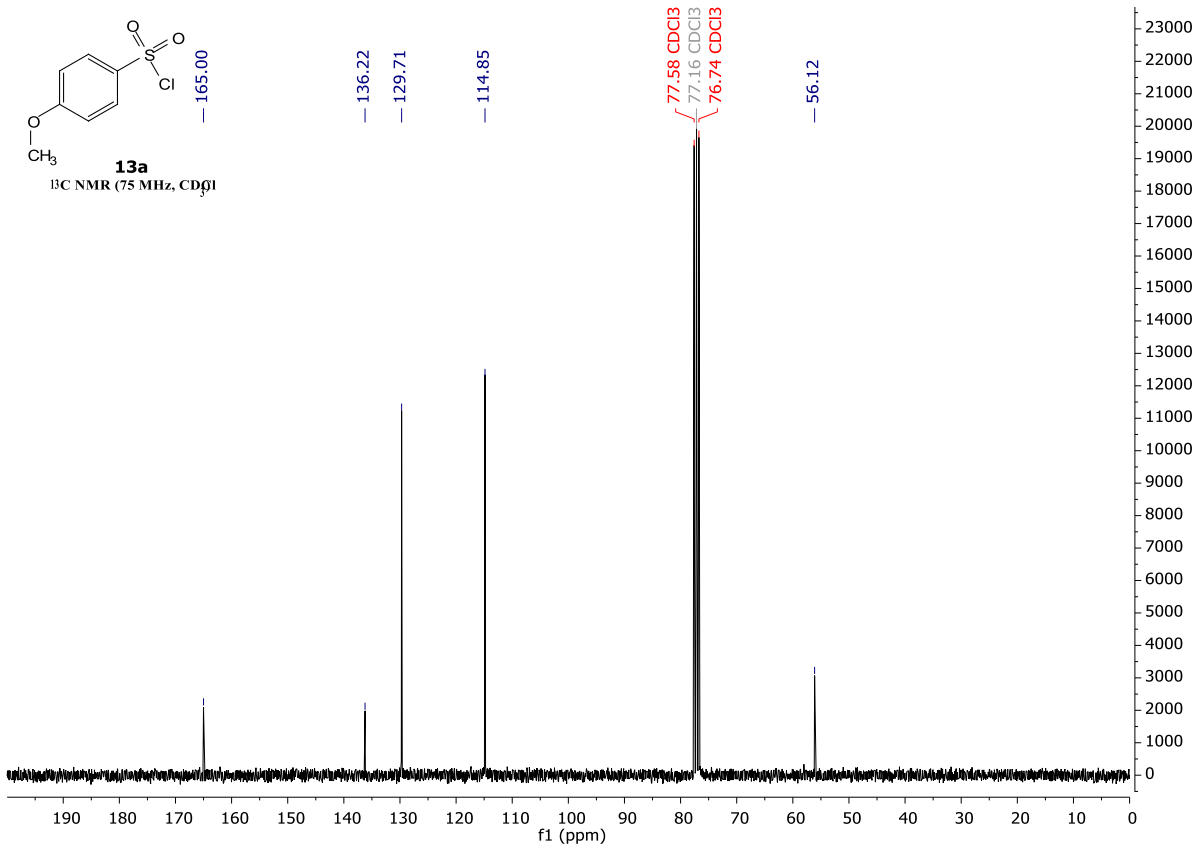
10.7Cyclohexanesulfonyl chloride (12a)



