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ReactNMR and ReactIR as Reaction Monitoring and Mechanistic Elucidation Tools: The NCS Mediated Cascade Reaction of α-Thioamides to α-Thio-β-chloroacrylamides

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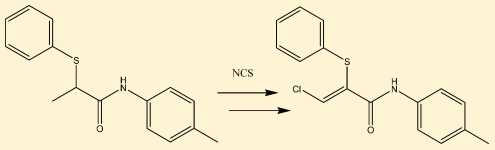
Supporting Information

ABSTRACT: On-flow ReactIR and ^{1}H NMR reaction monitoring, coupled with in situ intermediate characterization, was used to aid in the mechanistic elucidation of the *N*-chlorosuccinimide mediated transformation of an α-thioamide. Multiple intermediates in this reaction cascade are identified and characterized, and in particular, spectroscopic evidence for the intermediacy of the chlorosulfonium ion in the chlorination of α-thioamides is provided. Further to this, solvent effects on the outcome of the transformation are discussed. This work also demonstrates the utility of using a combination of ReactIR and flow NMR reaction monitoring (ReactNMR) for characterizing complex multicomponent reaction mixtures.



INTRODUCTION

The use of high-resolution NMR spectroscopy enables the characterization of organic compounds in a nondestructive and noninvasive way, using relatively small quantities of material. Under the appropriate experimental conditions, qualitative and quantitative data can be mined from multicomponent mixtures. However, this technique traditionally employs the use of expensive deuterated solvents, which has been prohibitive in the expansion of this application to reaction monitoring, particularly on a medium to large scale. With the advent of NMR solvent suppression techniques such as WET and low drift magnets the restrictions placed by the necessary use of deuterated solvents has been greatly reduced.[1,2] These advances, in tandem with the progress made in flow NMR and ReactIR technologies, provide a unique opportunity in the field of reaction monitoring and process analytical technology (PAT), particularly in the development of flow and continuous chemistry.[3,4]

Much of the early work in the area of flow NMR was focused on coupling this technology with LC separation as a means of identifying and characterizing compounds.[5] Its application to multisample analysis[6] and combinatorial chemistry[7] has also been reported.

The advances outlined above paved the way for increased utility of NMR in the area of reaction monitoring. Varying experimental setups have been published to date.[8−10] Some have used traditional deuterated solvent media, while others have attempted to move away from these expensive solvents, by employing alternative methods. A report on no-D NMR spectroscopy in reaction monitoring appeared in 2004.[11] This took advantage of specific cases where reactions were run neat or at increased concentrations in protonated solvents. Another method of overcoming the issue of large solvent proton resonances is to monitor the progress of the reaction via an alternative nucleus.[12−14] The use of NMR as a medium for monitoring biocatalyzed reactions in aqueous systems is well established in the biotechnology field.[15,16] The issues associated with swamping of analyte resonances by that of water in the reaction medium is circumvented by the use of presaturation techniques. The use of NMR in protonated solvents to monitor reactions has been reported.[9] Work by Fyfe et al. in the 1970s used low-temperature flow NMR studies to investigate the reactions of amines with 2,4,5-trinitroanisole, conducted in a DMSO/MeOH solvent mixture.[17,18] Recently, flow NMR was utilized to identify an intermediate in formation of an imidazole species and hence enhance the mechanistic understanding to optimize the process.[19] 2D NMR techniques, including HSQC,[20] HMBC,[21] TOCSY,[22] and DOSY,[23,24] have also been exploited as reaction monitoring tools. Magic angle spinning NMR has been utilized to study adsorption and reaction kinetics in nanocages.[25]

While employing high-resolution NMR as a probe into reaction mechanisms and monitoring is well established, the vast majority of the work conducted to date involves small scale reactions in deuterated solvents, which are carried out in standard NMR tubes. This has obvious limitations, not only in terms of scale but also the types of reactions that can be

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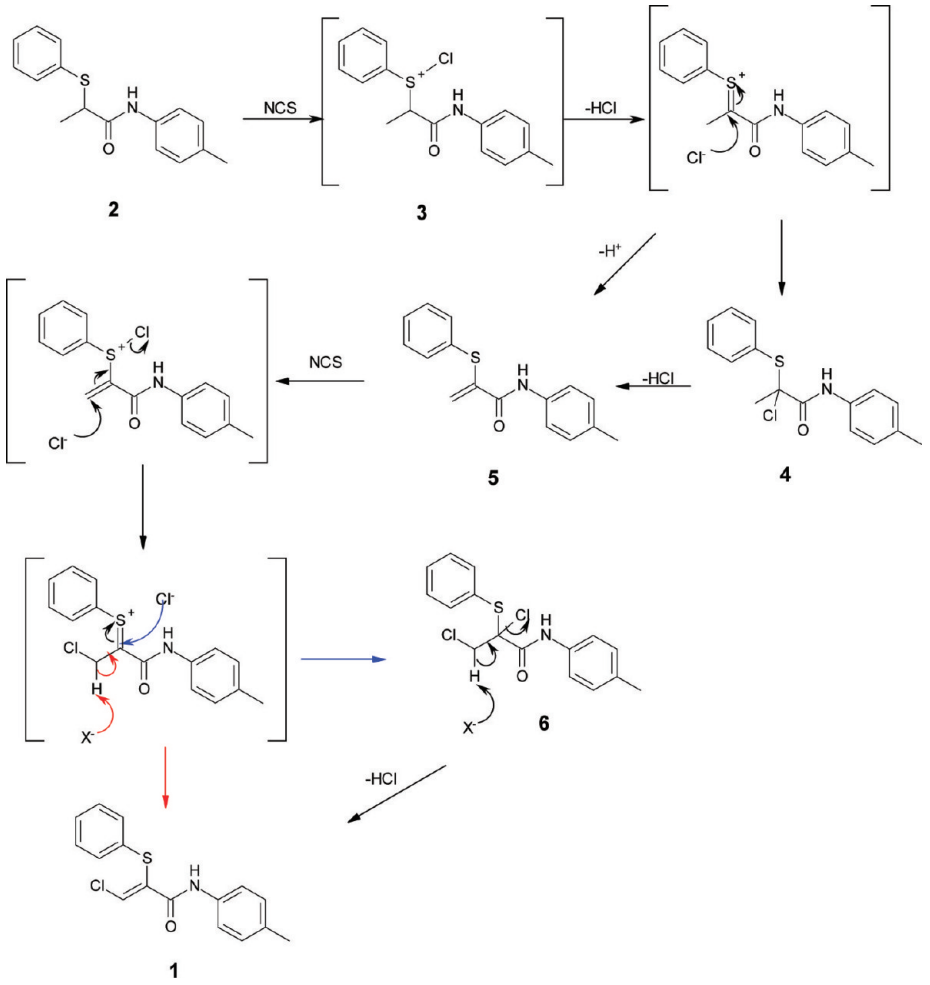
Scheme 1. Mechanism Proposed by Maguire et al.



investigated. Reactions normally run under high temperature and pressure conditions, as well as heterogeneous systems, present challenges to traditional NMR monitoring in tubes. Another issue associated with reactions conducted in conventional NMR tubes is the delay in acquiring the initial spectrum in a series due to the necessity of locking, shimming, etc., which can be restrictive in the case of rapid onset of reaction. Although physical solutions to this problem have been devised,[26−28] some drawbacks still remain. A number of flow NMR reaction monitoring instrumental setups have been reported in recent years, which couple the reaction vessel to the spectrometer via transfer lines.[9,29−31]

Here we present the use of a combination of traditional tube based NMR, online flow NMR, and IR reaction monitoring, to aid the mechanistic elucidation of a multicomponent reaction cascade, identifying and monitoring reactive intermediates involved in the conversion of α-thioamides to α-thio-β-chloroacrylamides.

