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Development of a Process for the Preparation of Chloromethyl Chlorosulfate

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Supporting Information

ABSTRACT: A new and efficient synthesis of chloromethyl chlorosulfate (CMCS) from chloroiodomethane and chlorosulfonic acid is described. This process leverages a chlorosulfonic acid-mediated iodide oxidation to drive the equilibrating displacement process to full conversion. The resulting iodine byproduct is further oxidized and removed as iodate, to prevent iodide-induced decomposition of CMCS. This new process provides an efficient and scalable protocol for the preparation of CMCS in 92% solution yield and high purity (>99 GC area %).

INTRODUCTION

Chloromethyl chlorosulfate (CMCS) is a highly versatile reagent for the chloromethylation of dialkyl phosphates,[1] carboxylic acids,[2] and protected aminoacids.[3] The chloromethylated products are an important class of compounds used in the synthesis of pro-drugs.[2−4] In addition, CMCS has found application in the synthesis of citalopram, *S*-citalopram[5] and as a voltage delay inhibitor in lithium batteries.[6] Despite the importance and the apparent structural simplicity of this molecule, efficient methods to prepare high quality CMCS are rather limited.

In 1927, Fuch and Katscher[7] reported the first synthesis of CMCS in low yield (30%), through the high temperature (>80 °C) reaction of paraformaldehyde and chlorosulfonic acid. Another early report prepared CMCS from chloromethyl chloroformate and chlorosulfonic acid with modest yield and still requiring high reaction temperatures.[8] Binderup and Hansen[2a] showed that CMCS could be prepared by refluxing chlorobromomethane and chlorosulfonic acid; however, this procedure again produced CMCS in low yield. More recently, Power et al. demonstrated that SO_3 could directly insert into one of the carbon−chlorine bonds of dichloromethane (DCM) when catalyzed by trimethyl borate.[9] This process has significant advantages over the previous procedures; for example, only ambient temperature is required, and the reaction proceeds quickly. However, CMCS is again produced in low yield (33%). The insertion process exhibits poor selectivity, producing a significant amount of methylene bis(chlorosulfate), for which multiple distillations were required for purification. Additionally, liquid SO_3 (the metastable γ-form) is required for this process, which is difficult to obtain on a commercial scale due to its spontaneous conversion to the polymeric β- or α-forms. Once solidified it cannot be used in the process as both solid forms are highly insoluble. In this note we describe our efforts towards developing a more efficient and scalable process for the preparation of CMCS, which delivers the product in excellent yield and quality from chloroiodomethane and chlorosulfonic acid.

RESULTS AND DISCUSSION

Initially, we examined the known literature procedures[2a,7−9] to develop a preliminary knowledge of the key challenges in preparing this molecule, which we hoped to leverage in our development of a more scalable process for the preparation of CMCS. However, all the current processes proved unfavorable for large scale use and little useful information was gained from the processes; the reaction conditions were not suitable for our use, and the reactions produced complex mixtures of products requiring extensive purification. As such, we felt that all the previously described procedures would be difficult to optimize for the preparation of CMCS in large quantities.

In reviewing the literature we were unable to find examples of chloroiodomethane being used in the preparation of CMCS. This seemed like an interesting and obvious omission, given the use of bromochloromethane described above.[2a] However, analogues of CMCS, such as 1-chloroethyl chlorosulfate, were synthesized from the corresponding chloroiodo derivatives, albeit in low yields.[2a,10] Thus, we decided to investigate the use of chloroiodomethane.

Using Hansen's bromochloromethane procedure as a starting point,[2a] the results of our initial experiments reacting chlorosulfonic acid with chloroiodomethane were encouraging. Treating chloroiodomethane with chlorosulfonic acid resulted in rapid initial reaction to CMCS, although with only modest conversion (Scheme 1). The reaction seemed to stall, and it appeared as though an equilibrium was established (the HI produced potentially providing an avenue for reversibility of the reaction). An additional key observation was the dark-purple reaction mixture and the presence of dense metallic solids, suggesting some iodine formation, presumed to be from HI oxidation. In developing balanced chemical equations to describe these key observations (Scheme 1, reactions 1 and 2), we reasoned that chlorosulfonic acid maybe responsible for the oxidation of HI—thus, if the reaction was in equilibrium,

