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# Development of an Extremely Efficient Oxidative Chlorination Reaction: The Value of Routine Data Collection

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**Abstract:**

**This contribution describes the development of an extremely efficient process for the oxidative chlorination of a benzyl, alkyl thioether to yield an alkylsulfonyl chloride. This process was subsequently run on >100 kg scale. The product alkylsulfonyl chloride was required as an intermediate, being used by several drug projects, to prepare sulfonamides. Routine data collection and reaction profiling has led to understanding, which has allowed an alternative reaction pathway to be exploited for the development of a two-step, oxidation−chlorination process. The scope of this new two-step process was briefly examined. The results of this study have allowed us to propose an empirical method for predicting the course of these oxidative chlorination reactions. During these studies we have developed a simple laboratory rig, constructed from inexpensive, readily available equipment, which allows the controlled accurate delivery of known volumes (100s of milliliters) of chlorine gas at a given rate. In our laboratories, this has made the use of gaseous chlorine a considerably less onerous task. This work is testimony to the fruit which may be borne from attempts to gain process understanding, even of an already high-yielding reaction.**

## 1. Introduction

Sulfonyl chlorides are extremely important intermediates exploited by a host of 21st century industries. They are of particular importance to the agrochemical and pharmaceutical industries where they are often used to prepare biologically active sulfonamides.[1] As an indication of their pharmaceutical importance, a recent cross-pharma survey found that 9% of candidate drugs contained a sulfonamide. Furthermore, of the top 200 branded and generic drugs, those containing a sulfonamide moiety accounted for ~$10 billion and $2 billion worldwide sales, respectively, in 2007.[2]

Various methods for the preparation of sulfonyl chlorides are known.[3] In the absence of sensitive functionality, the oxidative chlorination of a sulfur(II) species using gaseous chlorine[3t,u] appears to be the most widely adopted and general method. These oxidative chlorinations, or chloroxidations, are typically run in aqueous acidic media or, when solubility or hydrolytic stability is problematic, in two-phase systems consisting of an inert solvent (usually DCM, $CHCl_3$, or $CCl_4$) and water or an aqueous acid. There are examples of acetic acid/water mixtures,[4] and more recently (while our work was in progress), an efficient large-scale formic acid/water system was described.[3u] Navigation through the wealth of literature relating to the oxidation of sulfur species with chlorine is an arduous task with general trends difficult to come by. However, it is clear that injudicious choice of either solvent or sacrificial sulfur substituent can have a profound effect on reaction selectivity. Sulfone formation and chlorodesulfurisation can compete with sulfonyl chloride formation; water also plays an important, but not well-defined, role in the course of these reactions. Depending on the reactivity of the sulfonyl chloride, its thermal and hydrolytic stability can also hamper efforts to isolate clean product. Although reaction selectivity and solvent system must largely still be determined from empirical observation, our brief study of different sacrificial sulfur substituents has led to the proposal that there are four distinct pathways by

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(2) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4* (12), 2337. (b) Information compiled by the Njardarson group at Cornell University. http://www.chem.cornell.edu/jn96/outreach.html.

(3) For reviews see (a) Taylor; P. C. *Comprehensive Organic Functional Group Transformations*; Pergamon: Elsevier Science Ltd., 1995; Vol. 2, pp 674, 717. (b) Hudlicky, M. *Oxidations In Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington DC, 1990. For leading references see: (c) Nishiguchi, A.; Maeda, K.; Miki, S. *Synthesis* **2006**, 4131. (d) Hanagan, M. A. EP 0237292, 1987. (e) Prakash, G. K. S.; Mathew, T.; Panja, C.; Olah, G. A. *J. Org. Chem.* **2007**, *72*, 5847. (f) Sohmiya, H.; Kimura, T.; Fujita, M.; Ando, T. *Tetrahedron* **1998**, *54*, 13737. (g) Park, Y. J.; Shin, H. H.; Kim, Y. H. *Chem. Lett.* **1992**, 1483. (h) Ruano, J. L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008**, *2*, 311. (I) Brownbridge, P.; Jowett, I. C. *Synthesis* **1988**, *3*, 252. (j) Monnee, C. F. M.; Marijne, M. F.; Brouwer, A. J.; Rob, M. J.; Liskamp, R. M. *J. Tetrahedron Lett.* **2000**, *41*, 7991. (k) Seto, N.; Kamio, T. JP 11060977, 1999. (l) Chantarasriwong, O.; Jang, D. O.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 7489. (m) Barco, A.; Benetti, S.; Pollini, G. P.; Taddia, R. *Synthesis* **1974**, 877. (n) Kataoka, T.; Iwama, T.; Setta, T.; Takagi, A. *Synthesis* **1998**, *4*, 423. (o) Trost, B. M., Ed; *Comprehensive Organic Chemistry*; Pergamon: Oxford, 1991; Vol 3, pp 179, 339. (p) Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. *Chem Commun.* **2007**, 1074. (q) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, *68*, 8274. (r) Gareau, Y.; Pellicelli, J.; Laliberte, S.; Gauvreau, D. *Tetrahedron Lett.* **2003**, *44* (42), 7821. (s) Frost, C. G.; Hartley, J. P.; Griffin, D. *Synlett* **2002**, 1928 For use of gaseous chlorine see. (t) Zincke, T.; Frohneberg, W. *Ber.* **1909**, *42*, 2721. (u) Wang, C.; Hamilton, C.; Meister, P.; Menning, C. *Org. Process Res. Dev.* **2007**, *11*, 52, and refs 2−5 therein.

(4) (a) Mosher, C. W.; Silverstein, R. M.; Crews, O. P.; Baker, J. R.; Baker, B. R. *J. Org. Chem.* **1958**, *23*, 1257. (b) Langler, R. F. *Can. J. Chem.* **1976**, *54*, 498. (c) Kwart, H.; Miller, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 5008. (d) Hardstaff, W. R.; Langler, R. F.; Leahy, J. *Can. J. Chem.* **1975**, *53*, 2664.


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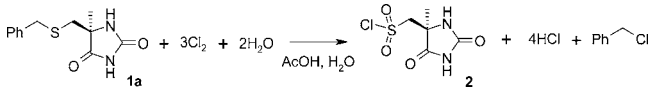
which these substrates react (under a standard set of conditions used by us). Only one of these mechanistic manifolds has been described before.[4b−d] This has allowed us to draw some general conclusions about reactivity which should aid choice of substrate.

A brief survey of the literature surrounding sulfonyl chloride preparations revealed that Mosher et al. had prepared the desmethyl analogue of the sulfonyl chloride **2** *via* oxidative chlorination of the disulfide cystine hydantoin in aqueous acetic acid.[4a] Langler et al. had also shown that use of the benzyl group to mask sulfur led to high yields of a range of alkylsulfonyl chlorides (from alkyl benzyl thioethers) *via* oxidative chlorination in acetic acid in the presence of water.[4b] Forearmed with this information, a minimal development led to a process for the preparation of **2** which was run in our kilo lab; see First-Generation Oxidative Chlorination Procedure in the Experimental Section for details. This reaction was conveniently found to be self-indicating; on completion, the reaction temperature dropped, green (chlorine) colouration could be seen and product started to crystallize. At this stage of development the workup and isolation involved two tedious toluene put-and-takes and an isohexane drown out. Neverthelesss, the product was isolated in an average of 93% yield, 99.6% purity over three batches.




Clearly, this reaction had performed extremely well on scale-up. However, we had little or no understanding of the process and so were able to apply for minimum resource to support further work based around process understanding—which in our experience is never wasted.

We also had concerns around the production of benzyl chloride[5] as a byproduct. This material is a suspect carcinogen; as such, it is a potential genotoxic impurity (PGI),[6] and its environmental emission limits are extremely low.[7] As we had limited information on how benzyl chloride was partitioned throughout our process, we also decided to examine the use of alternative sacrificial sulfur substituents; with *tert*-butyl being the most favored.

## 2. Results and Discussion

**2.1. Handling Gaseous Chlorine in the Lab.** We had found, during early development work, that obtaining mass balance information was difficult due to our inability to accurately dispense small quantities of chlorine. In order to conveniently obtain process understanding information we required this capability. Although there are mass flow devices, which are compatible with corrosive gases (chlorine and more particularly damp HCl), their cost was considered prohibitive for a short study such as this. Instead we set about constructing a lab rig from inexpensive, readily available equipment. A diagram showing the setup that we developed is given in Figure 1.