RESULTS AND DISCUSSION

A report by Maguire et al. on the generation of α-phenylthio-β-chloroacrylamides via the chlorination of α-thioamide precursors[32] was followed by a subsequent publication that included a proposed mechanism for the formation of the β-chloroacrylamide product **1** from thioamide **2**, involving multiple intermediates shown in Scheme 1.[33] Some of these intermediates (**5**, as well as the labile compounds **4** and **6**) were isolated from the reaction mixture by tailoring the reaction conditions to enhance the production of a particular compound in the cascade, which was then characterized offline. Some of the transient species (e.g., **3**) in the mechanistic sequence could not be isolated or observed spectroscopically in the original study. This reaction provided a potential multicomponent process with which to demonstrate the unique capabilities that reactNMR and reactIR provide, both in terms of reaction monitoring and structural elucidation of reactive intermediates.

NMR spectroscopy is of particular use in monitoring the progress of reactions (in particular this reaction cascade), as not only does this method provide inherent quantitation, but it also provides detailed structural identification of the intermediates involved. A number of distinct resonances displayed by each component in solution also allows for excellent selectivity, especially when the reaction mixture contains a complex mixture of starting material, intermediates, and product. These features mean that reactNMR has a number of advantages over other reaction monitoring techniques, including IR, HPLC, and UV, which provide a dearth of structural information and require calibration in order to achieve truly quantitative data. However, the authors do acknowledge that the lifetime of certain reactive intermediates means that their detection cannot be observed on the NMR time-scale. Also a lack of sensitivity is associated with the use of NMR, but monitoring of flowing solutions means that increased concentration of species is possible as a method of addressing this issue.

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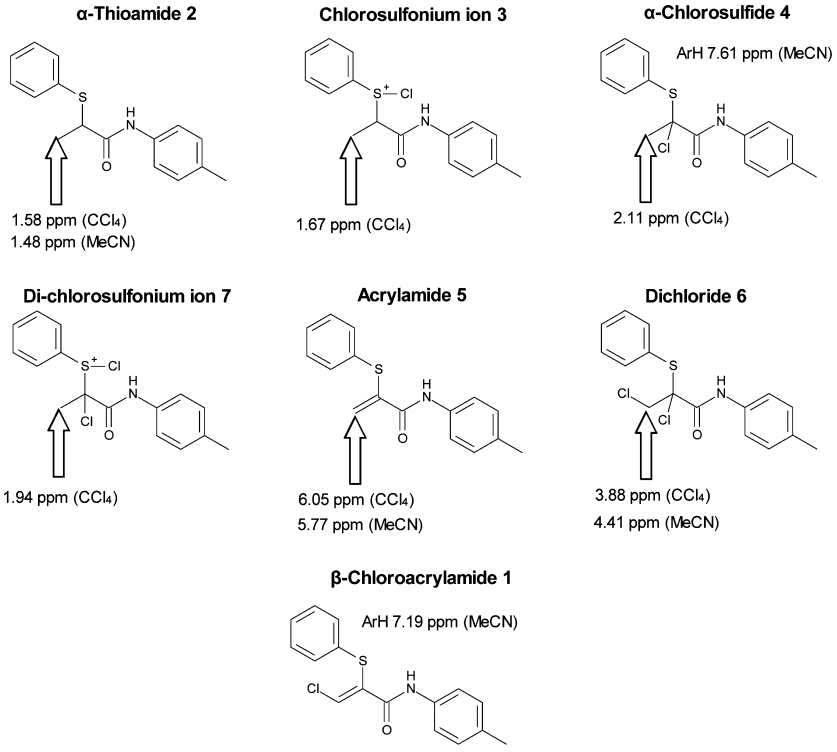
Scheme 2. ^{1}H NMR Resonances Used for ReactNMR Reaction Monitoring in CCl_4 and MeCN



Spectra recorded in CCl_4, signals are referenced to DCE singlet at δ_H 3.68 ppm
Spectra recorded in MeCN, signals are referenced to MeCN singlet at δ_H 1.94 ppm

Reaction monitoring using this technique does not require the use of isotope labeled compounds or deuterated solvents, which has cost and time benefits for the synthetic organic chemist, allowing increased mechanistic information to be gained using regular unlabeled materials. Thus the need to revisit the synthesis with expensive labeled material to obtain this information is obviated. This also has application in the area of process development, where advanced synthetic intermediates involving multiple steps would need to be synthesized with isotopic labels, delaying progress; again, reactNMR eliminates this inconvenience. With the reactor and flow NMR experimental setup outlined here, reactions may be monitored on kilogram scale, without prohibitive reagent costs.

Preliminary work was conducted in toluene-d_8 using 1.95 equiv of *N*-chlorosuccinamide (NCS), as these were the optimum conditions described by Maguire et al.[33] Prior to performing this reaction in flow, an initial investigation in an NMR tube enabled characterization of the starting materials in toluene-d_8, as well as the viability of observing components of the reaction mixture. A number of intermediates were identified, and distinct characteristic resonances were assigned to these compounds; however, many of these overlapped with those of the reaction solvent, particularly in the aromatic region of the spectrum. With the ultimate goal of conducting this reaction in nondeuterated solvents on a larger scale, this overlap proved to be too restrictive. While multiple resonance WET solvent suppression could be achieved, this would have resulted in decreased signal intensity in these regions, giving nonquantitative data. Therefore, the choice of reaction solvent has implications for which areas of the spectrum become unusable as analytical handles for reaction monitoring, and to overcome this constraint a different solvent system was used in subsequent investigations.

In the publication on this transformation by Maguire et al.,[33] carbon tetrachloride was used as an alternative solvent to toluene. This has a distinct advantage from an NMR standpoint, as the use of a ^{1}H NMR transparent solvent would greatly enhance the clarity of the spectra under investigation, allowing for any subtle changes in the composition of the reaction mixture to be observed, and therefore it was decided to conduct further investigations in this solvent. In the current work, initial characterization of the starting α-thioamide **2** in carbon tetrachloride was carried out in a 5-mm NMR tube, with one drop of 1,2-dichloroethane (DCE) added as a reference signal, which was set at δ_H 3.68 ppm.

In an attempt to observe all of the components of the reaction cascade, the reaction was conducted at 25 °C in carbon tetrachloride. The progress of the reaction was monitored by ^{1}H NMR at 10 s intervals, with an acquisition of 4 scans. Once the species were observed in the reaction mixture, each entity was characterized by conducting a number of homo- and heteronuclear 2D NMR experiments (^{1}H COSY, ^{1}H−^{13}C HSQC, ^{1}H−^{13}C HMBC) offline in a 5-mm NMR tube. The component of interest was formed to its maximum level, at which time the 2D experiments were recorded. The characterization of each observable compound is reported in the Experimental Section, and the individual characteristic resonances used for reaction monitoring in carbon tetrachloride and subsequently in acetonitrile are shown in Scheme 2.