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Scheme 1. Reactions of chloroiodomethane and chlorosulfonic acid

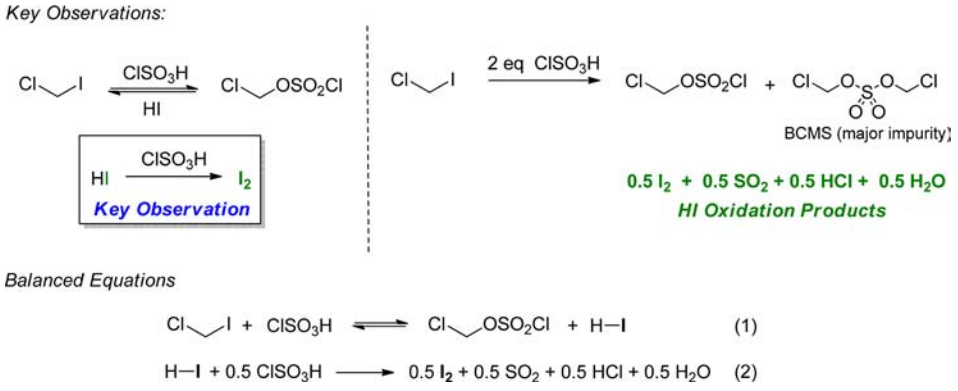


Table 1. Initial results of CMCS preparation using chlorosulfonic acid and chloroiodomethane

entry	$ClSO_3H$ (equiv)	solvent, (vol)[a]	temp, time	unreacted $ClCH_2I$ (%)[b]	in-process yield (%)[c]	BCMS (M %)[d]
1	1.1	DCM (3)	0–21 °C, 18 h	37	41	10
2	1.5	DCM (3)	0–21 °C, 18 h	4	48	13
3	2.0	none	0 °C, 2 h	<1	52	15
4	2.0	DCM (3)	21 °C, 3 h	<1	63	11
5	2.0	DCM (6)	21 °C, 18 h	<1	65	9

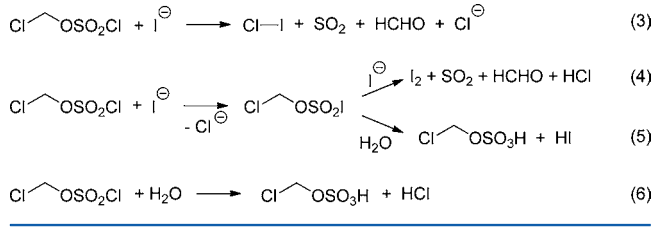
[a]Reactions were carried out on 0.5 g of chloroiodomethane. Solvent volumes were measured in mL/g chloroiodomethane. [b]Determined by proton NMR analysis. [c]Yield calculated from QNMR with 1,4-dichlorobutane as an external reference standard. [d]Ratio to CMCS as determined by proton NMR analysis.

oxidative removal of HI may be able to drive the reaction to completion (Scheme 1, reaction 2). In corroboration of this thesis, addition of excess chlorosulfonic acid had an immediate impact on the yield of the process; the results are summarized in Table 1.[11]

The reaction of chloroiodomethane with 2 equiv of chlorosulfonic acid was driven to completion by the rapid oxidation of the byproduct hydrogen iodide to iodine with the production of SO_2 and HCl. The reaction mixture was relatively free of impurities, except for bischloromethyl sulfate (BCMS, Scheme 1), which ranged from 15 M% in the absence of solvent to 9 M % under more dilute conditions (Table 1). With a reliable process in place, which we felt could be further optimized, we turned our attention to a more challenging problem – handling the iodine byproduct.

