

Improved Process for Chloroxidation of Aryl Sulfides to Aryl Sulfonyl Chlorides in Commercial Grade Formic Acid

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Abstract:

This paper discusses the process advantages of using commercial grade formic acid as the solvent for chlorine gas oxidation of aryl sulfides to sulfonyl chlorides. Compared to chloroxidation in methylene chloride, the chloroxidation in formic acid gave a consistently higher yield and easy product isolation for a sulfonyl chloride intermediate which was used in the production of the sulfonamide herbicide, penoxsulam.

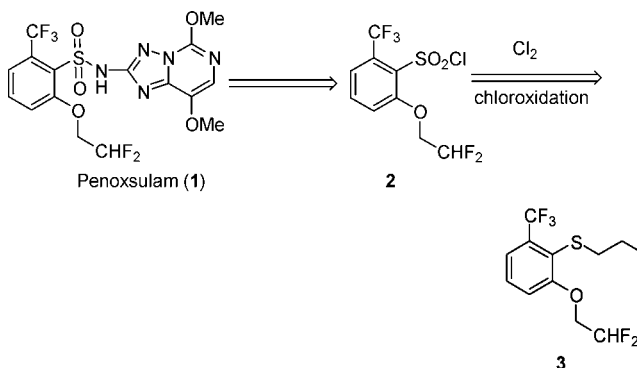
1. Introduction

Sulfonyl chlorides are common intermediates for sulfonamides, many of which are medicinal or crop protection agents.¹ One widely used method for preparing sulfonyl chlorides is reaction of chlorine gas with mercaptans, sulfides, disulfides, sulfoxides, or other precursors in aqueous acidic solutions.² This chlorine gas oxidation, or chloroxidation, has the advantage of using low-cost chlorine gas at production scales.

However, chloroxidation of certain aryl sulfur precursors in an aqueous solution alone can be problematic. Inadequate solubility of starting material or product in the reaction medium hinders the reaction from completion or causes material transfer problems. Also, sulfonyl chloride products often hydrolyze at an appreciable rate in an aqueous solution, resulting in yield loss. Therefore, a binary solvent has been commonly employed to overcome the solubility and stability issues. The binary solvent is typically composed of an inert chlorinated solvent such as methylene chloride and water or an aqueous acid solution.³

Methylene chloride is a confirmed human carcinogen readily absorbed through contact with human eyes, skin, and respiratory system. It is beneficial to identify an alternative for methylene chloride. Although acetic acid/water has been

Scheme 1. Synthetic route to penoxsulam (1) via chloroxidation



reported as a solvent for chloroxidation reactions,⁴ complete removal of acetic acid from products, which is generally required for its sequential coupling reaction with an amine, often meets with difficulties at tonnage scales.

Another complication in the chloroxidation of sulfides is the competing simple oxidation to sulfones. Some literature indicates that hypochlorite, generated from chlorine gas with water, could oxidize sulfides directly to sulfone.⁵ The preference for a sulfonyl chloride over a sulfone is dependent on the reaction conditions such as choice of solvent and the sulfide substrate. Benzyl aryl sulfides are usually good derivatives for minimal sulfone formation. However, for the consideration of atom economy and byproduct separation, lower alkyls, acetyl, or other alkyl derivatives are preferred at production scales.

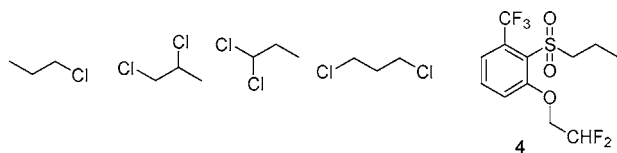
During a multikilogram sample campaign of the Dow AgroSciences, sulfonamide herbicide penoxsulam **1**, sulfonyl chloride **2** was prepared by chloroxidation of the aryl propyl sulfide **3** in a methylene chloride/water mixture (Scheme 1). While the chloroxidation reaction was a clean reaction under the two-phase chloroxidation conditions, its isolated yield at pilot scales was ~10% lower than that of smaller laboratory scales, primarily due to difficulties in the product isolation step. As development work continued, it was recognized that it was highly desirable to find an alternative solvent which could improve process performance and be more environmentally friendly for use in commercial production.