A stacked plot of the ^{1}H NMR spectra recorded as the reaction proceeded is shown in Figure 1. This shows that the α-thioamide starting material **2** began to be consumed within 16 min of NCS addition to the amide solution; this was tracked by

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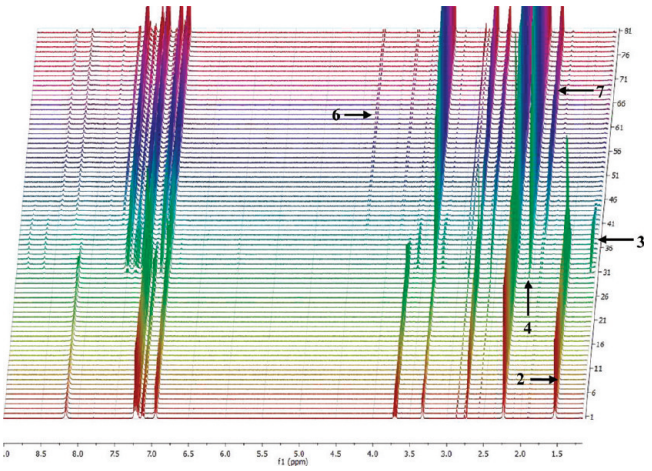

Figure 1. ^{1}H NMR reaction profile in carbon tetrachloride at 25 °C. α-Thioamide **2**, chlorosulfonium ion **3**, α-chlorosulfide **4**, Dichloride **6**, dichlorosulfonium ion **7**.

monitoring the doublet for the methyl group of **2** at δ_H 1.58 ppm. A possible explanation for this delay will be outlined later. As can be seen in Figure 2, the solubility of NCS in CCl_4 reaches a maximum at 15 min and during this time no reaction is observed. The consumption of α-thioamide **2** occurs rapidly once the NCS level in solution decreases and the reaction cascade begins. Following this the level of NCS in solution increases slowly due to a slow down in its consumption. The signals pertaining to the methylene signal of NCS were observed as a singlet at δ_H 2.80 ppm, but due to the low solubility of NCS in CCl_4 at room temperature this signal represented the amount of NCS in solution. The succinimide byproduct of the reaction, also of low solubility, appeared at δ_H 2.63 ppm as the reaction proceeded.

As the α-thioamide **2** was consumed, appearance of a new set of signals was observed. Two separate doublets at δ_H 1.28 and 1.67 ppm emerged simultaneously as the reaction progressed. These have been assigned as the diastereomeric methyl signals, resulting from the formation of a new stereogenic center in the chlorosulfonium ion **3**, by chlorination of sulfur. The corresponding methine protons, alpha to the chlorosulfonium moiety, were observed at δ_H 3.33 and 3.67 ppm, while two diastereomeric NH resonances were also present at δ_H 8.70 and 8.92 ppm in the proton NMR spectrum (Figure 3). During

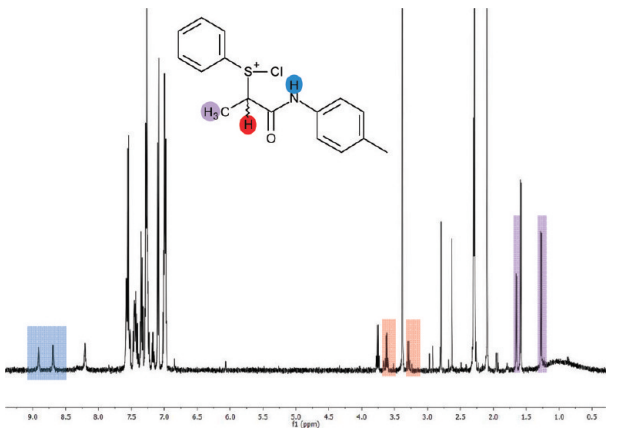

Figure 3. ^{1}H NMR spectrum of chlorosulfonium ion intermediate **3**.

characterization of this intermediate, a ^{1}H−^{13}C HSQC experiment revealed the corresponding carbon-13 signals for the methine carbons at δ_C 61.6 ppm, which correlated to a proton at δ_H 3.67 ppm. A diastereomeric resonance at δ_C 62.8 ppm, with the corresponding proton at δ_H 3.33 ppm was also observed. These values compare favorably with those reported

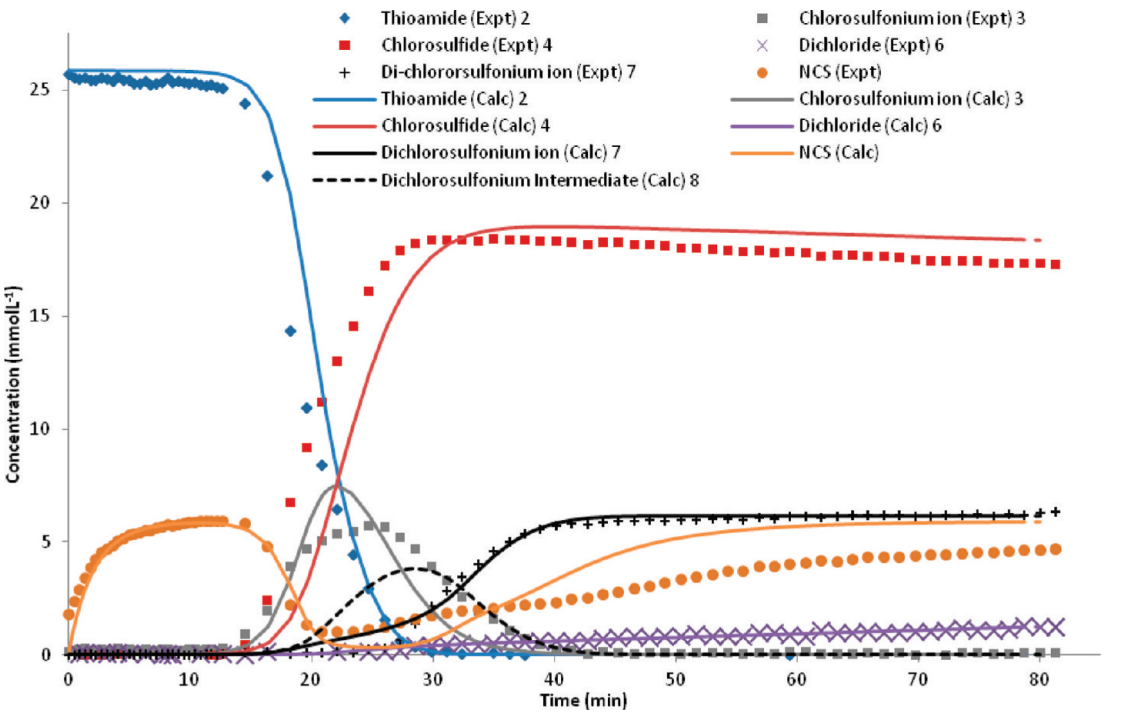

Figure 2. Reaction profile in carbon tetrachloride at 25 °C. Experimental data are displayed as symbols and the corresponding computationally optimized data are displayed as solid lines.