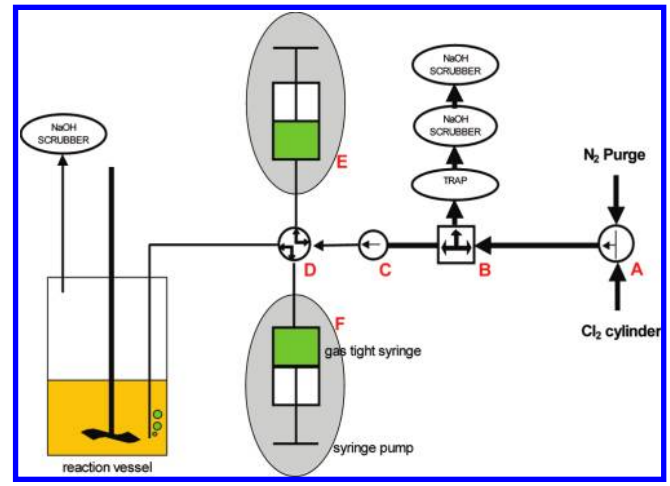



***Figure 1.*** **Atmospheric pressure chlorine gas delivery system. Valve A is corrosive gas regulator, B is a three-way polypropylene tap, C is a universal variable tubing connector, D is a 4-port/2-way diagonal flow valve, E and F are gas-tight syringes mounted on syringe pumps connected by Luer-locking syringe connectors.[8]**

*2.1.1. Description of Operation.* The chlorine cylinder is opened and the regulator adjusted so that the gas bubbles slowly through the first scrubber. Valve **D** is turned so that syringe **E** is connected to the chlorine supply. Syringe **E** is filled manually. Valve **D** is switched so that syringe **F** is now connected to the chlorine supply, and syringe **E** is connected to the reaction vessel. The contents of syringe **E** are delivered to the reaction vessel at a specified rate using syringe pump **E** while syringe **F** is filled manually with chlorine. This process is repeated until the required volume of chlorine has been delivered to the reaction.[8]

**2.2. Understanding the Workup and Isolation.** It was clear that the two, 5-volume put-and-takes of toluene followed by an isohexane drown out were the time-limiting part of this process. It had previously been assumed that these toluene put-and-takes were necessary to remove acetic acid. Some detailed examination of the reaction mixture and distillate solvent composition during these distillations was extremely enlightening. We found, perhaps not surprisingly, that after the toluene put-and-takes the acetic acid content was still fairly high but that the water content was extremely low. It appeared that the

(5) The production of benzyl chloride is accompanied by the concomitant production of benzyl acetate in this reaction in a ratio of ~ 3:1. Trace amounts of benzyl alcohol, benzaldehyde, and benzoic acid are also produced.

(6) (a) International Conference on Harmonization Guideline Q3A(R); Impurities in New Drug Substances; February 2002. (b) European Medicines Agency, Committee for Medicinal Products for Human Use; Guideline on the limits of genotoxic impurities, CPMP/SWP/5199/02; London, U.K., June 2006. PGIs present as impurities in drug substance are limited to levels "below the threshold of toxicological concern" which is currently <1.5 $\mu$g day$^{-1}$.

(7) Carries an R-45 (may cause cancer) risk phrase, and as such the EU solvent emissions directive limits emissions to <10 g h$^{-1}$ or 2 mg m$^{-3}$.

(8) Equipment list: valve A, corrosive gas regulator, ideally with cross purge (Sigma-Aldrich Z40,605-8), alternative without cross purge (Z148512-1EA), or basic control valve (Sigma-Aldrich Z146978-1EA)—caution check lecture bottle thread size before ordering; valve B, 3-way polypropylene tap (Thermo Fisher ADF-890-050R); connector C, universal variable connector (Radleys 991008); valve D, 4-port diagonal flow valve (Radleys 991114); tubing, 5 mm id portex (Thermo Fisher TWT-200-064A), 1.6 mm id Teflon (Radleys 993011); Luer locking syringe connectors (Sigma-Aldrich Z117366-1EA); gas-tight syringes, 100 mL Hamilton (www.esslab.com, cat. no. 86020); syringe pumps, two-directional Harvard Apparatus (model 70-2211).

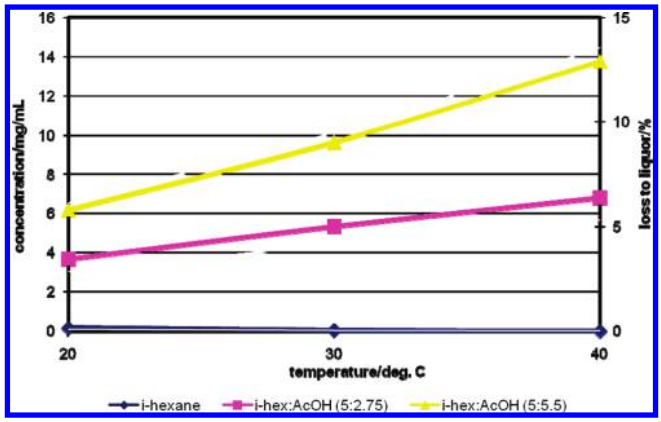



***Figure 2.*** **Solubility of 2 in isohexane and isohexane/acetic acid mixtures. 2 was slurried in the relevant solvent or solvent mixture (ratios are given in vol:vol) and solution concentrations were measured after an equilibration period. The solution concentration in mg/mL has also been related to loss of 2 to liquor as a percentage of yield.**

large toluene distillation volume, while removing some acetic acid, was mainly removing water.[9]

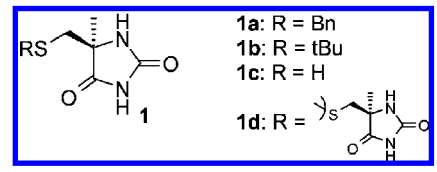
This led to the hypothesis that it was residual water that solublised **2**, and not acetic acid. We ran two sets of solubility experiments to test this. The first, shown in Figure 2, was to determine the solubility of **2** in various solvent mixtures representative of workup compositions. The second, shown in Figure 3, was to determine the effect of water on the solubility of **2** in our actual workup mixture. We found that the presence of acetic acid did indeed increase the solubility of **2**, but this effect was minor compared with that of water, which had a dramatic effect on solubility. Spiking our workup with 5 and 10 mol equiv of water increased losses to liquor by 12% and 21%, respectively.

Conventional wisdom suggests that this reaction required 2 mol equiv of water,[4d] while our process was using 1 vol equiv (~14 mol equiv) of water. If our process would run with less water, we would have less to remove after completion of the reaction. We found that when using 4 mol equiv of water, the process ran identically; whilst with 2 mol equiv, the theoretical requirement, yield and purity were compromised. Running the reaction with less water (4 mol equiv) completely removed the need for the toluene put-and-takes. Overall this resulted in a reduction in cycle time of 17% and total material usage by 33%,[10] —illustrating the value of gaining process understanding on an already high-yielding reaction. Figure 4 shows the advantage of our new process from an operational point of view. The final process conditions are described under Second-Generation Oxidative Chlorination Procedure in the Experimental Section. This process has been successfully run on 115 kg of starting hydantoin **1a**, yielding 99.95 kg (92% yield) of sulfonyl chloride **2**.

**2.3. Examination of Alternative Sacrificial Sulfur Substituents.** While running our oxidative chlorinations we routinely compiled reaction profile plots using LC/MS data,[11] and recorded temperature profile[12] information. This routine data collection led to an unexpected mechanistic observation in the reaction of substrate **1a**. Langler proposed, in 1976, that this reaction type most likely proceeded *via* initial loss of the benzyl cation and concomitant formation of the sulfenyl chloride.[4b] Scheme 1 shows a possible mechanistic pathway which may follow initial sulfenyl chloride formation proposed by Langler (extrapolated to our substrate).[4b] We have designated this as *path A*, and putative intermediates are shown in blue. We found that, under our conditions and with the substrate **2**, this reaction proceeded *via* initial formation of the sulfoxide **8a** and not the proposed sulfenyl chloride **3**. Scheme 2 shows the reaction pathway observed by us, *path B*, and again putative intermediates are shown in blue, whereas observed intermediates are shown in black.

As previously mentioned, our favored alternative sacrificial sulfur substituent was *tert*-butyl, mainly because t-butyl chloride is more hydrolytically labile and so is not a potential carcinogen or genotoxin;[13] It also has the advantage of being more atom efficient than a benzyl group.

When we subjected the *tert*-butyl masked hydantoin **1b** to our standard oxidative chlorination conditions, we were initially irritated to find that the product was routinely contaminated with 5−10% of sulfonic acid **10**.[14] Subjecting sulfonyl chloride **2** to our reaction conditions did not increase the level of sulfonic acid showing that this was not due to hydrolysis. Examination of the reaction profile led to the discovery that **1b** was reacting *via* two competing reaction pathways, see Scheme 3. The first, *path A*, is the same as that inferred by Langler,[4b] the second, *path C*, to the best of our knowledge has not previously been described in the literature. It seems that while the monomeric manifold, *path A*, leads to clean sulfonyl chloride, the dimeric manifold, *path C*, gives rise to the concomitant production of sulfonic acid **10**. We also examined the oxidative chlorination of thiol **1c** and disulfide **1d**. To our surprise both of these substrates also led to the production of sulfonic acid **10** in 5−10% yield.[16]




We investigated two methods whereby this reaction could be diverted to proceed *via* only *path B* and so eliminate sulfonic

(9) At the same time we modeled the ternary solvent system, and model data confirmed our findings. The software used was Aspen BatchSep, using physical properties modeled from Aspen Properties. The property method employed was the NRTL method with the Hayden-O'Connell equation of state for the vapor phase to account for any dimerisation of the acetic acid.

(10) The process was modeled using Aspen BatchPlus with an internal AstraZeneca "standard" plant configuration consisting of vessels up to 6.3 $m^3$.

(11) It is important to realize the limitations of the analytical techniques being used. Using LC/MS we were aware that we would not see hydrolytically unstable intermediates. In the LC traces we would not see compounds without a UV chromophore; in the MS traces we were restricted to an $ES^+$ ionization source, and so only molecules able to protonate would ionize.