The oxidation of HI to I_2 had removed the possible reversibility of the process, but had created a secondary issue; highly dense iodine solids now settled at the bottom of a reactor, complicating potential transfers of the reaction stream. It was therefore envisioned to convert the iodine into a more soluble form. Initially we attempted this through a general reductive procedure, employing aqueous sodium thiosulfate, which readily reduces iodine to sodium iodide.[2a] However, this quench protocol provided a solution of CMCS in DCM in only 47% solution yield (a decrease of ~20% during a lab-scale quench procedure). Subsequent investigation revealed that the CMCS was unstable to the biphasic workup conditions, with a greater than 50% potency loss observed after agitating the quenched mixture for 2 h. It appeared that the iodide produced by the reductive quench was capable of causing decomposition of CMCS. Several possibilities exist to explain this instability; reductive elimination (Scheme 2, pathways 3 and 4), hydrolysis through the more reactive iodosulfate (formed through Finkelstein exchange, Scheme 2, pathway 5) or direct hydrolysis of CMCS (Scheme 2, pathway 6)[12]- all avenues

Scheme 2. Iodide mediated redox or hydrolysis of CMCS



could result in the observed decrease in yield.[13] Isolation of pure CMCS allowed us to determine that direct hydrolysis was slow (Scheme 2, pathway 6) but could be catalyzed by iodide (pathway 5). This incompatibility indicated that a direct reductive aqueous workup strategy was not viable – due to the production of iodide.

A far less common method to remove iodine is through oxidation.[14] With the above hypothesis in mind, an oxidative protocol would convert the iodine to the corresponding iodate, reducing the propensity for nucleophilic reactivity of the iodine byproducts. A quick screen of common oxidants revealed that bleach effectively served this purpose (Table 2). Implementing a bleach based workup dramatically increased the solution yield to 60%, and importantly, stability studies on the reaction stream with various amounts of bleach (0.1 – 3.5 equiv) indicated a

Table 2. Screen of common oxidants to quench iodine to iodate

oxidants	qualitative observations
H_2O_2	very slow oxidation
$K_2S_2O_8$	slow (~18 h)
oxone	0.5–1 h (large quantity required)
bleach	<0.5 h, well controlled
$NaClO_2$	extremely fast (safety hazards)

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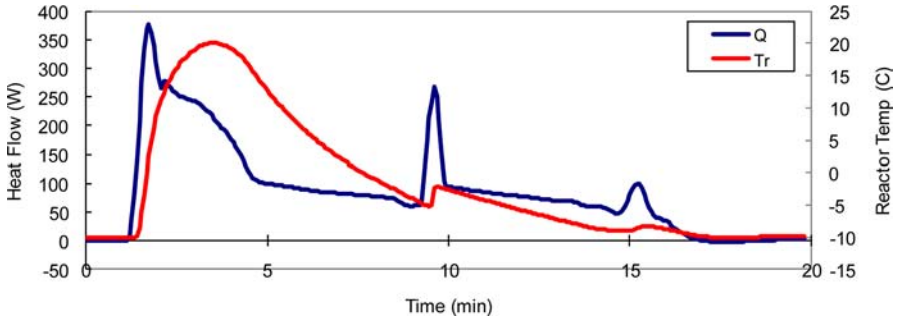

Figure 1. RC1 data of heat flow (Q) and batch temperature (T_r) for a continuous addition of 10 wt % bleach over 15 min into a completed reaction stream (initial temperature −10 °C).

less than 6% drop in CMCS potency over 24 h. This result suggested that a slow quench or an extended hold postquench would not result in significant product loss.

Although this procedure for the synthesis of CMCS doubled the yield found in the literature, it was still modest (~60%). It was envisioned that further study of the reaction parameters could lead to further improvements. The primary focus was to reduce the formation of the major impurity (BCMS), since the reaction generated 9 M% of this compound, corresponding to an 18% loss in yield. We hypothesized that the formation of BCMS was the result of the water produced by the *in situ* chlorosulfonic acid mediated oxidation of HI to I_2 (Scheme 1); hydrolysis of either CMCS or chlorosulfonic acid to the corresponding sulfonic acid and subsequent reaction with chloroiodomethane would yield BCMS.

To our delight, this hypothesis was supported by significant reductions in the observed BCMS level (to 1−2% from 9%) when a water scavenger, such as acetyl chloride, was added into the reaction mixture. After screening multiple potential chemical desiccants, thionyl chloride was identified as the optimal water scavenger. It not only tolerates the harsh reaction conditions (chlorosulfonic acid and iodine), but is also an excellent chlorinating reagent that may be able to return any hydrolyzed sulfuric acid or chloromethylsulfonic acid back to the active sulfonyl chloride or CMCS. Furthermore, no additional treatment is required to remove the excess thionyl chloride since it readily decomposes during the aqueous bleach quench.