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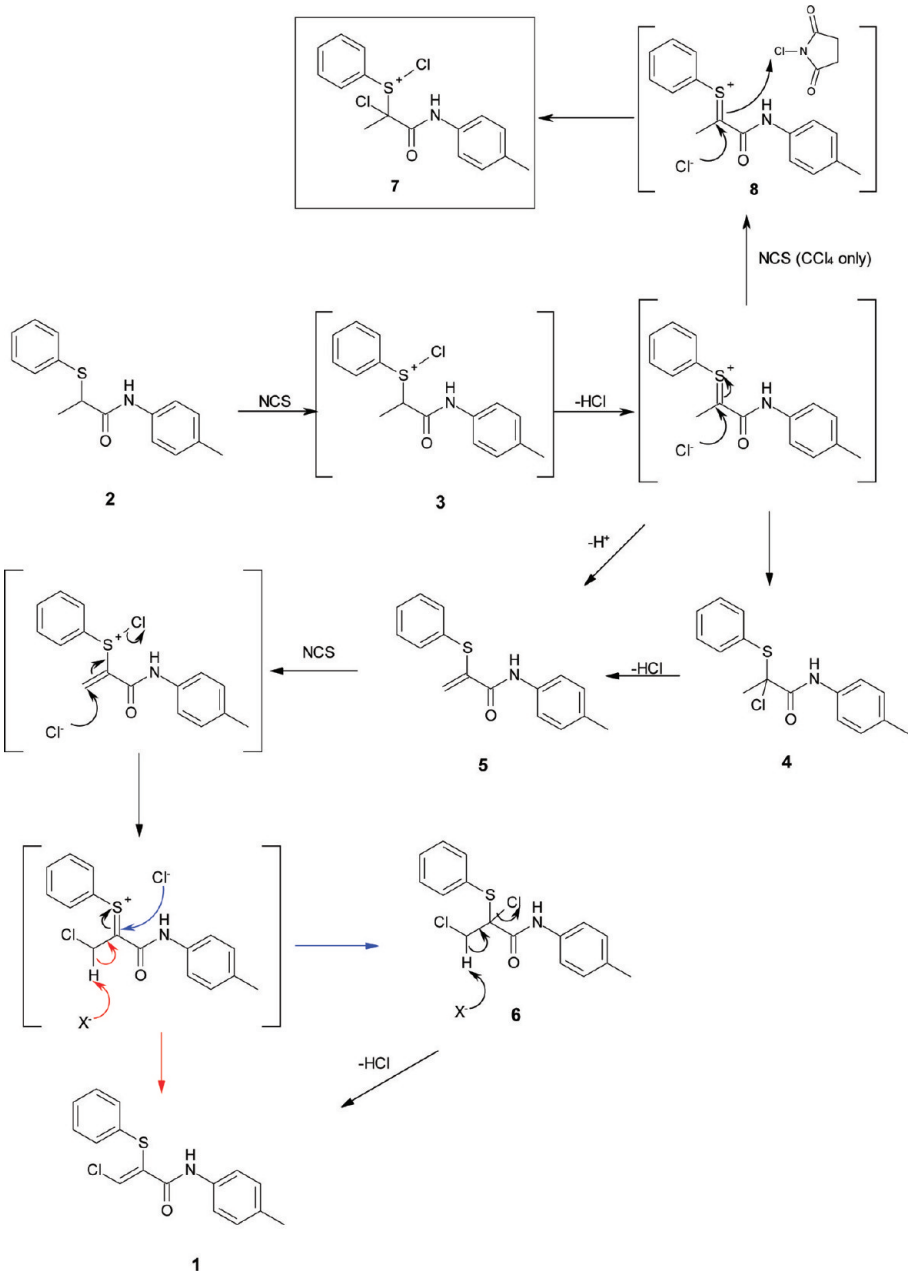
Scheme 3. Revised Mechanism



by Liu and Vederas, who report a downfield shift in chlorosulfonium ion methylene carbons adjacent to sulfur to δ_C ~66 ppm.[34] The methyl signals at δ_H 1.28 and 1.67 ppm corresponded to carbon signals at δ_C 9.3 and 14.3 ppm, respectively. Chlorosulfonium ion species have been reported previously in the literature as intermediates in the NCS mediated chlorination of sulfides[35] and was hence proposed as an intermediate in the cascade by Maguire. This current work provides spectroscopic evidence for the intermediacy of this species in the reaction pathway. This intermediate was detected by ^{1}H NMR only when the reaction was conducted in carbon tetrachloride, while experiments using toluene or acetonitrile as the solvent showed no detectable evidence for this transient species. This will be discussed below.

At steady state, the chlorosulfonium intermediate **3** is present only at low levels in the reaction mixture (~22 mol %); its rapid conversion through to the α-chlorosulfide **4** is evident, as the presence of **3** coincides with the appearance of the methyl resonance for **4** at 2.11 ppm. A decrease in the level of this methyl signal related to **4** is observed in the ^{1}H NMR spectrum once the chlorosulfonium ion is consumed, demonstrating that this ion is a precursor to α-chlorosulfide **4** formation, and **4** undergoes subsequent transformations. This is demonstrated graphically in Figures 1 and 2. Because **4** proved to be labile on isolation,[33] its characterization was incomplete, and therefore in situ "stopped flow" 2D NMR experiments, as well as offline NMR tube spectra, aided in the complete ^{1}H and ^{13}C NMR structural assignment.

The next intermediate in the cascade, the acrylamide **5**, had been isolated and structurally characterized in the original study,[33] employing just 1 equiv of NCS. In the current in situ study, elimination of HCl from α-chlorosulfide **4** provided acrylamide **5**, although interestingly, this could only be detected at very low levels in the ^{1}H NMR spectrum. From the

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Chart 1

Amide **2** + NCS	⟶	Chlorosulfonium ion **3**	$k_1 = 5.23 \times 10^{-1}$ Lmol^{-1}s^{-1}
Chlorosulfonium ion **3**	⟶	Intermediate **8**	$k_2 = 1.40 \times 10^{-3}$ s^{-1}
Intermediate **8** + NCS	⟶	Di-chlorosulfonium ion **7**	$k_3 = 2.20$ Lmol^{-1}s^{-1}
Chlorosulfonium ion **3**	⟶	α-Chlorosulfide **4**	$k_4 = 4.36 \times 10^{-3}$ s^{-1}
Chlorosulfonium ion **3**	⟶	Acrylamide **5**	$k_5 = 7.72 \times 10^{-5}$ s^{-1}
α-Chlorosulfide **4**	⟶	Acrylamide **5**	$k_6 = 1.43 \times 10^{-5}$ s^{-1}
Acrylamide **5** + NCS	⟶	Dichloride **6**	$k_7 = 1.35$ Lmol^{-1}s^{-1}

experiments conducted in this work, it was observed that the chlorination steps occur rapidly, while the rate of elimination to form vinylic moieties is much slower. This explains why the acrylamide **5** does not build to significant levels in the reaction mixture, as it is quickly transformed via the second NCS mediated chlorination to the dichloride **6**. The acrylamide intermediate **5**, which is formed preferentially when 1 equiv of NCS is employed, could also be detected and characterized with 2D NMR experiments.

When carbon tetrachloride was employed as the reaction solvent, a byproduct formed as the reaction progressed. This species, tentatively identified as dichlorosulfonium ion **7** (Scheme 3), which coincided with the total consumption of starting amide, appeared to be diastereomeric in nature. As was described earlier for the chlorosulfonium ion **3**, a doubling of isolated resonances was noted in the ^{1}H NMR and ^{1}H−^{13}C HMBC spectra. Two methyl singlets at δ_H 1.93 and 1.94 ppm displayed two bond ^{1}H−^{13}C coupling to separate tetrasubstituted carbons at δ_C 82.8 and 84.4 ppm. Long-range coupling to the carbonyl carbon at δ_C 161.9 ppm was also observed, although it could not be determined definitively if this was composed of two unique correlations due to resolution limitations in the HMBC experiment.

On examination of the experimental reaction profile (Figure 2), it appears that this dichlorosulfonium species **7** is derived from **3**. Signals for the chlorosulfonium ion **3** and dichlorosulfonium ion **7** were detected only in carbon tetrachloride and were not seen in toluene-d_8 or acetonitrile. This implies that the lifetime of the chlorosulfonium ion **3** is much shorter in either toluene or acetonitrile than in carbon tetrachloride. As the characteristic resonance of the dichlorosulfonium ion **7** would be suppressed in experiments conducted in protonated acetonitrile (both at δ_H 1.94 ppm), a control experiment was carried out in acetonitrile-d_3, where no evidence for the chlorosulfonium **3** or dichlorosulfonium ion **7** was observed. Thus, the relative rates of the elimination process from the chlorosulfonium ion **3** and the second chlorination to the dichlorosulfonium ion **7** are solvent-dependent, presumably due to differences in polarity. Once formed, the dichlorosulfonium ion **7** is not transformed further through the cascade and therefore results in a reduction in overall yield. In the publication by Maguire et al. the transformation was conducted at various temperatures.[33] There, it was reported that at 20 °C reaction progress was sluggish, producing only mixtures of the acrylamide **5** and dichloride **6** after 48 h. This indicates that in carbon tetrachloride at lower temperatures a second chlorination of the chlorosulfonium ion **3** is a significant competing pathway. A combination of factors support this hypothesis: byproduct formation begins once starting material consumption is complete; as conversion to the acrylamide **5** is a rate-determining step, therefore the second equivalent of NCS can react with the chlorosulfonium ion **3**. Upon isolation of the reaction mixture, labile intermediate **7** was not observed.