(12) We have a proprietary in-house system which allows remote control and monitoring of reactions.

(13) At least in part, as a result of the hydrolytic lability of *tert*-butyl chloride, it carries only the risk phrase R-11 (highly flammable).

(14) A post-isolation re-work procedure, which involved slurrying the product in water, did remove the sulfonic acid; however, this resulted in a much-reduced yield.

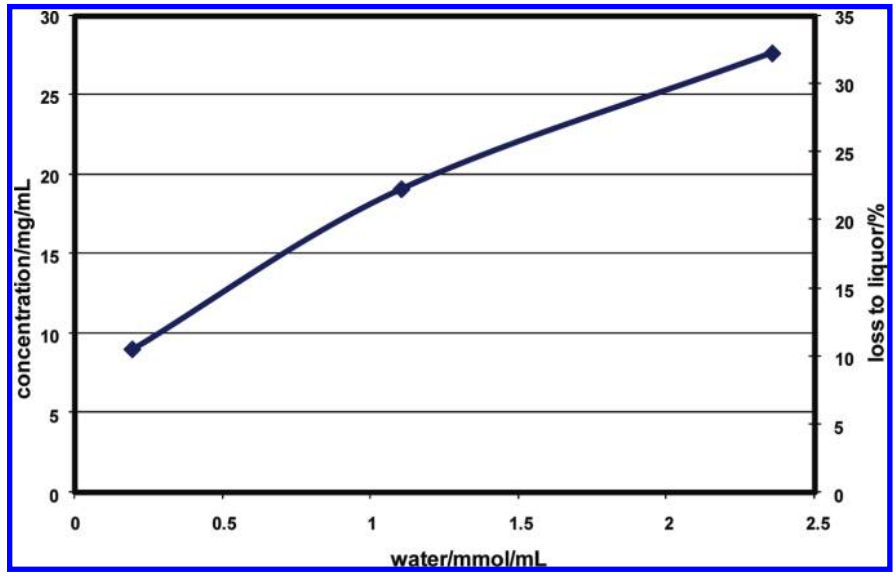



***Figure 3.*** **Effect of water on the solubility of 2 in isohexane/acetic acid workup mixture. After our standard reaction workup the solution concentration of 2 and the water content were measured. The mixture was subsequently spiked with 5 mol equiv of water, and after an equilibration period the same measurements were taken. This process was repeated once more.**

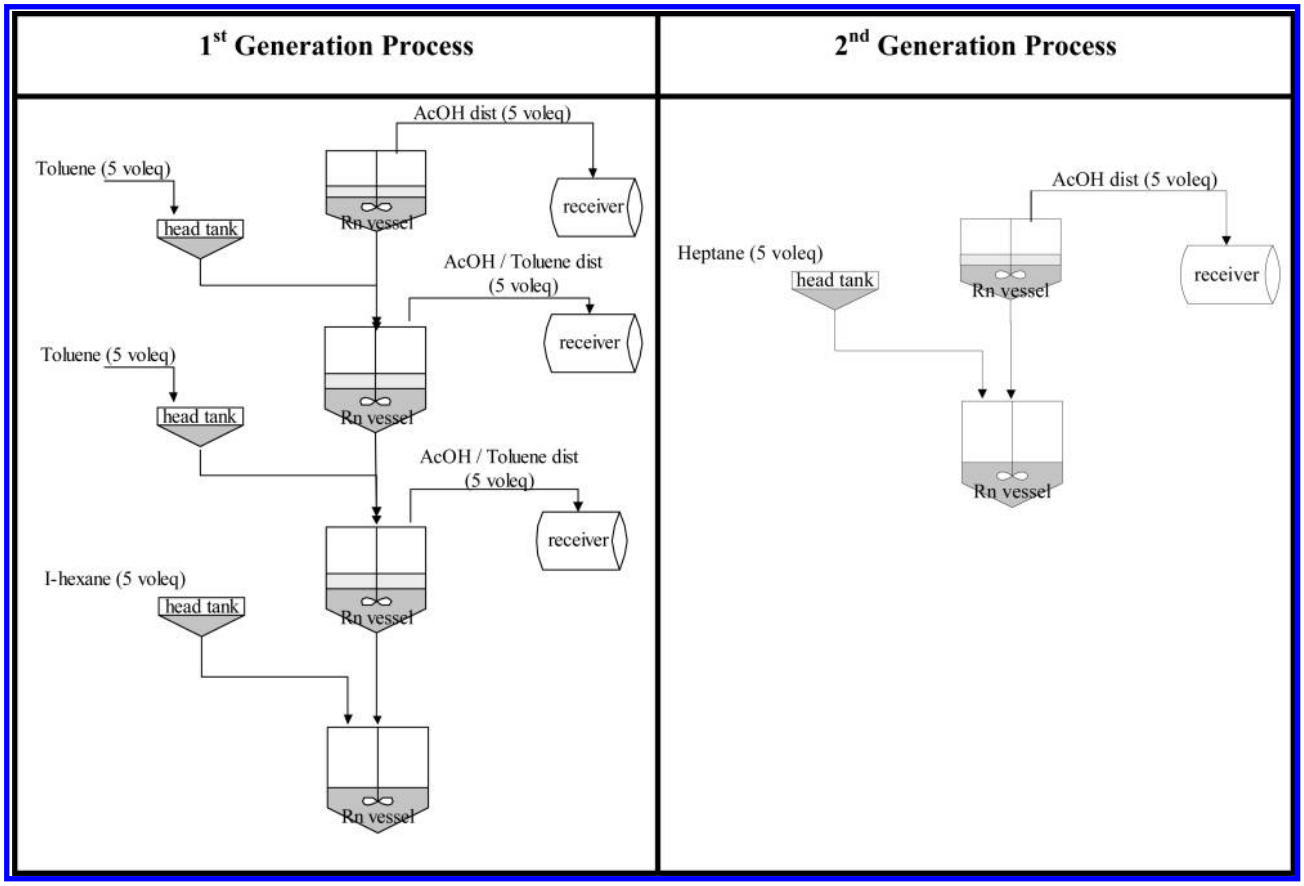


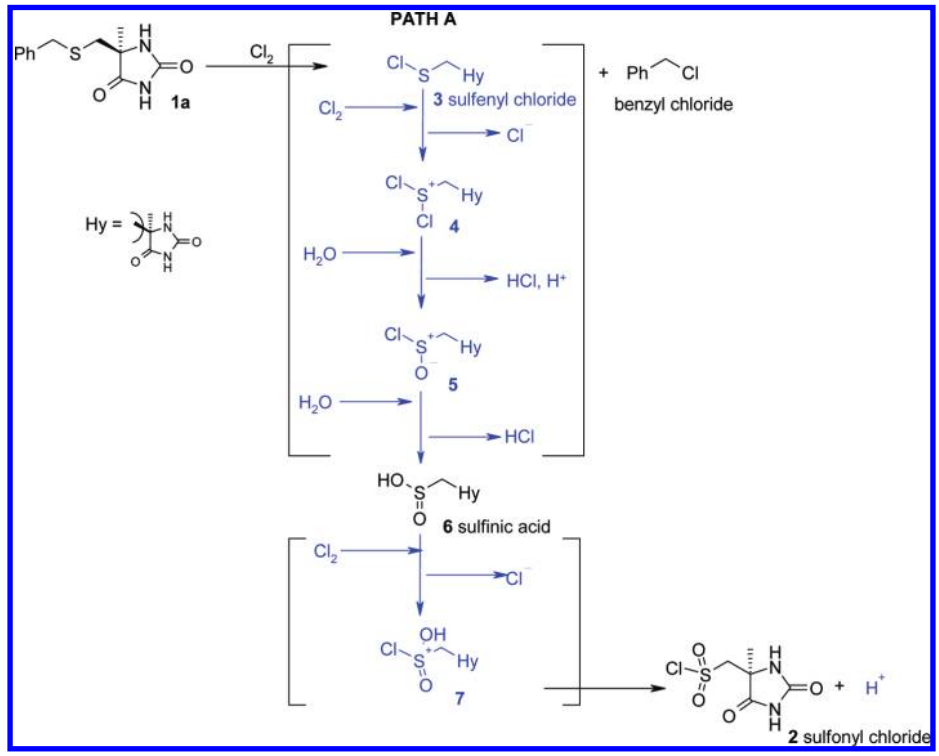

***Figure 4.*** **Visio diagram showing workup unit operations pre- and post- process development.**

acid formation. In the first instance we attempted to force the *tert*-butyl masked substrate **1b** to behave in the same manner as **1a** by partially oxidizing to the equivalent sulfoxide **8b** prior to chlorine treatment. This was achieved using hydrogen peroxide and was extremely successful; product being isolated in quantitative yield in the absence of sulfonic acid; see Scheme 4. This was also developed into a one-pot process which we are confident can compete with our oxidative chlorination of **1a**. This two-step one-pot process has the added advantage of requiring less chlorine; the transformation from sulfoxide to sulfonyl chloride requires only 2 mol equiv (compared to 3 mol equiv with the original process).[15,16]

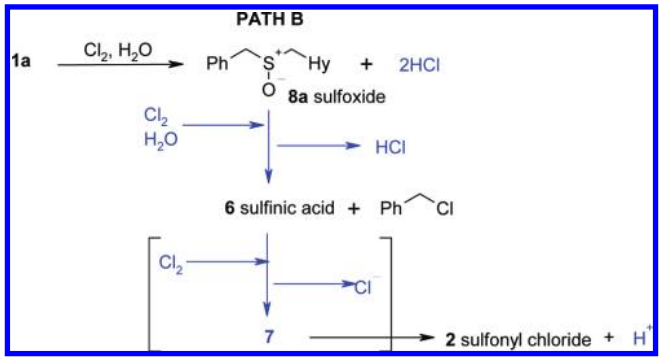
In the second instance we reasoned that limiting the substrate concentration would reduce formation of disulfide **1d** and so preclude formation of sulfonic acid **10**. This was achieved by slow addition of **1b** to a chlorine-saturated aqueous acetic acid

(15) Cornwall, P.; Horner, D. WO/2007/106021, 2007.