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Scheme 2. Major byproducts in chloroxidation of 3



The search for a methylene chloride alternative led to a survey of a number of solvents. From these studies, formic acid was found to be excellent for chloroxidation of aryl alkyl sulfides, providing consistently high yields with minimal sulfone formation. It also provided certain processing advantages with the corresponding product isolation smoothly incorporated into the next process step. Formic acid is not a carcinogen and is environmentally more friendly than methylene chloride. This chloroxidation method has been successfully applied to several other sulfur substrates.

2. Results and Discussion

Some incomplete information about the mechanism of chloroxidation of an aryl alkyl sulfide to its aryl sulfonyl chloride is in the literature. Sulfoxide (Ar-SO-R'), sulfenyl chloride (Ar-S-Cl), sulfinyl chloride (Ar-SO-Cl), disulfide (Ar-S-S-Ar) are some possible intermediates that can be eventually converted to sulfonyl chloride.^{4,5}

In theory, a chloroxidation reaction needs only 2 equiv of water and 3 equiv of chlorine gas to convert sulfide **3** to sulfonyl chloride **2** with the release of 1 equiv of propyl chloride and 4 equiv of HCl. However, this reaction typically requires 4–5 equiv of chlorine to drive the reaction to completion.

Several dichloropropanes were detected in the reaction at less than 5 mol % of the total chloropropanes (Scheme 2). The mechanism for the dichloropropane formation is not apparent. Sulfone **4** was confirmed as a byproduct in a yield of 2–5%. It was found inert to chloroxidation and could not be further converted to **2**. It was postulated that **4** is a side oxidation product from a sulfoxide intermediate.⁴

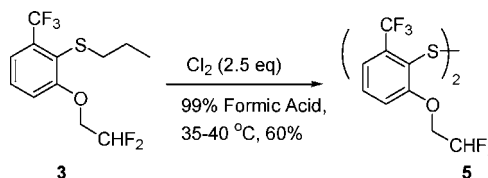
2.A. Solvent Screen. For solvent screening experiments, chloroxidation of sulfide **3** was conducted at a 5-g scale using 10 equiv of water and excess chlorine gas. This chloroxidation reaction is exothermic (-90 kcal/mol),⁶ and a water bath may be needed. Product **2** was not isolated but was extracted into an organic phase. Its yield was calculated on the basis of the weight of the organic phase and its assay in the organic phase.

Table 1 lists the in-pot yields of **2** and **4** in various solvents, mostly at 50–60 °C. Polar solvents such as carboxylic acids gave better yields than nonpolar ones such as toluene. Short-chain aliphatic organic acids are among the best, giving **2** in ~90% yield with less than 1% of **4**. For chlorinated solvents, methylene chloride gave the best yield at 78% with 3.5% of **4**. Both water and 2 N HCl aqueous solutions gave fair yields of **2** but generated a significant amount (~12%) of **4**. For the reactions in aqueous solutions, compounds **2** and **4** precipitated out and agglomerated upon cooling to below 30 °C, which could be a significant process issue at large scales.

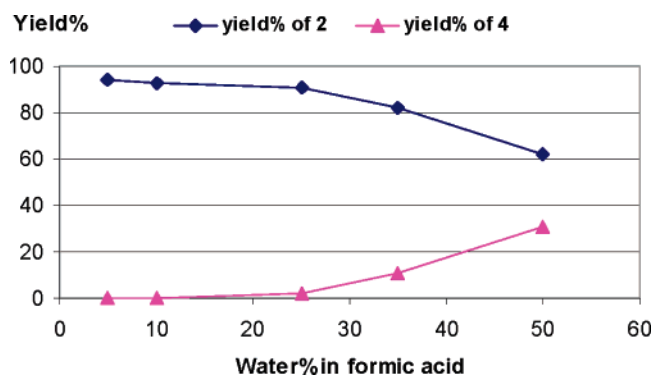
Table 1. Solvent screen for chloroxidation of **3** to **2**

solvent	temp (°C)	yield % of 2	yield % of 4
methylene chloride	38	78	3.5
1,2-dichloroethane	50–55	61	1.9
chlorobenzene	55–60	69	0.8
dichlorobenzene	55–60	70	1.2
toluene	50	44	2.3
acetonitrile	50–60	83	2.8
diglyme	55–60	71	6.7
tetraglyme	60	66	6.7
tetraglyme	20	59	15
nitrobenzene	55–60	74	2.7
nitromethane	55–60	82	0.9
sulfolane	55–60	72	3.1
water	50	78	12
2 N HCl aq	50	75	13
formic acid	50	92	0.3
acetic acid	55–60	91	0.8
propionic acid	50–60	92	1.0
trifluoroacetic acid	38	83	0.0
hexanoic acid	55–60	89	4.7

Scheme 3. Chloroxidation of **3** in absence of water



Scheme 4. Yields of **2** and **4** vs water percent in formic acid



Both acetic acid and formic acid gave very similar chloroxidation results for yield and impurity levels. Unlike methylene chloride, they are not carcinogens. For reasons to be mentioned later, formic acid was selected and further investigated for its process feasibility and compatibility.