The experiment conducted in carbon tetrachloride provided definitive evidence for the early part of the reaction cascade, from sulfide **2** to chlorosulfide **4**, to acrylamide **5**, to dichloride **6**, with the chlorination steps proceeding more rapidly than the elimination steps. Elevated temperatures (40 °C) in carbon tetrachloride were used in attempts to form and monitor the final compound in the cascade, the *β*-chloroacrylamide **1**. However, this increase in temperature resulted in significant broadening of signals in the recorded proton NMR spectra, therefore data at this temperature could not be used.

The data generated from the experiment conducted in carbon tetrachloride was subjected to reaction modeling analysis, which showed that while the chlorosulfonium ion **3** is converted to the *α*-chlorosulfide **4**, a competing pathway was the formation of the dichlorosulfonium ion **7**. The delayed onset of **7** suggests that an experimentally unobserved intermediate **8** is involved in its formation, and this is represented in the model.

A computationally optimized model was fit to the experimental data (Figure 2) to calculate rate constants for each of the steps involved in the reaction cascade detailed in Chart 1.

A second experiment was conducted in an attempt to observe conversion of the dichloride **6** to the *β*-chloroacrylamide product **1**. In order to achieve this final transformation, an elevated temperature (>40 °C) was required to promote HCl elimination at a rate sufficient for effective monitoring. The progress of the reaction was monitored by ^{1}H NMR (Figure 4) and now included simultaneous in-line IR monitoring to provide a mobile analytical tool that can easily be moved from lab to lab for subsequent reaction monitoring. The IR bands were assigned to the individual reaction components using a combination of the ConcIRT software and the trend plot assignments obtained from the NMR. A typical IR trend plot is shown in Figure 5, and while the IR was not capable of detecting all of the components in the reaction mixture, it provided sufficient data to monitor the reaction progression. A number of stopped flow solvent suppressed 2D NMR experiments were also recorded throughout the experiment. In an attempt to circumvent the issues outlined previously with loss of line shape in carbon tetrachloride, the process was repeated in acetonitrile. A fully protonated solvent was used on this occasion, therefore WET solvent suppression was applied to each 1D and 2D spectrum acquired. Figure 6 illustrates the trend plots obtained from the on-flow ^{1}H NMR spectra of the

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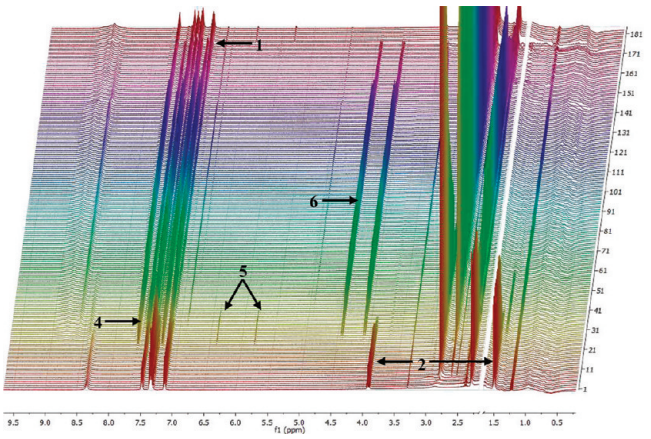

Figure 4. ^{1}H NMR reaction profile in acetonitrile. The solvent suppressed region of the spectra has been removed for clarity. *α*-Thioamide **2**, *α*-chlorosulfide **4**, acrylamide **5**, dichloride **6**, *β*-chloroacrylamide **1**.

reaction. Acquisition of the 2D data during the reaction resulted in gaps in the ^{1}H NMR derived spectral trend plots.

As was used in the experiment conducted in carbon tetrachloride, 1.95 equiv of NCS was added to an acetonitrile solution of the *α*-thioamide **2** at 25 °C, and again a delayed reaction onset was observed. The reaction mixture was stirred at this temperature for 5 h, before being heated to 45 °C for the latter stages of the process. While the cascade proceeded in a similar manner as outlined in carbon tetrachloride, a number of differences were identified. As the starting amide **2** was consumed, the *α*-chlorosulfide **4** was generated, although the chlorosulfonium ion precursor **3** that was observed previously in carbon tetrachloride was not detected in acetonitrile. The doublet representing the methyl signal of **2** at δ_H 1.48 ppm was utilized for reaction monitoring purposes. The methyl resonance for the *α*-chlorosulfide **4** could not be integrated, as it was affected by the solvent suppression applied to the acetonitrile singlet at δ_H 1.94 ppm. Instead, the aromatic proton resonance at δ_H 7.61 ppm was tracked to monitor its progression. The chlorosulfide formed to a maximum of approximately 50 mol %, limited by its conversion to the acrylamide **5**. The elimination of HCl from *α*-chlorosulfide **4** to form acrylamide **5** was detected at low levels for an initial period, before further chlorination resulted in rapid conversion to the dichloride **6**. The acrylamide **5** was identified by characteristic terminal alkene resonances at δ_H 5.77 and 6.37 ppm. It was also noted that the level of acrylamide increased toward the end of reaction monitoring, as the remaining NCS is consumed, thereby reducing the rate of further chlorination.

As was outlined earlier, no evidence for the formation of the dichlorosulfonium ion **7** was found when acetonitrile was used as the reaction solvent.

A delay in the reaction onset was observed in the transformations conducted in CCl_4 and acetonitrile, which suggests that some form of activation of the NCS is involved, possibly activated by HCl that is produced as the reaction proceeds. This hypothesis was supported by a slow pH drop once NCS was added, followed by a rapid pH drop once consumption of the amide starting material commenced. Since HCl is liberated as part of the reaction mechanism, this pH drop was expected. In another experiment conducted to confirm that HCl decreased the induction period, it was noted that addition of 1 drop of conc HCl to the reaction mixture immediately triggered the reaction cascade. In separate experiments conducted in both CCl_4 and acetonitrile, a reverse addition (stirring NCS in the reaction solvent for 25 min prior to addition of the amide **2**) also resulted in a faster reaction initiation (see Supporting Information).

Formation of the dichloride **6** was observed at 25 °C and reached maximum concentration after 5 h. The integral for the AB quartet signal for the diastereotopic methylene protons at δ_H 4.07 and 4.41 ppm was utilized to monitor its concentration in the reaction medium over time. The flow was stopped temporarily to record a ^{1}H−^{13}C HSQC of the reaction mixture (Figure 7), providing in situ proton−carbon correlations for the dichloride **6**, which could not be isolated for complete characterization in previous studies.[33] A second HSQC provided proton−carbon correlations for the acrylamide **5**, which formed at a minor level in the reaction mixture. The flow was restarted once the 2D acquisitions were complete, and reaction monitoring was continued.

In order to push the reaction cascade to completion, the temperature of the system was increased to 45 °C. The aromatic resonance at δ_H 7.19 ppm was used to monitor the formation of the final product in the cascade, **1**. The temperature rise increased the rate of HCl elimination from the dichloride **6** furnishing the *β*-chloroacrylamide **1**, which was complete after 12 h at elevated temperature, mirroring the

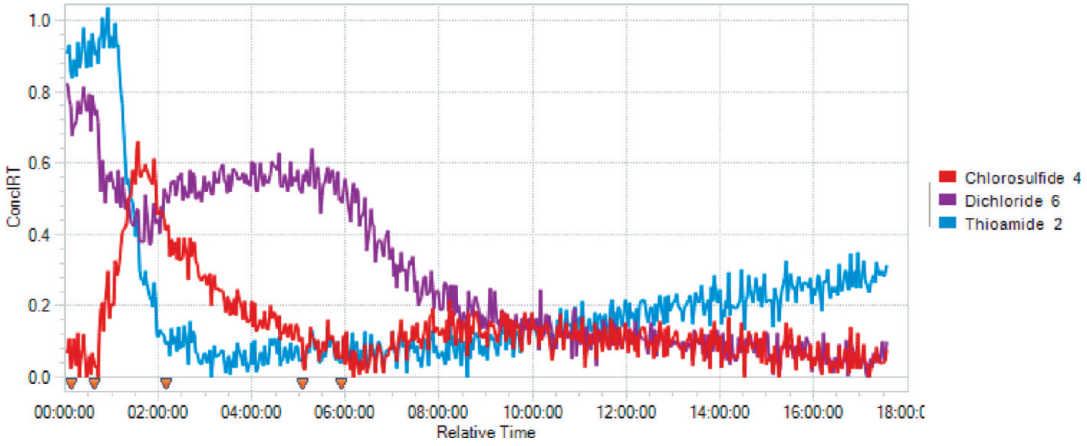

Figure 5. Plot of IR data showing reaction components over time (hours).