***Scheme 1.*** **Possible mechanistic pathway following initial sulfenyl chloride formation; structures in black have been identified, and structures in blue are proposed intermediates and byproducts**




***Scheme 2.*** **Mechanistic pathway observed by us in the oxidative chlorination of benzyl alkyl sulfide 1a**




solution. Again, this hypothesis proved successful as no sulfonic acid was observed when **1b** was added to the chlorination solution over a 1 h period. Sulfonyl chloride **2** being isolated in 96% yield and 99.8% purity. The chlorine usage was not measured in this experiment, so cannot be compared to our standard chlorination of **1a**, or our two-step oxidation-chlorination of **1b**.

Neither of the two alternative processes described above was progressed past the proof of concept stage, as by this time we had data to show that we could control benzyl chloride, both with respect to environmental emissions and contamination of product.[17] However, both processes remain as viable, economically attractive alternatives to our current method.

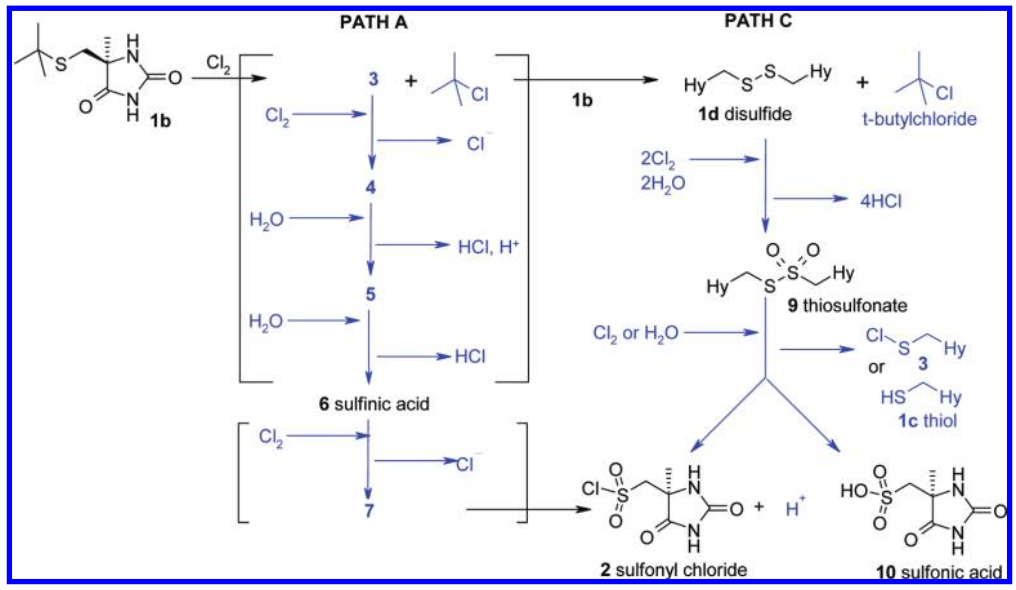
**2.4. Understanding Sacrificial Sulfur Substituents.** Although there is a large body of literature concerning the use of chlorine in oxidations of sulfur(II) species, the majority of mechanistic information is directly related to the so-called *sulfohaloform reaction*;[18a] whereby an alkyl group α-to sulfur is exhaustively chlorinated prior to cleavage and oxidation of the resulting sulfenyl chloride to a sulfonyl chloride, see Scheme 5.[18f] A large portion of this work is focused around explaining the regiochemistry of chlorine attack on variously substituted dialkyl thioethers.[18a–e] On close examination of this work we found that the results which are reported did not correspond to our findings for **1a**−**d**. For instance, it is asserted that chlorination of thioethers proceeds *via* initial formation of a sulfoxide only when there is a strongly electron withdrawing group α-to sulfur,[18a] whereas we had found that the benzyl masked substrate **1a** proceeded initially through a sulfoxide. Also, as the benzylic methylene is not exhaustively chlorinated, benzyl chloride being the byproduct, we felt that this substrate did not fit the criteria at all for the *sulfohaloform reaction*; the literature puts forward no explanation for this.[18b] Assessment of the relative electronegativity (Xp) of the groups on either side of sulfur has been

(16) This was not intended to be a rigorous mechanistic study. The mechanistic information was gained as a result of routine data collection. We do not profess to have fully elucidated these mechanisms, and questions still remain around sulfonic and sulfinic acid formation. Notably: (i) only a small proportion of the material that progresses via *path C*, the dimer path, becomes sulfonic acid; (ii) in all cases sulfonic acid is formed towards the end of the reaction when the thiosulfonate concentration tends to be at its highest; (iii) we see no cross-over from *path C* to *path A* with substrate **1d** even though we might expect to.

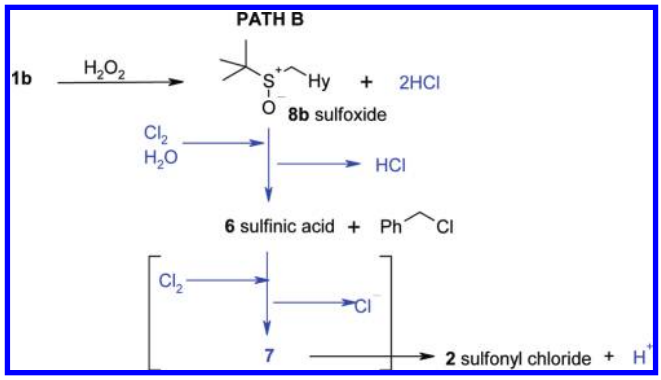
(17) Due to the relatively low vapor pressure of benzyl chloride we were able to demonstrate that the potential air emissions could be successfully controlled either by manipulating the distillation conditions or by utilizing an efficient condenser.

(18) (a) Baum, J. C.; Hardstaff, W. R.; Langler, R. F.; Makkinje, A. *Can. J. Chem.* **1984**, *62*, 1687. (b) Langler, R. F.; Marini, Z. A.; Spalding, E. S. *Can. J. Chem.* **1979**, *57*, 3193. (c) Ahern, T. P.; Kay, D. G.; Langler, R. F. *Can. J. Chem.* **1978**, *56*, 2422. (d) Potvin, M.; Albrecht, L.; Darvesh, K. V.; Langler, R. F. *Aust. J. Chem.* **2005**, *58*, 143. (e) Ginsburg, L. G.; Darvesh, K. V.; Axworthy, P.; Langler, R. F. *Aust. J. Chem.* **1997**, *50*, 517. (f) Grossert, J. S.; Langler, R. F. *Can. J. Chem.* **1977**, *55*, 407.

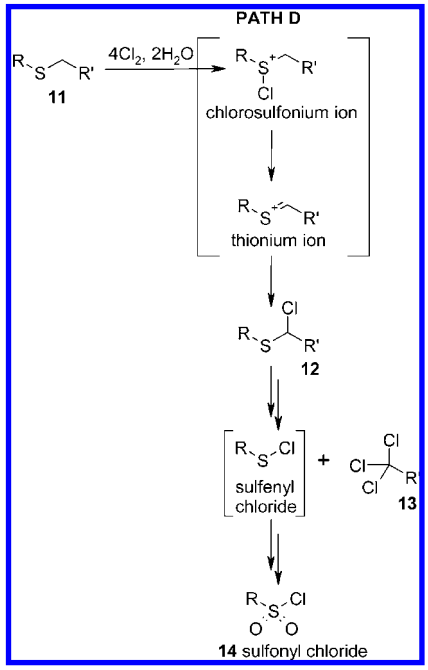
***Scheme 3.*** **Mechanistic pathway observed by us in the oxidative chlorination of *tert*-butyl alkyl thioether 1b**




***Scheme 4.*** **Two-step oxidation−chlorination process**

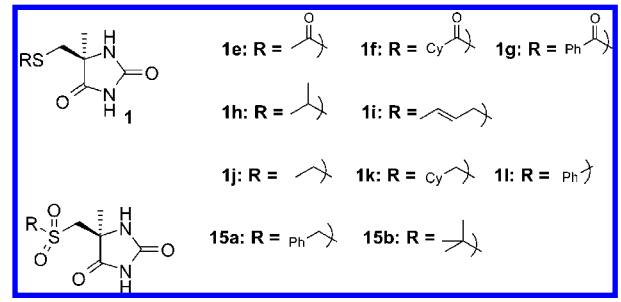



***Scheme 5.*** **Postulated mechanistic pathway for the *sulfohaloform reaction***




used successfully to predict the regiochemistry of chlorine attack; chlorine attacking the side with the largest relative electronegativity.[18c] This breaks down when sulfur is masked by a group capable of stabilizing a carbocation. Putting a theoretical basis to this empirical observation has not proven to be trivial.[18d,e] Also, these treatments, while extremely interesting, cover only a narrow substrate scope, which is not immediately helpful from the point of view of predicting preparatively useful trends for sulfonyl chloride formation.