2.B. Water Limits in Formic Acid. Water is needed for chloroxidation reaction in formic acid. When chloroxidized in 99% formic acid with only 2.5 equiv of chlorine gas, **3** was converted to disulfide **5** predominantly (Scheme 3). When water content was above 25% in formic acid, formation of sulfone **4** became a major issue, mirroring a similar observation of chloroxidation in water. Therefore, the recommended water content is about 10%. Commercial grade formic acid has ~12% water and can be used directly (Scheme 4).

2.C. Isolation of Solid Product. The solubility of **2** in formic acid containing 14% water is about 3.0 wt % at room

(6) This information was obtained through an internal test.

temperature. This solubility decreased to 0.1 wt % when the water content was 18% and could be further reduced to 0.02 wt % when cooled to 0 °C. Therefore, the yield loss of **2** to formic acid can be limited to less than 2% by quenching the reaction with cold water and then cooling to below 5 °C. The amount of the cold water was about 30% of the weight of the formic acid used. The precipitated **2** is needle-like crystalline and was easily stirred and collected by a simple gravity filtration. Both GC and LC analyses of the isolated crude **2** showed a purity of ~97% with the remainder being mostly formic acid and water. The yield of **2** was consistently in a range of 92–94% starting with **3** in a purity range of 92–98%.

The residual water and formic acid in crude wetcake **2** needed to be removed before its next coupling reaction with an amine to produce **1**. This removal was achieved at laboratory scales by vacuum drying overnight at room temperature. Drying at a temperature higher than 50 °C caused **2** to partially hydrolyze to its sulfonic acid. However, these mild drying conditions are not efficient for drying metric tons of **2**.

2.D. Product Extraction Solvent. Practical inconvenience in removal of trace water and formic acid trapped in the crude wetcake **2** drove the search for a suitable solvent which can extract **2** from its formic acid reaction solution, dissolve **2** in reasonably high concentrations, and undergo azeotropic distillation to remove water and formic acid without causing **2** to hydrolyze.

Toluene was chosen on the basis of the following criteria. First, toluene is immiscible with formic acid or water. The solubility of **2** in toluene is ~45 wt % at room temperature, whereas its solubility in formic acid is less than 3 wt %. The partition coefficient for **2** between toluene and the formic acid reaction mixture is ~17. Therefore, toluene can extract and dissolve **2** efficiently. Second, for the corresponding azeotropes with toluene, water has 14 wt % vapor fraction at 84 °C, and formic acid has 50 wt % vapor fraction at 86 °C. This allows an easy removal of both water and formic

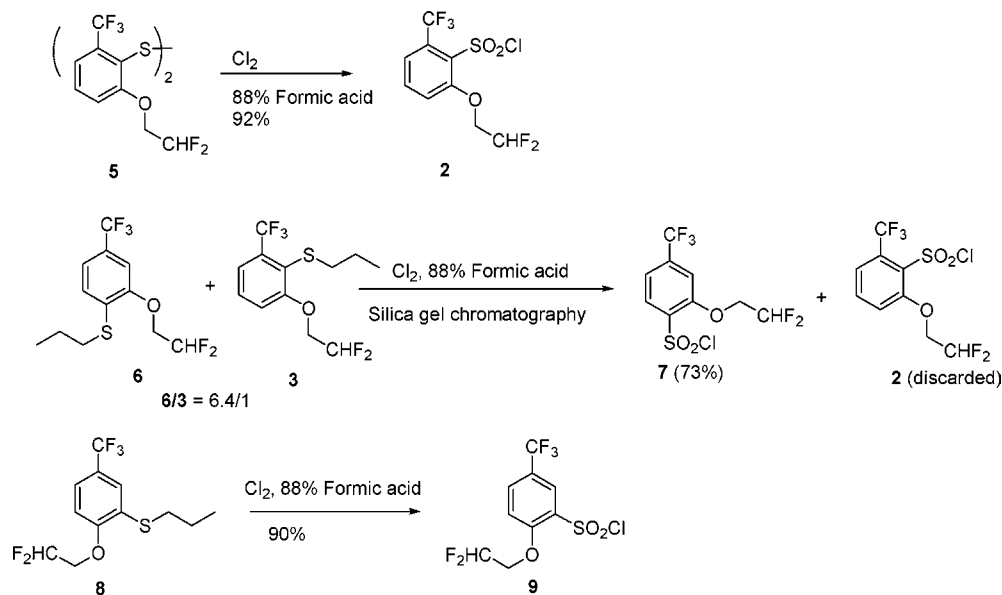
acid from the toluene solution of **2**, eliminating a solid product isolation step. Additionally, used formic acid may be recycled if it has low water content.