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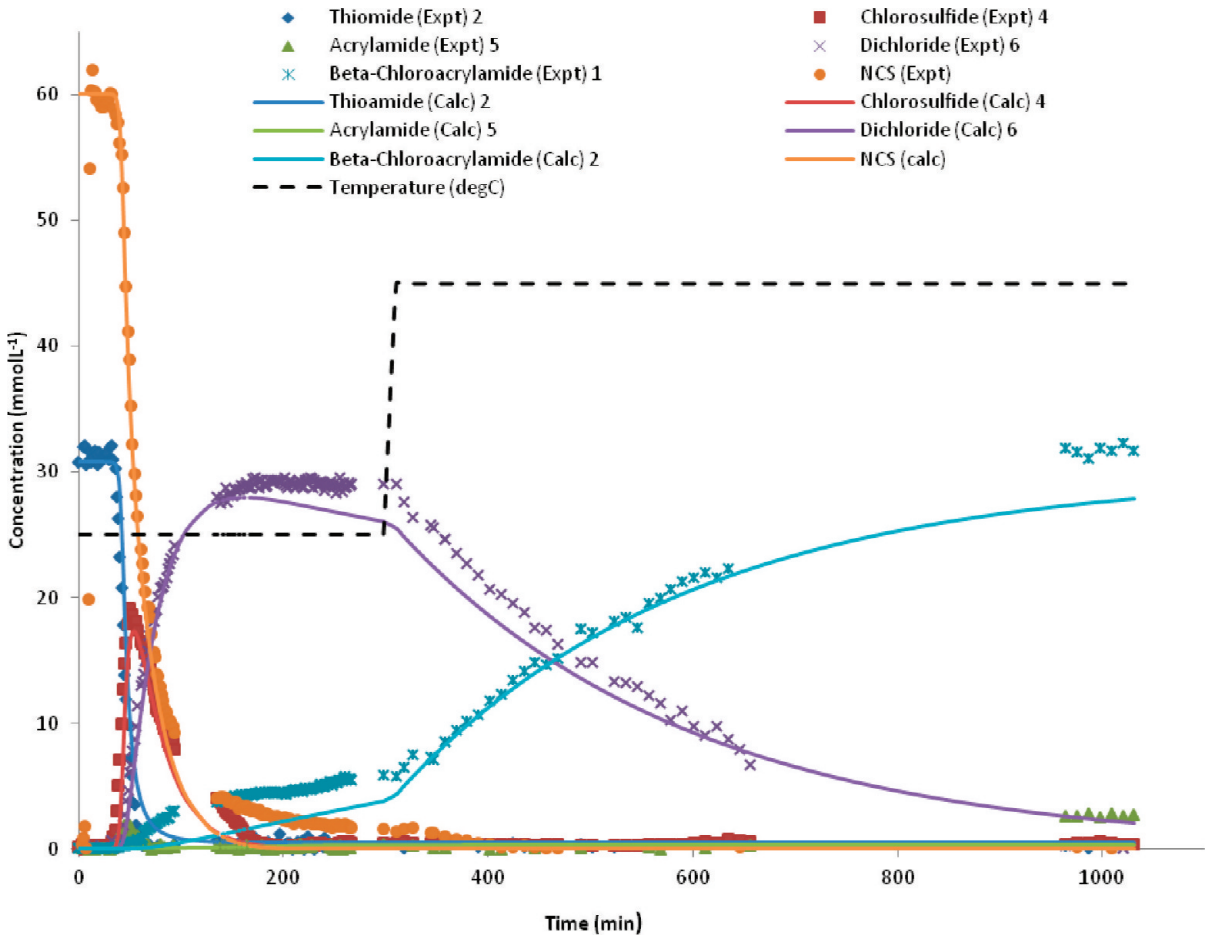

Figure 6. Plot of component concentration versus time for the reaction of NCS with thioamide **2** in acetonitrile. Experimental data are displayed as symbols, and the corresponding computationally optimized data are displayed as solid lines. Gap in data between 650 and 950 min due to 2D NMR acquisitions.

observation from the original synthetic work. Again, a computationally optimized model was fit to the experimental (Figure 6) to calculate rate constants for each of the steps involved in the reaction cascade detailed in Chart 2.

It should be noted that the lack of agreement for the experimental and calculated trends for the β-chloroacrylamide product **1** in the later time points is due to tuning changes in the NMR.

The use of data rich detection was critical in making structural assignments, and the quantitative nature of NMR spectroscopy provided accurate concentrations used to determine the reaction rates. The quantitative and qualitative results were combined from the reaction in acetonitrile and carbon tetrachloride, giving a full picture of the mechanism described in Scheme 3.

CONCLUSION

This study clearly illustrates the power of monitoring complex multistep reaction sequences via ReactNMR and ReactIR, enabling direct observation of each of the intermediates including those that are too labile to isolate. Mechanistic insight is gained through the reaction profile, which shows the relative rates at which each of the intermediates is formed and consumed. Specifically in relation to this reaction cascade, direct determination of the spectroscopic features of the chlorosulfonium ion was enabled for the first time in over 15 years of research. While this intermediate is widely accepted in chlorination of sulfides, there have been very few reports of spectroscopic characterization of these intermediates. Furthermore this NMR study provided evidence for the first time of the formation of the dichlorosulfonium ion as a "cul-de-sac" side reaction in the overall reaction cascade, having clear implications in terms of yield reduction.

EXPERIMENTAL SECTION

The apparatus used (Figure 8) was a multiport 100-mL HEL AutoLAB jacketed reaction vessel, which was fitted with an overhead stirrer, temperature probe, nitrogen flow line, and inlet and outlet ports for the sample transfer lines. The transfer lines from the reactor to the spectrometers consisted of 1/16 in. o.d. polytetrafluoroethylene (PTFE) tubing with 0.2 mm i.d. These were contained within thermostatically controlled temperature regulation lines, containing Syltherm as the heat transfer fluid. A hastelloy frit was attached to the base of the outlet transfer line to filter any solids from the reaction mixture, preventing them from reaching the flow cell. The reaction mixture was pumped through the transfer line by a Knauer pump (Preparative Pump 1800) to the flow cell and returned to the reactor vessel, thus maintaining the composition of the reactor. The flow rate was 1.5 mL min^{-1} with a total volume of less than 3 mL removed from the reactor at any time. It was determined that this flow rate was appropriate for this flow probe configuration to ensure ^{1}H integral intensities were not biased by inadequate polarization. Parameters such as temperature, pressure, stir rate, and rate of addition of reagents may be controlled through the HEL software.