In order to try and gain some understanding of the observed behaviour of sulfides **1a**−**d** and place them into a broader, and preparatively useful, reactivity context, we prepared a series of substrates with various sacrificial sulfur substituents **1e**−**l**, and also prepared the sulfones **15a**−**b**. We subjected each of the




substrates in turn, first to our oxidative chlorination conditions, and then to our two-step peroxide/chlorine oxidation-chlorination. We followed the course of each reaction generating profiles from LC/MS data, observing whether the reaction proceeded *via paths A, B, C, D* or multiple manifolds. The results are summarized in Table 1. See Supporting Information for LC and LC/MS traces, MS assignments, along with full data for isolated intermediates and products.

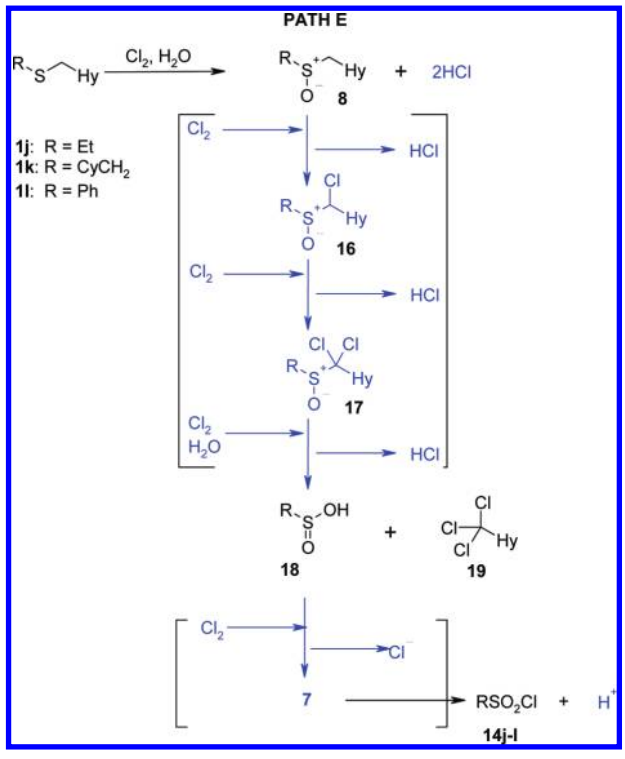
Whilst these reactions are far from fully characterized, it is apparent that the course of the reaction is strongly influenced by the groups masking sulfur.[16] The reactivity trend observed with varying sacrificial substituents was found to mirror the relative carbocation stabilizing ability of these substituents. i.e. Those sacrificial sulfur substituents that form, relatively, the most stable carbocations (acyl, **1e**, **1f**, **1g** and *tert*-butyl **1b**) react *via path A/C*. Those groups which may form carbocations of

***Table 1.*** **Observed reaction pathways for 1a−l, 15a−b**

| substrate | one-step chlorination | two-step oxidation−chlorination |
|---|---|---|
| **1a** | path B[a] | not done |
| **1b** | paths A and C[b] | path B[a] |
| **1c** | paths A and C[b] | not done |
| **1d** | path C[b] | not done |
| **1e** | paths A and C[b,c] | path C[d] |
| **1f** | paths A and C[b] | path C[d] |
| **1g** | paths A and C[b] | path C[d] |
| **1h** | path B[a] | path B[a] |
| **1i** | path B[a] | Path B[a] |
| **1j** | path E[e] | path E[e] |
| **1k** | path E[e] | path E[e] |
| **1l** | path E[e] | path E[e] |
| **15a** | no reaction[e] | no reaction[f] |
| **15b** | no reaction[f] | no reaction[f] |

[a] See Scheme 2 for proposed reaction path. [b] See Scheme 3 for proposed reaction path. [c] Substrate **1e** was a mixture of the thioester and thiol. Acyl groups of **1e**, **1f**, and **1g**, were slowly hydrolysed in acetic acid (cf.: reactivity of thioesters is much greater than carboxylic esters). [d] **1e**, **1f** and **1g** were oxidised to disulfide **1d** and not sulfoxides under the reaction conditions. [e] These reactions proceeded *via* the *sulfoxide−sulfohaloform* pathway, see Scheme 6 for proposed reaction path. [f] The sulfones, **15a** and 15**b**, were stable to the reaction conditions, however some monochlorination was seen after stirring overnight. We did not determine the position of chlorination.

***Scheme 6.*** **Observed path for sulfoxide−sulfohaloform reaction**




intermediate stability (benzyl **1a**, isopropyl **1h**, and crotyl **1i**) react *via path B*. Those groups which form the least stable carbocations (ethyl **1j**, cyclohexylmethyl **1k**, and phenyl **1l**) appear to react *via* an entirely different manifold, *path E*, which we have designated the *sulfoxide−sulfohaloform reaction*, see Scheme 6. In sharp contrast to literature precedent, in all cases, except **1e**, **1f**, **1g** and **1b** where the sacrificial group is cleaved immediately, we see sulfoxide formation as the first step, prior to α-chlorination.[18a] We herein propose four mechanistic manifolds for the reaction of sulfides under our aqueous chlorination conditions, *paths A*, *B*, *C*, and *E*, only one of which has been partly described in the literature previously. We saw no evidence for the *sulfohaloform reaction*, *path D*, under these conditions. We suggest that the manifold by which a substrate reacts is empirically predictable from the carbocation stabilizing ability of the sacrificial sulfur substituent. This order of reactivity is consistent with the relative carbocation stabilities shown in Table 2.[19]

In theory our alkyl-alky- and alkyl-aryl-substituted thioethers reacting *via* the *sulfoxide−sulfohaloform reaction*, *path E*, consume 4 mol equiv of chlorine, i.e. are less efficient in terms of chlorine usage.

We have LC/MS evidence only for the proposed mono- and dichlorosulfoxide intermediates, **16** and **17**, shown in Scheme 6. We have isolated and characterized the trichloromethylhydantoin byproduct **19** from this reaction. The regiochemistry of the reaction with **1l** is unambiguous, **14l** being identical to an authentic sample of phenylsulfonyl chloride. Whereas, we cannot rule out mixtures of regioisomers with **1j** and **1k** although no sulfonyl chloride **2** was detected, suggesting that these reactions are also regioselctive (it is unlikely that we would observe 1,1,1-trichloroethane or trichloromethylcyclohexane by LC/MS).

## 3. Conclusions

We hope that this piece of work highlights the value of seeking process understanding as a stand-alone aim and that routine data collection is a tool to this end. We have described a low-tech solution to the problems associated with chlorine delivery, which has reduced the inertia towards the use of gaseous chlorine in our laboratories.

This work has implications for choice of sulfur substituents when preparing sulfonyl chlorides using gaseous chlorine under aqueous conditions.

In order to maximize yield and limit loss to sulfonic acid formation, extremely labile, carbocation stabilizing groups, should probably be avoided (although, we have developed a two-step one-pot procedure which precludes sulfonic acid formation with these substrates). With aryl-alkyl sulfides, primary alkyl groups will perform the masking function adequately, although chlorine usage would be minimized with a secondary alkyl group. The isopropyl group would appear to be the sacrificial group of choice, from the point of view of atom efficiency and chlorine usage. From an environmental and hazard point of view there is little difference between isopropyl and *tert*-butyl sacrificial groups (the byproduct being isopropylchloride and *tert*-butylchloride). Use of the ethyl group to mask sulfur is much less attractive, the byproduct being 1,1,1-trichloroethane which is highly toxic to humans, the environment and a potential carcinogen.

Of course, a range of considerations must be taken into account in order to successfully "design" the ideal substrate for an oxidative chlorination. For instance, stability of product sulfonyl chloride (can it be isolated); how the product may be isolated (distillation, crystallization); will byproduct interfere with down-steam chemistry, etc.? Although the above study is

(19) (a) Schultz, J. C.; Houle, F. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 3917. (b) Lossing, F. P.; Holmes, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 6917.

***Table 2.*** **Gas-phase dissociation energies for R−H → $R^+$ + $H^-$, in kJ $mol^{-1}$**

| | | | |
|---|---|---|---|
|  886 |  no data[a] |  962 |  970 |
|  996 |  1043 |  no data[b] | |
|  no data[a] |  1158 |  1230 | |

[a] No literature data available for gas-phase dissociation energies. [b] No data available, allyl cation = 1070 kJ $mol^{-1}$.

not exhaustive, we hope that it will help guide chemists towards an informed choice of sulfur substituents, which will give byproduct with acceptable properties, when preparing sulfonyl chlorides.