For this product extraction from formic acid to toluene, no water was added after the reaction except the water in the sodium bisulfite solution which was used for chlorine quenching. The formic acid reaction mixture was extracted with toluene. The toluene extract was distilled in vacuo to give a toluene solution of **2** at 35 wt %. The overall yield was above 90% for this chloroxidation reaction.

Acetic acid is less expensive than formic acid. Chloroxidation in acetic acid is similar to that in formic acid. However, a higher solubility of **2** in acetic acid caused 2–5% higher yield loss when **2** was isolated by water quench and filtration process. Removal of the acetic acid residing in the isolated wetcake **2** was more difficult. When toluene extraction was used, the percent of acetic acid in the toluene was 35 wt % after the first phase separation, and ~10 wt % after a water wash. These levels are much higher than the typical 2–6 wt % of formic acid in toluene extract without a water wash. Therefore, formic acid was chosen over acetic acid for the chloroxidation process.

2.E. Chloroxidation of Other Sulfonyl Chloride Precursors. The optimized chloroxidation conditions have been applied to other sulfur precursors. Disulfide **5** can be chloroxidized similarly in 88% formic acid to give **2** in a similar high yield. Sulfonyl chlorides **7** and **9** were also prepared similarly from the corresponding arylsulfides **6** and **8**, respectively. Sulfide **6** was obtained as a mixture with its isomer **3** in a ratio of 6.4/1. Separation of **6** and **3** by chromatography was very difficult. However, the corresponding sulfonyl chlorides **2** and **7** could be easily separated by silica gel chromatography. Sulfide **8** was converted to sulfonyl chloride **9** under the similar chloroxidation conditions in 90% yield. Both **7** and **9** were sequentially used to make impurity standards for **1**.

Scheme 5. Chloroxidation of sulfides in formic acid



2.F. Hazard Evaluation of Formic Acid in Chloroxidation. Hazard evaluation of formic acid in chloroxidation was conducted in our process research. Formic acid is flammable and should be isolated from heat and flame. It is corrosive and has moderate toxicity. However, worker exposure can readily be managed with appropriate personal protection equipment and engineering controls.

This chloroxidation is exothermic (90 kcal/mol) in nature.⁶ An internal accelerated-rate calorimetry testing indicated an onset exothermal temperature at about 80 °C. Therefore, the reaction temperature should be controlled, typically at 30–40 °C, by slow chlorine gas addition and appropriate cooling. The slow chlorine addition can limit the accumulation of excess chlorine in the reaction solution and headspace, preventing an instantaneous reaction.

Formic acid can react slowly with chlorine to produce HCl and CO₂.⁷ GC analysis of the reaction headspace during a typical run revealed CO₂ being generated at the end of the reaction. Its amount was less than 1% gas volume fraction. The total amount of chlorine gas required for a chloroxidation reaction in formic acid was similar to that in other solvents, such as methylene chloride which does not have the potential to react with chlorine. Therefore, it appears that the formic acid/chlorine reaction does not compete significantly with

the chloroxidation of the sulfide. Trace amounts of chlorine at the end of the reaction can be quenched by the addition of aqueous sodium bisulfite solution. However, the residual chlorine was often observed to diminish over time, indicated by a starch iodide paper, possibly as the result of slow reaction with formic acid.

3. Conclusions

Our work has clearly demonstrated that commercial-grade formic acid is an excellent solvent for chloroxidation of aryl sulfides or disulfides with chlorine gas to prepare sulfonyl chlorides. Chloroxidation in formic acid gave a consistently higher yield and easy product isolation through precipitation or extraction. Compared to commonly used chlorinated solvents such as methylene chloride, formic acid is not listed as a carcinogen and can be managed readily in a production plant. This improved process has been successfully demonstrated during commercial production of the herbicide, penoxsulam **1**.

Supporting Information Available

Additional experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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