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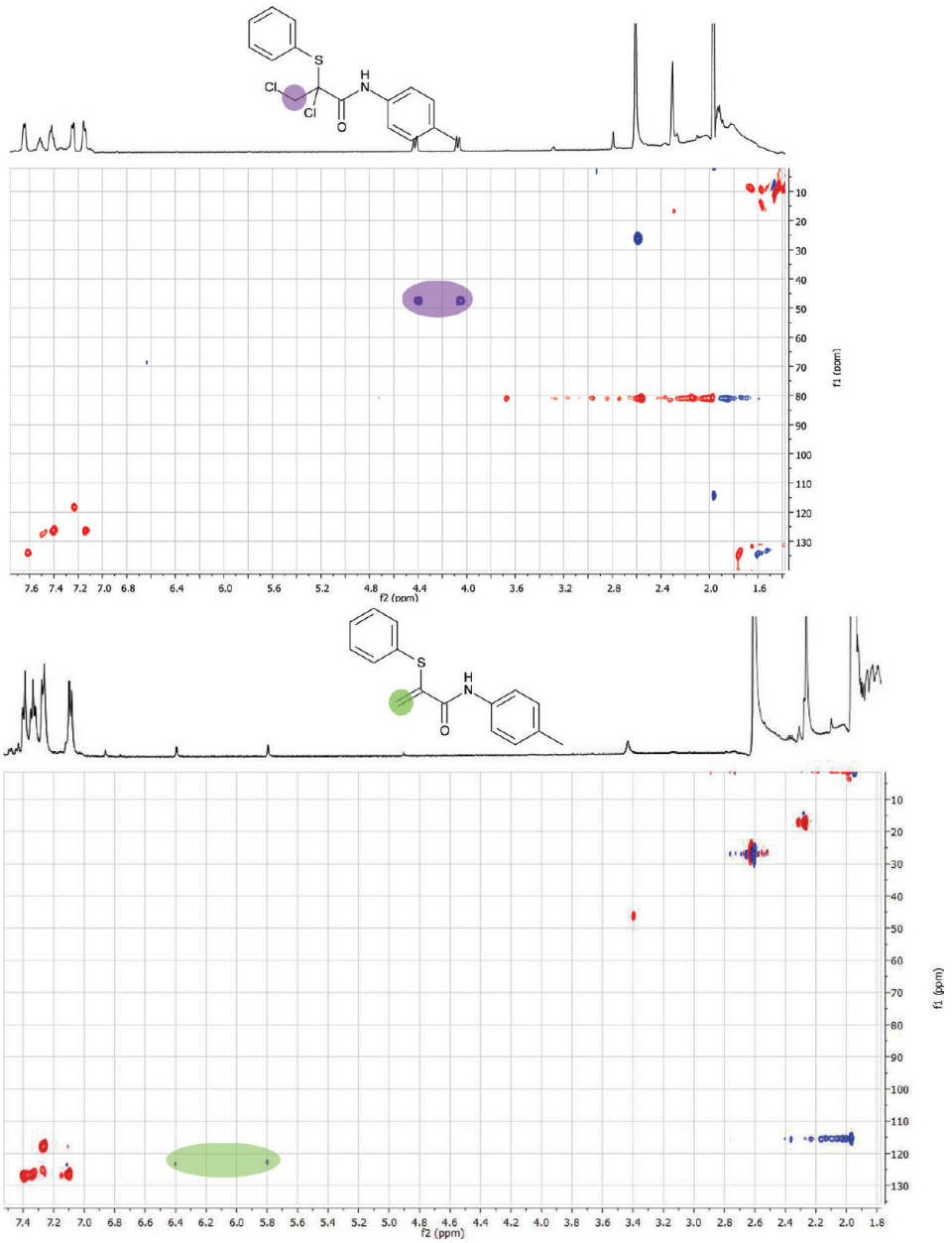

Figure 7. Stopped flow $^{1}H-^{13}C$ HSQC spectra of dichloride **6** and acrylamide **5** as a minor component in the reaction mixture.

Chart 2

Amide **2** + NCS	⟶ α-Chlorosulfide **4**	$k_1 = 5.43 \times 10^{-2}$ $Lmol^{-1}s^{-1}$
α-Chlorosulfide **4**	⟶ Acrylamide **5**	$k_2 = 6.37 \times 10^{-4}$ s^{-1}
Acrylamide **5** + NCS	⟶ Dichloride **6**	$k_3 = 5.45$ $Lmol^{-1}s^{-1}$
Dichloride **6**	⟶ β-Chloroacrylamide **1**	$k_4 = 1.02 \times 10^{-5}$ s^{-1}

Proton NMR and stopped flow WET suppressed standard 2D NMR experiments on the reaction mixture were acquired using a Bruker 500 MHz Avance III spectrometer, with a custom flow BBFO probe containing a 240-μL flow cell. Tube reactions and material characterization were carried out in 5 mm NMR tubes, using a Bruker 600 MHz Avance III equipped with cryoprobe. NMR spectra were recorded unlocked, and acetonitrile was injected into the flow cell to obtain a shim set prior to beginning the experiment. NMR spectra recorded in carbon tetrachloride were spiked with 1−2 drops of dichloroethane to provide a chemical shift reference, which was set at δ_H 3.68 ppm and δ_C 43.2 ppm. NMR spectra recorded in acetonitrile-d_3 were referenced at δ_H 1.94 ppm and δ_C 118.7 ppm. Topspin 2.1 was used to acquire and process the NMR data. Shimming was conducted using Topshim. IR spectra were obtained using Metler Toledo ReactIR 4000 and processed using iC IR, with ConcIRT enabled to assist in monitoring the change in concentration of components (version 4.4.26). A custom hastelloy and PEEK flowcell was attached to the ReactIR lightpipe to provide IR spectra on the flowing reaction stream.

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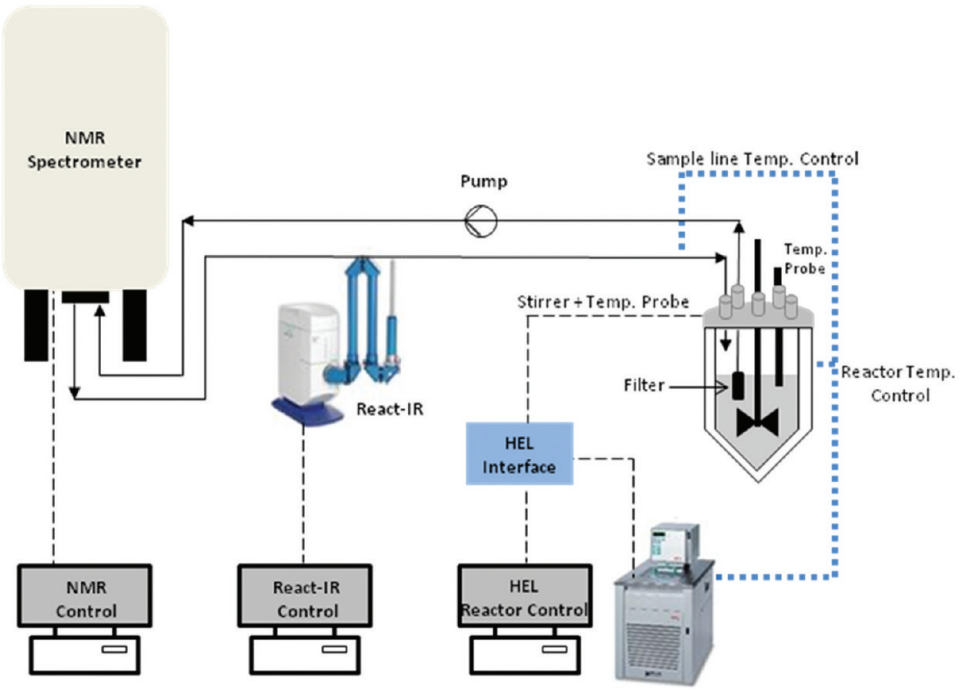

Figure 8. Schematic representation of ReactNMR configuration.

NMR data was processed and analyzed using Mnova NMR (Mestrelab Research) data analysis package, and the data produced was then imported into DynoChem (version 3.3.0.0) for computational analysis and Microsoft Excel to produce graphical output.