## 4. Experimental Section

**4.1. General.** NMR spectra were run on Varian Unity Inova spectrometers running at proton frequency of 300 or 400 MHz, coupling constants are quoted in hertz. HPLC samples were run on HP 1100 series with binary pump and diode array detector, using a Metachem Polaris C18 (3 $\mu$m × 150 mm × 3 mm) column and mobile phases water (containing 0.05% TFA) and acetonitrile (containing 0.04% TFA), running with gradient elution. LC/MS spectra were run using the same HPLC system described above connected to an Agilent 1100 series SL LC/MSD, using APESI +ve ionization mode. Accurate masses were obtained using a Waters LCT time-of-flight MS (lockspray internal calibration) with loop injection and ESI +ve ionization mode. FTIR spectra were obtained using a Perkin-Elmer Spectrum One spectrometer; all samples were run neat. Melting points were obtained using a Buchi melting point B-545.

**4.2. First-Generation Oxidative Chlorination Procedure (2).** Glacial acetic acid (22 L, 8 vol equiv) was charged to the reactor followed by **1a** (2.75 kg). Distilled water (2.75 L, 1 vol equiv) was added, and the reaction mixture was cooled to 8 °C. Chlorine gas was introduced *via* a dip pipe at such a rate that $T_{internal}$ remained around 12 °C. After completion of the reaction (∼2.5 h) the solution turned green and the reaction temperature dropped. The gas flow was stopped, the temperature was raised to 25 °C and nitrogen was passed through the mixture for 1 h. Acetic acid was removed by reduced pressure distillation (down to 11 L, 4 vol equiv remaining, $T_i$ <40 °C). Two toluene put-and-takes were carried out (2 × 13.75 L, 2 × 5 vol equiv). Isohexane (13.75 L, 5 vol equiv) was added followed by an 18 h room temperature stir out. The product was collected by filtration, and the filter cake was washed with isohexane (2 × 11 L, 2 × 4 vol equiv) and dried overnight in a vacuum oven at 45 °C to give the product, 2.35 kg (94% yield, 99.6% purity by LC area), as a white crystalline solid.

**4.3. Second-Generation Oxidative Chlorination Procedure (2).** The reactor was charged with **1a** (114.9 kg) followed by glacial acetic acid (964 kg, 8 vol equiv) and purified water (33 L, 0.2 vol equiv, 4 mol equiv), at ambient temperature. The solution was warmed to 33 °C. Chlorine gas (110.44 kg, 3.3 mol equiv) was blown into the reaction mixture over ∼28 h, maintaining $T_i$ at 32−37 °C resulting in an intense yellow suspension which was stirred at 32−37 °C for a further 10 h. The mixture was purged with nitrogen for ∼3 h, then degassed *in vacuo* at 230 mbar, $T_i$ = 35−25 °C for 28 h. The reaction mixture was distilled (770 L solvent mixture removed (acetic acid, water, benzyl chloride)) *in vacuo* (230 → 19 mbar, $T_i$ = 37.5−40 °C). The contents were cooled to 30 °C and stirred for 8 h. Heptane (114 kg, 1 vol equiv) was charged, and the product was collected in portions by means of a centrifuge. Each portion was washed with warm (40 °C) heptane. The isolated material was dried under vacuum at 3 bar, 45 °C to constant weight, yielding the product, **2**, 95.95 kg (91.8% yield, 98.7% w/w by $^1$H NMR), as a white crystalline solid (GC: benzyl chloride: 9 ppm).

**4.4. ((*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-yl)methanesulfonyl Chloride (2).**[15] $^1$H NMR (400 MHz, $d_8$-THF) $\delta$ 1.52 (3H, s), 4.44 (1H, d, J 14.6), 4.53 (1H, d, J 14.6), 7.58 (1H, s), 9.92 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 22.980, 55.682, 60.017, 156.207, 177.820. Mp = 185−190 °C. FTIR 1704, 1408, 1287 $cm^{-1}$. *m/z* (%) from LC/MS: 127.20 (100), 227.20 (9, $[M + H]^+$).

**4.5. (*R*,*S*)-5-Methyl-5-phenylmethanesulfinylmethyl-imidazolidine-2,4-dione (8a).** To a solution of (*rac*)-**1a** (4.10 g, 16.4 mmol) in acetone (100 mL) was added 35% $H_2O_2$ (1.62 mL, 1.1 mol equiv). The solution was stirred at ambient temperature overnight. The solution was tested with a peroxide strip and found to contain no peroxide. It was then concentrated to dryness *in vacuo* to give the product, 4.4 g (100%), as a white solid which was not purified further.

Ratio of diastereoisomers = 59:41 by LC area. $^1$H NMR (400 MHz, $d_6$-DMSO) major isomer $\delta$ 1.34 (3H, s), 2.75 (1H, d, J 13.8), 3.2 (1H, d, J 13.8), 4.02 (2H, d, J 12.8), 7.30−7.40 (5H, m), 8.07 (1H, bs), 10.83 (1H, bs); minor isomer $\delta$ 1.36 (3H, s), 2.97 (1H, d, J 13.5), 3.15 (1H, d, 13.5), 4.17 (2H, t, J 13.4), 7.30−7.40 (5H, m), 8.31 (1H, bs), 10.67 (1H, bs). $^{13}$C (75 MHz, $d_6$-DMSO) It was not possible to separate major and minor isomers, so signals are quoted in pairs, except for the benzylic carbons signals which are coincedent $\delta$ 23.53, 24.39; 57.28; 57.74, 58.11; 60.41, 59.32; 127.82, 127.84; 128.519, 128.43; 130.20, 130.35; 130.96, 131.29; 156.09, 155.75; 176.67,

176.76. Mp = 208−210 °C. *m/z* (%) from LC/MS: minor isomer 267.20 (100, $[M + H]^+$), 533.20 (2, $[2M + H]^+$); major isomer 267.20 (100, $[M + H]^+$), 533.20 (13, $[2M + H]^+$).

**4.6. (*S*)-5-Methyl-5-(2-methyl-propane-2-sulfinylmethyl)imidazolidine-2,4-dione (8b).**[15] To a solution of **1b** (3.93 g, 18.2 mmol) in acetone (200 mL) was added 35% $H_2O_2$ (1.8 mL, 1.1 mol equiv). The solution was stirred at ambient temperature for 19 h. It was tested with a peroxide strip and found to contain no peroxide. The solvent was removed *in vacuo* to give the product, 4.403 g (104% yield), as a white solid.

Mixture of diastereoisomers, 71:29, by comparison of $^1$H NMR integral. $^1$H NMR (500 MHz, $d_6$-DMSO) major isomer $\delta$ 1.13 (9H, s), 1.40 (3H, s), 2.39 (1H, d, 14), 3.25 (1H, d, J 14), 8.28 (1H, s), 10.78 (1H, s); minor isomer $\delta$ 1.14 (9H, s), 1.38 (3H, s), 2.85 (2H, s), 8.07 (1H, s), 10.78 (1H, s). FTIR of mixture 1705, 1016 cm$^{-1}$. $^{13}$C NMR (75 MHz, $d_6$-DMSO) major isomer $\delta$ 22.01, 22.28, 60.57, 53.11, 54.93, 155.75, 176.89; minor isomer $\delta$ 22.25, 24.64, 59.33, 52.57, 50.22, 156.10, 176.68. Mp = 166−170 °C. *m/z* (%) from LC/MS: major isomer 233.20 (56, $[M + H]^+$), 465.20 (100, $[2M + H]^+$); minor isomer 177.20 (100), 233.20 (11, $[M + H]^+$), 465.20 (1, $[2M + H]^+$).

**4.7. ((*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-yl)methanesulfinic Acid (6).**[20] To a solution of sodium sulfite (16.68 g, 132.37 mmol) in water (85 mL) was added **2** (10 g, 44.12 mmol) in one portion. After 2 h the reaction was acidifed with HCl to pH 1−2 then concentrated *in vacuo*. The resulting solid was slurried in hot IPA, filtered, and washed twice with hot IPA. The combined organics were concentrated *in vacuo* to give the product, 2 g (24% yield), as a white solid. NMR analysis revealed that this material was a mixture of sulfinic acid and sulfonic acid in a ratio of 5.9:1, 84.4% w/w by $^1$H NMR.

$^1$H NMR (300 MHz, $D_2O$) $\delta$ 1.54 (3H, s), 2.69 (1H, d, *J* 13.5), 2.92 (1H, d, *J* 13.6). *m/z* (%) from LC/MS: 193.20 (100, $[M + H]^+$), 234.20 (5, $[MH + MeCN]^+$) 256.40 (8, $[MH + Na + MeCN]^+$).

**4.8. ((*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-yl)methanesulfonic Acid (10).**[15] A slurry of **2** (2 g, 8.82 mmol) in water (10 mL) was heated at reflux for 24 h. The resulting solution was allowed to cool and concentrated *in vacuo*. The white solid obtained was dried to constant weight, slurried in hot MeCN and collected by filtration to give the product 1.808 g (98% yield) as a white crystalline solid.

$^1$H NMR (400 MHz, d8-THF) $\delta$ 1.46 (3H, s), 3.37 (1H, d, J 14.9), 3.45 (1H, d, J 14.6), 7.21 (1H, s), 9.66 (1H, s). $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 24.09, 56.12, 61.76, 158.84, 180.25. Mp = 137−139 °C.