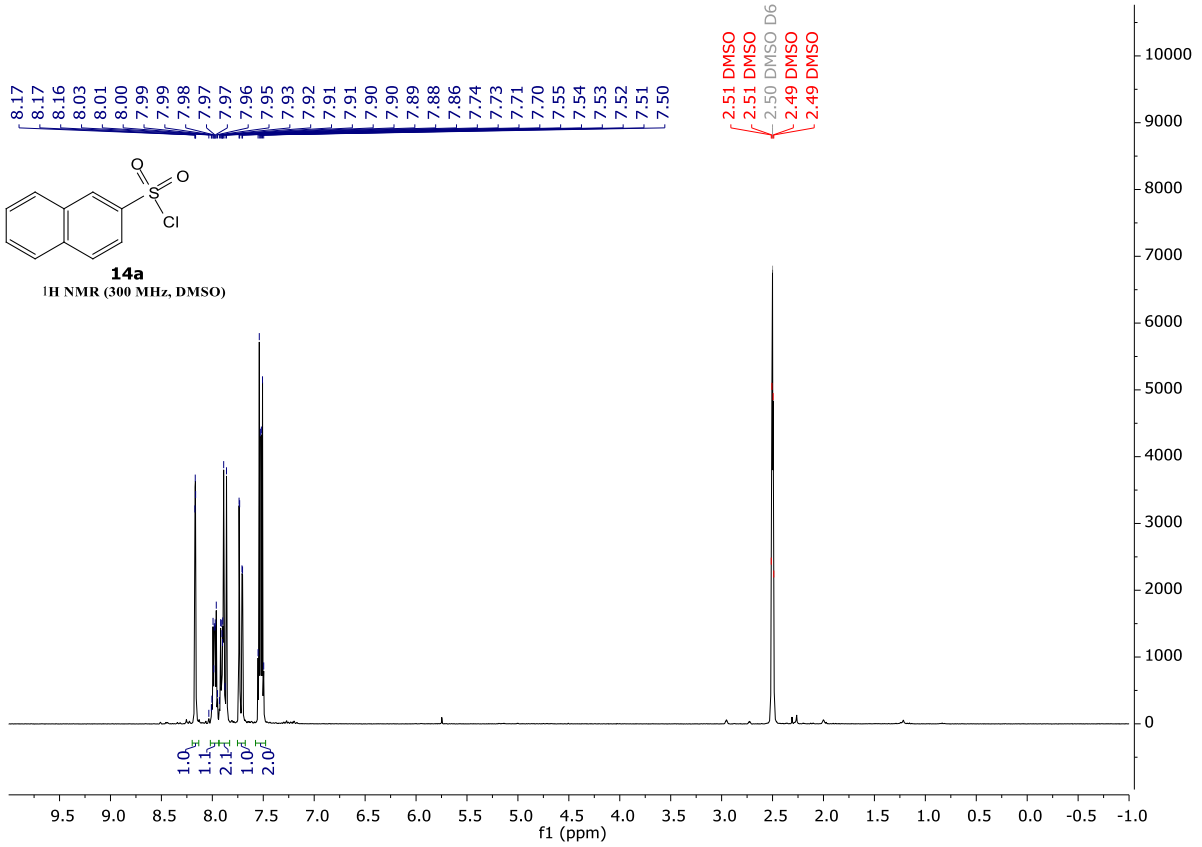


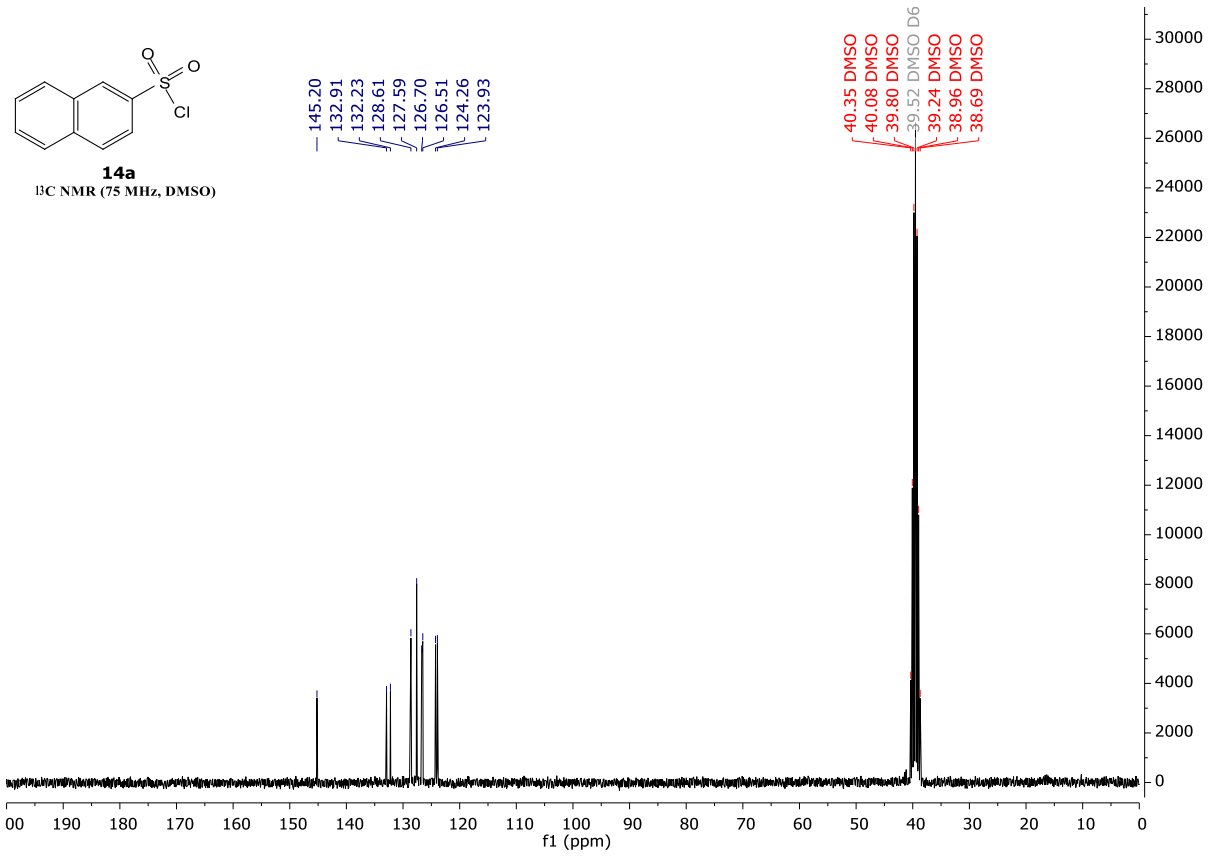
10.8 4-Methoxybenzenesulfonyl chloride (13a)





10.9Naphthalene-2-sulfonyl chloride (14a)





10.10 Ethyl 3-(chlorosulfonyl)propanoate (15a)