Acetonitrile (99.9%, Acros) and carbon tetrachloride (99.5%, Aldrich) were used as the reaction solvents. The sample of *N*-4′-methylphenyl-2-(phenylthio)propanamide was supplied by the Maguire group.

In Flow Reaction NMR and IR Monitoring of the NCS Chlorination of *N*-4′-Methylphenyl-2-(phenylthio)-propanamide 2. *Carbon Tetrachloride as Reaction Solvent.* *N*-4′-Methylphenyl-2-(phenylthio)propanamide **2** (0.50 g, 1.85 mmol) was dissolved in carbon tetrachloride (70 mL) and was stirred at room temperature under an atmosphere of nitrogen. The solution was pumped to the NMR spectrometer at a flow rate of 1.5 mL/min, and a ^{1}H NMR spectrum was recorded of the α-thioamide **2**. NCS (0.49 g, 3.60 mmol) was then added to the solution in one portion. The progress of the reaction was monitored by ^{1}H NMR at 10 s intervals with an acquisition of 4 scans. The reaction mixture was stirred at 25 °C for 1.5 h.

Acetonitrile as Reaction Solvent. *N*-4′-Methylphenyl-2-(phenylthio)propanamide **2** (0.71 g, 2.62 mmol) was dissolved in acetonitrile (88 mL) and was stirred at room temperature under an atmosphere of nitrogen. The solution was pumped to the NMR spectrometer at a flow rate of 1.5 mL/min and a ^{1}H NMR spectrum was recorded of the α-thioamide **2**. NCS (0.69 g, 5.10 mmol) was then added to the solution in one portion. The progress of the reaction was monitored by ^{1}H NMR at 30 s intervals with an acquisition of 8 scans. The reaction mixture was stirred at 25 °C for 5 h. The temperature of the system was then increased to 45 °C, and the progress of the reaction was again monitored by ^{1}H NMR at 10 min intervals, with an acquisition of 8 scans.

***N*-4′-Methylphenyl-2-(phenylthio)propanamide 2.** ^{1}H NMR (600 MHz, CCl_4, δ) 1.58 [d, J = 7.3 Hz, 3H, C(3)H_3], 2.29 [s, 3H, C(4′)CH_3], 3.76 [q, J = 7.2 Hz, 1H, C(2)H], 7.01 [d, J = 7.6 Hz, 2H, 2 × C(3′)H], 7.11−7.38 (m, 7H, ArH), 8.28 (br s, 1H, NH); ^{13}C NMR (151 MHz, CCl_4, δ) 18.7 (C-3), 21.6 [C(4′)CH_3], 48.0 (C-2), 119.9 (2 × C-2′), 127.8 (aromatic CH), 129.8 (2 × C-3′), 129.9, 130.7 (4 × aromatic CH), 133.5 (C-4′), 134.3 (quaternary aromatic C), 136.0 (C-1′), 168.5 (C═O).

Chlorosulfonium Ion 3. *Isomer A.* ^{1}H NMR (600 MHz, CCl_4, δ) 1.66 [d, J = 7.4 Hz, 3H, C(3)H_3], 3.33 [q, J = 7.4 Hz, 1H, C(2)H]; ^{13}C NMR (151 MHz, CCl_4, δ) 14.3 (C-3), 62.6 (C-2), 164.7 (C═O).

Isomer B. ^{1}H NMR (600 MHz, CCl_4, δ) 1.28 [d, J = 7.2 Hz, 3H, C(3)H_3], 3.67 [q, J = 7.2 Hz, 1H, C(2)H]; ^{13}C NMR (151 MHz, CCl_4, δ) 9.3 (C-3), 61.5 (C-2), 163.1 (C═O).

***N*-4′-Methylphenyl-2-chloro-2-(phenylthio)propanamide 4.** ^{1}H NMR (600 MHz, CCl_4, δ) 2.11 [s, 3H, C(3)H_3], 2.31 [s, 3H, C(4′)CH_3], 7.01 [d, J = 8.1 Hz, 2H, 2 × C(3′)H], 7.11 [d, J = 8.3 Hz, 2H, 2 × C(2′)H], 7.28 (m, 2H, 2 × ArH), 7.37 (t, 1H, J = 7.3 Hz, ArH), 7.56 (d, J = 8.1 Hz, 2 × ArH), 7.59 (br s, 1H, NH); ^{13}C NMR (151 MHz, CCl_4, δ) 21.6 [C(4′)CH_3], 29.9 (C-3), 79.9 (C-2), 120.0 (2 × C-2′), 129.7 (2 × aromatic CH), 129.8 (aromatic CH), 130.0 (2 × C-3′), 137.6 (2 × aromatic CH), 133.5 (quaternary aromatic C), 134.1 (C-4′), 135.9 (C-1′), 164.5 (C═O). Note: Some overlap of signals with those of the α-thioamide **2** was observed in the NMR spectra of the reaction mixture characterized.

***N*-4′-Methylphenyl-2-(phenylthio)propenamide 5.** ^{1}H NMR (600 MHz, CCl_4, δ) 2.28 [s, 3H, C(4′)CH_3], 6.08, 6.86 [2 × s, 2 × 1H, C(3)H_3]; ^{13}C NMR (151 MHz, CCl_4, δ) 21.4 [C(4′)CH_3], 133.9 (C-3), 135.9 (C-2), 160.3 (C═O). Note: Aromatic resonances overlapping with those of other compounds in the NMR spectra of the reaction mixture characterized.

***N*-4′-Methylphenyl-2,3-dichloro-2-(phenylthio)-propanamide 6.** ^{1}H NMR (600 MHz, CCl_4, δ) 2.32 [s, 3H, C(4′)CH_3], 3.84−4.44 [ABq, J = 11.6 Hz, 2H, C(3)H_2], 7.04 [d, J = 8.3 Hz, 2H, 2 × C(3′)H], 7.18 [d, J = 8.4 Hz, 2H, 2 × C(2′)H], 7.31 (t, J = 7.6 Hz, 2H, ArH), 7.39 (t, J = 7.4 Hz, 1H, ArH), 7.58 (d, J = 7.4 Hz, 2H, ArH), 7.88 (br s, 1H, NH); ^{13}C NMR (151 MHz, CCl_4, δ) 21.6 [C(4′)CH_3], 50.4 (C-3), 82.1 (C-2), 120.4 (2 × C-2′), 128.4 (quaternary aromatic C), 129.6 (2 × aromatic CH), 129.8 (2 × C-3′), 131.1 (aromatic CH), 134.6 (C-4′), 134.8 (C-1′), 137.9 (2 × aromatic CH), 162.2 (C═O).

Dichlorosulfonium Ion 7. *Isomer A.* ^{1}H NMR (600 MHz, CCl_4, δ) 1.93 [s, 3H, C(3)H_3], ^{13}C NMR (151 MHz, CCl_4, δ) 19.5 (C-3), 82.8 (C-2), 161.9 (C═O).

Isomer B. ^{1}H NMR (600 MHz, CCl_4, δ) 1.94 [s, 3H, C(3)H_3], ^{13}C NMR (151 MHz, CCl_4, δ) 19.5 (C-3), 84.4 (C-2), 161.9 (C═O). Other resonances obscured by those of other components in the reaction mixture.

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***N*-4′-Methylphenyl-*Z*-3-chloro-2-(phenylthio)propenamide 1.** ^{1}H NMR (500 MHz, CH_3CN, δ) 2.25 [s, 3H, C(4′)CH_3], 7.02−7.41 (m, 9H, ArH), 7.61 [s, 1H, C(3)H].

■ ASSOCIATED CONTENT

Supporting Information

^{1}H−^{13}C long-range correlation data of individual components available. This material is available free of charge via the Internet at http://pubs.acs.org.

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