**4.9. (*S*)-5-Methyl-5-phenylmethanesulfonylmethyl-imidazolidine-2,4-dione (15a). 1a** (20.06 g, 72.13 mmol) was slurried with oxone (150 g, 243.99 mmol) in acetone (200 mL) at 45 °C overnight. Inorganics were removed by filteration and washed with acetone. The filtrate was concentrated to a white foam, then reconcentrated from methanol. The resulting material was dried *in vacuo* to give the product 22.74 g (111% yield) as a white solid (95.6% w/w by $^1$H NMR assay).

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.34 (3H, s), 3.43 (1H, d J 15), 3.55 (1H, d, J 15), 4.45 (1H, d, J 13.6), 4.49 (1H, d, J 13.6), 7.36−7.43 (5H, m), 8.18 (1H, s), 10.82 (1H, s); $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 24.46, 55.96, 59.05, 60.12, 128.02, 128.46, 131.12, 156.23, 176.35. Mp (decomp.) 182−183 °C. FTIR 1114, 1307, 1706 cm$^{-1}$. *m/z* (%) from LC/MS: 283.20 (39, $[M + H]^+$), 300.20 (100, $[M + NH_4]^+$), 301.20 (19, $[M + H_2O + H]^+$), 321.20 (1, $[M + K]^+$), 565.20 (62, $[2M + H]^+$). Accurate mass, calc. for $[M + NH_4]^+$ $C_{12}H_{18}N_3O_4S$ = 300.1018, found = 300.1044 (8.7 ppm error).

**4.10. (*S*)-5-Methyl-5-(2-methyl-propane-2-sulfonylmethyl)imidazolidine-2,4-dione (15b). 1b** (1.0129 g, 4.68 mmol) was dissolved in acetone (25 mL) and added dropwise to a slurry of oxone (9.4027 g; 15.29 mmol) in acetone (20 vol equiv) with ice cooling. The exotherm was allowed to subside and the reaction was heated at 40 °C for 4 h. The resulting slurry was filtered and the filtrate concentrated *in vacuo* then dried to give the product 1 g (64% yield) as a white solid (74% w/w by $^1$H NMR assay).

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.27 (9H, s), 1.36 (3H, s), 3.22 (1H, d, J 14.5), 3.71 (1H, d, J 14.5), 7.99 (1H, s), 10.67 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 22.25, 24.99, 50.23, 58.94, 59.14, 156.03, 176.40. Mp (decomp.) 202−209 °C. FTIR 1109, 1285 1707 cm$^{-1}$. *m/z* (%) from LC/MS: 193.20 (100, $[M\text{-}C(CH_3)_3 + H]^+$), 249.20 (100, $[M + H]^+$), 266.20 (59, $[M + NH_4]^+$), 267.20 (9, $[M + H_2O + H]^+$), 290.20 (8, $[M + H + MeCN]^+$), 497.20 (90, $[2M + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_{11}H_{20}N_3O_4S$ = 290.1175, found = 290.1198 (7.9 ppm error).

**4.11. (*S*)-5-Mercaptomethyl-5-methyl-imidazolidine-2,4-dione (1c). 1b** (45 g, 208 mmol) was heated at reflux in concentrated HCl (720 mL, 16 vol equiv) at 90 °C for 7 h then allowed to cool to room temperature overnight. Onset of rapid gas evolution occurred at 55 °C; the exhaust was scrubbed (water, and 10 M NaOH trap). The reaction mixture was concentrated i*n vacuo* then reslurried in toluene. The resulting free-flowing solid was collected by filtration and dried overnight *in vacuo* to give the product, 33.3 g (100% yield, 90% w/w purity by $^1$H NMR).

$^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$ 1.31 (3H, s, *J* 5.4), 2.24 (1H, dd, *J* 9.8, 7.6), 2.64 (1H, dd, *J* 13.8, 7.6), 2.75 (1H, dd, *J* 13.8, 9.8), 7.85 (1H, bs), 10.69 (1H, bs). $^{13}$C NMR (75 MHz; $d_6$-DMSO) $\delta$ 22.73, 30.87, 63.16, 158.57, 177.09. Mp = 150−153 °C. *m/z* (%) from LC/MS: 116.20 (100), 161.20 (20, $[M + H]^+$).

**4.12. (5*S*,5′*S*)-5,5′-Disulfanediylbis(methylene)bis(5-methylimidazolidine-2,4-dione) (1d).**[21] **1b** (5 g, 23.12 mmol) was stirred in acetic acid (15 mL, 3 vol equiv) with DMSO (1.65 mL, 23.12 mmol) at 5−10 °C. Hydrogen bromide (15.17 mL, 134.1 mmol) was added dropwise *via* syringe. Gas evolution and an endotherm were noted. The reaction was allowed to warm to room temperature. After 5 h crushed ice was added, and the resulting solid was collected by filtration and dried *in vacuo* to give the product 3.64 g (99% yield) as a white solid (97% w/w assay by $^1$H NMR assay).

(20) Method adapted from that described by King, J. F.; Hillhouse, J. H. *Can. J. Chem.* **1983**, *61*, 1583.

(21) (a) Shibuya, A.; Saito, M. JP 2004043309, 2004. (b) Matsumoto, S.; Murao, H.; Yamaguchi, T.; Izumida, M.; Ueda, Y. WO/2005/026110, 2005.

Single crystals were grown from water, and the structure was confirmed by X-ray analysis.

$^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$ 1.30 (6H, s), 3.08 (4H, s), 7.98 (2H, bs), 10.75 (2H, bs). $^{13}$C NMR (75 MHz; $d_6$-DMSO) $\delta$ 23.02, 48.05, 62.34, 156.13, 176.67. Mp = 278−281 °C. *m/z* (%) from LC/MS: 319.20 (100, $[M + H]^+$). Accurate mass, calc. for $[M + H]^+$ $C_{10}H_{15}N_4O_4S_2$ = 319.0535, found = 300.0524 (3.4 ppm error).

**4.13. *S*-((*S*)-4-Methyl-2,5-dioxoimidazolidin-4-yl)methy((*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl)methanesulfonothioate (9). 1b** (18.1 g, 83.7 mmol) was charged to a mixture of acetic acid (145 mL, 8 vol equiv) and water (4.52 mL, 3 mol equiv). Chlorine gas was bubbled through the reaction mixture until the reaction mixture turned bright green ($T_i$ kept <10 °C). The uptake of chlorine to this point was ∼1.70 mol equiv. A sample of the reaction mixture (11.4 g) was removed and concentrated *in vacuo* to give an oil that solidified on standing. This material was slurried in isohexane and collected by filtation to give the product 0.9 g as a white solid.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.33 (3H, s), 1.39 (3H, s), 3.45 (2H, m), 4.03 (2H, m), 8.15 (1H, d, J 1.4), 8.19 (1H, d, J 1.4), 10.87 (1H, s), 10.93 (1H, s).

**4.14. General Procedures for the Preparation of Masked Intermediates.** *4.14.1. Acyl-Masked 1e, 1f, and 1g.* To a solution of **1c** in MeCN (5−8 vol equiv) and an alkylating agent (1 mol equiv) at −5 °C was added $Et_3N$ (1 mol equiv) dropwise. When complete, the reaction was filtered, the filtrate concentrated *in vacuo* and the resulting solid hot slurried in water then dried to constant weight *in vacuo*. Alkylating agents: for **1e** acetic anhydride was used, for **1f** cyclohexanoyl bromide was used, for **1g** benzoyl bromide was used. Deviation from general procedure: $Et_3NHOAc$ was separated from **1e** by precipitation with acetone; **1e** was then crystallised from toluene.

*4.14.2. Alkyl-Masked 1h, 1i, 1j, and 1k.* To a solution of **1c** and an alkylating agent (2 mol equiv) in MeOH (10 vol equiv) at 60 °C was added NaOMe solution (25% w/w in MeOH, 8 mol equiv) over ∼15 min. After the reaction was complete (by HPLC) it was quenched with HCl (5 M, 9 mol equiv). The resulting solid was removed by filtration, and the filtrate was concentrated to dryness. The residue was slurried with water, collected by filtration, and dried to constant weight. Alkylating agents: for **1h** isopropyl bromide was used, for **1i** crotyl bromide was used, for **1j** ethyl bromide was used, and for **1k** bromomethylcyclohexane was used.

**4.15. Thioacetic Acid *S*-((*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethyl) Ester (1e). 1e** was isolated in 63% yield, 96.5% w/w by $^1$H NMR assay.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.32 (3H, s), 2.35 (1H, s), 3.13 (1H, d, J 13.8), 3.21 (1H, d, J 13.8), 7.99 (1H, s), 10.72 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 22.63, 30.46, 34.98, 61.59, 156.04, 176.69, 193.62. Mp = 89−90 °C. FTIR 1699. *m/z* (%) from LC/MS: 114.20 (100), 203.20 (27, $[M + H]^+$), 220.20 (5, $[M + H_2O + H]^+$), 405.20 (4, $[2M + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_9H_{14}N_3O_3S$ = 244.0756, found = 244.0734 (9 ppm error).

**4.16. Cyclohexanecarbothioic Acid *S*-((*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethyl) Ester (1f). 1f** was isolated in 85% yield, 91.5% w/w by $^1$H NMR assay.

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.18−1.94 (10H, m), 1.55 (3H, s), 2.53 (1H, tt, J 3.59, 11.28), 3.07 (1H, d, J 14.2), 3.39 (1H, d, J 14.2), 5.45 (1H, s), 7.99 (1H, s). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 23.19, 26.42, 26.48, 26.76, 30.60, 30.90, 35.44, 53.95, 64.42, 158.80, 178.97, 202.30. Mp = 195−197 °C. FTIR 1702, 2854, 2935 cm$^{-1}$. *m/z* (%) from LC/MS: 288.20 (4, $[M + H_2O + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_{14}H_{22}N_3O_3S$ = 312.1382, found = 312.1402 (6.4 ppm error).

**4.17. Thiobenzoic Acid *S*-((*S*)-4-Methyl-2,5-dioxo-imidazolidin-4-ylmethyl) Ester (1g). 1g** was isolated in 92% yield, 97% w/w by $^1$H NMR assay.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.40 (3H, s), 3.38 (1H, d, 13.8), 3.44 (1H, d, J 13.8), 7.55−7.94 (5H, m), 8.08 (1H, s), 10.76 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) 22.74, 34.85, 61.79, 126.94, 129.15, 134.17, 135.85, 156.08, 176.71, 189.38. Mp = 161.4−162 °C. FTIR 1706 cm$^{-1}$. *m/z* % from LC/MS: 176.20 (100), 265.20 (11, $[M + H]^+$), 282.20 (11, $[M + H_2O + H]^+$), 529.00 (10, $[2M + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ = 306.0912, found = 306.0914 (0.7 ppm error).

**4.18. (*S*)-5-Isopropylsulfanylmethyl-5-methyl-imidazolidine-2,4-dione (1h).[22] 1h** was isolated in 51% yield, 98.8% w/w by $^1$H NMR assay.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.16 (6H, t, J 5.7), 1.30 (3H, s), 2.73 (1H, d, J 13.6), 2.78 (1H, d, J 13.6), 2.94 (1H, sep, J 6.6), 7.88 (1 H, s), 10.63 (1 H, s). $^{13}$C (75 MHz, $d_6$-DMSO) $\delta$ 23.36, 35.43 (broad), 37.19, 62.82, 156.34, 177.41. Mp = 185.3−186.6 °C (*lit.* 161−162 °C).[22] FTIR: 1705 cm$^{-1}$. *m/z* (%) from LC/MS: 203.20 (100, $[M + H]^+$), 244.20 (33, $[M + MeCN + H]^+$), 405.20 (10, $[2M + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_{10}H_{18}N_3O_2S$ = 244.1120, found = 244.1143 (9.4 ppm error).

**4.19. (*S*)-5-[((*E*)-But-2-enyl)sulfanylmethyl]-5-methyl-imidazolidine-2,4-dione (1i). 1i** was isolated in 62% yield, 95% w/w by $^1$H NMR. Product was ∼85:15 mixture of trans:cis Major isomer only is reported.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.28 (3H, s), 1.65 (3H, d, J 6.3), 2.61 (1H, d, J 13.9), 2.71 (1H, d, J 13.9), 3.10 (2H, d, J 7.3), 5.32−5.40 (1H, m), 5.51−5.60 (1H, m), 7.29 (1H, s), 10.66 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 17.39, 23.12, 34.31, 37.25, 62.94, 127.11, 127.95, 156.38, 177.45. Mp = 132−134 °C. FTIR: 960, 1705 cm$^{-1}$. *m/z* (%) from LC/MS: 190.20 (100), 215.20 (9, $[M + H]^+$), 233.20 (1, $[M + H_2O + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_{11}H_{18}N_3O_2S$ = 256.112, found = 256.1128 (3.1 ppm error).

**4.20. (*S*)-5-Ethylsulfanylmethyl-5-methyl-imidazolidine-2,4-dione (1j).[22] 1j** was isolated in 44.5% yield, 98% w/w by $^1$H NMR assay.

$^1$H NMR (400 MHz, CD3OD) $\delta$ 1.19 (3H, t, J 7.43), 1.39 (3H, s), 2.51−2.64 (2H, m), 2.79 (1H, d, J 14.1), 2.86 (1H, d, J 14.1). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 14.83, 23.15, 26.67, 38.33, 63.04, 156.40, 177.47. Mp = 129.1−129.5 °C (*lit.* 113−114 °C).[22] FTIR: 1704 cm$^{-1}$. *m/z* (%) from LC/MS: 189.20 (100, $[M + H]^+$), 377.20 (30, $[2M + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_9H_{16}N_3O_2S$ = 230.0963, found = 230.0986 (10 ppm error).

(22) Tahara, S.; Obata, Y. *Agric. Biol. Chem.* **1971**, *35* (1), 53.

**4.21. (*S*)-5-Cyclohexylsulfanylmethyl-5-methyl-imidazolidine-2,4-dione (1k). 1k** was isolated in 88%, 100% w/w by $^1$H NMR assay.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 0.86−1.82 (11H, m), 1.28 (3H, s), 2.43 (2H, d, J 7.0), 2.69 (1H, d, J 13.9), 2.76 (1H, d, J 13.9). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 23.19, 25.43, 25.88, 31.95, 37.43, 63.10, 156.36, 177.42. Mp = 185.3−186.3 °C. FTIR: 1703, 2852, 2923 cm$^{-1}$. *m/z* (%) from LC/MS: 186.20 (100), 257.20 (20, $[M + H]^+$), 298.20 (25, $[M + MeCN + H]^+$). Accurate mass, calc. for $[M + MeCN + H]^+$ $C_{14}H_{24}N_3O_2S$ = 298.1589, found = 298.1583 (2 ppm error).

**4.22. (*S*)-5-Methyl-5-phenylsulfanylmethylimidazolidine-2,4-dione[23,25] (1l). 1l** was prepared using the procedure described by Xu et al.[24] and purified by column chromatography (eluant 2:1, EtOAc/iHex) to give the product 1.45 g (16%) as a white solid.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.35 (3H, s), 3.25 (2H, s), 7.20 (1H, t, J 7.2), 7.30 (2H, t, J 7.2), 7.36 (2H, d, J 7.2), 7.97 (1H, s), 10.74 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 23.18, 40.56, 62.52, 126.06, 128.79, 128.92, 135.84, 156.23, 176.96. Mp = 147−149 °C (lit. 155−157).[25] *m/z* (%) from LC/MS: 237.20 (100, $[M + H]^+$).

**4.23. General Procedure for One-Step Oxidative Chlorination of 1a−l and 15a,b.** Reactions were run on 1−2 g scale in 25 mL three-neck round-bottom flasks equipped with temperature probe, condenser and chlorine line. The sulfides to be oxidized were dissolved in acetic acid/water (9:1 v/v, 9 ± 2 vol equiv), with chlorine gas (~3 mol equiv) bubbled through with stirring. Temperature profiles were collected electronically. Chlorine was administered using the delivery system described earlier in this paper. Samples were taken at 5 min intervals and analyzed by LC/MS. Reaction profiles were constructed using LC/MS data.

**4.24. General Procedure for Two-Step Oxidation−Chlorination of 1a−l and 15a,b.** Solutions of the sulfide substrates were prepared as above. These solutions were treated with 35% hydrogen peroxide (1.08 mol equiv) at ambient temperature and stirred for ~2 h. The reactions were analysed by LC/MS to confirm completion, and then chlorine was administered as described above.

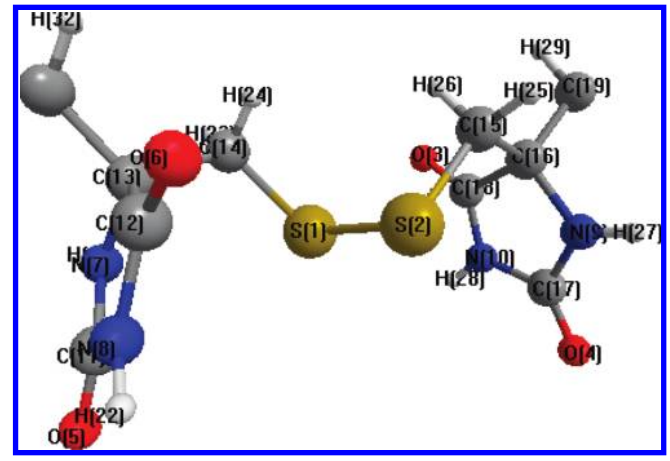



***Figure 5.*** **X-ray crystal structure of disulfide 9 (the Flack's × parameter was refined to −0.01(9)).**

**4.25. (*S*)-5-Methyl-5-trichloromethyl-imidazolidine-2,4-dione (19).** Following the oxidative chlorination of **1k**, the reaction was concentrated to dryness to afford an oily solid. A small portion of this material was purified by column chromatography (eluant 2:1, isohexane/ethyl acetate). This yielded the title compound (41 mg) as a white solid.

$^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 1.72 (3H, s), 8.95 (1H, s), 11.26 (1H, s). $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 19.32, 72.58, 101.45, 155.99, 171.02. HMBC and HSQC experiments helped to confirm that the NMR data was consistent with the proposed structure. Accurate mass, calc. for $[M + H]^+$ $C_5H_6Cl_3N_2O_2$ = 230.9489, found = 230.9494 (1.9 ppm error).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## Supporting Information Available

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