Further optimization of reagent stoichiometry, reaction volume and temperature led to reproducible and high yielding reaction conditions; 1.65 equiv of chlorosulfonic acid and 0.8 equiv of thionyl chloride in DCM (9 mL/g) at 35 °C. The reaction typically required 5−7 h for completion, following a quench with bleach (10 wt %, 2.6 equiv) and subsequent phase separation, CMCS was produced in 90−95% yield as a solution in DCM, with low BCMS levels (typically ~0.2 M%). Neat CMCS with higher quality can then be obtained by concentration of the rich DCM stream (>99% GC purity, excluding residual DCM).

During the development of this process, especially the oxidative iodine quench, process safety was a key consideration. To enable scale−up beyond lab scale, the reaction was examined in detail from a process-safety perspective, with several factors being identified as potential concerns for further investigation. As the chemicals used are highly corrosive, the material compatibility of the reaction streams needed to be assessed, additionally the off-gases and aqueous waste streams had to be investigated for safe handling and control. The critical safety concerns identified and discussed in detail here relate to thermochemistry, in particular, control and understanding of the heat-flow observed during the quench protocol and the concomitant off-gassing.

As one would expect, a strong exotherm is observed during the bleach addition. The hydrolysis of excess chlorosulfonic acid and thionyl chloride, along with the oxidation of iodine, all contribute to the observed heat flow. Calorimetric studies in an RC1 reactor found the quench to have an adiabatic temperature rise of 58 °C (enthalpy of 416 kJ/mol of input chloroiodomethane), higher than the boiling point of the solvent (DCM). More detailed testing found that CMCS is thermally stable to 180 °C at which point an exothermic decomposition was observed—this high temperature for decomposition onset providing an adequate safety window from the standard operating conditions. However, the high adiabatic temperature rise for the reaction itself meant that achieving reflux during the quench was likely; while this would cool the system, a significant risk exists for over pressurization or ejection of the process stream from the vessel if cooling is insufficient. Thus, it was important to develop a quench protocol that would be fundamentally safe, even with potential fluctuations (time, rate of charge, amounts, etc.) while operating on large scale.

Accurate measurement of the heat flow was therefore required to understand the complex triphasic (liquid−liquid−solid) quench. RC1 data proved crucial in developing a procedure with a fundamental basis of safety and was extensively utilized during the development of this process. Figure 1 shows the thermal profile of the quench performed by a continuous addition (10% aqueous bleach directly added to the reaction stream where both streams were precooled to −10 °C). The exotherm was predominantly found at the start of the addition with a minor delayed exotherm late in the addition.[15] Details of the analysis can be found in the Supporting Information.

Two control strategies were initially envisaged, both involving a metered addition of bleach (either controlled continuous or portion wise cubic addition protocols).

For a continuous addition mode, the RC1 heat transfer data, along with modeling, would allow the determination of the appropriate addition time to ensure reactor temperature control (target <30 °C). However, risks with this method are the reproducibility of the quench kinetics, variability in charge rate, sensitivity of the triphasic system to agitation and accumulation of bleach (due to potential fluctuations during large scale operations).

The second option is a controlled cubic addition. In this protocol, bleach would be charged in portions to a second

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reactor, cooled and then dosed into the reaction mixture. The ability to more accurately control and segregate the bleach charge (negating the impact of faster charge rates) prior to addition to the main reactor is an important component of the cubic addition protocol, especially during the initial phase of the addition when the exotherm is significant.

Unsurprisingly given the triphasic nature of the reaction, it was also found that adequate agitation is necessary during the quench to ensure the complete oxidation of iodine to iodate in this triphasic mixture. While, in both cases we could readily control the batch temperature below 30 °C, the portion wise cubic addition protocol is preferred. The heat-flow of the cubic addition protocol is shown in Table 3.

Table 3. Results of calorimetry from continuous and cubic quench protocols

	Reaction Calorimetry	
bleach addition	ΔH (KJ/mol)	T_{ad} (°C)
slow addition protocol: 100% (continuous)	461	58.2
cubic addition protocol: first 1.5%	71.3	13.1
next 3.5%	63.3	11.5
next 5%	64.5	11.1
next 10%	74.8	11.4
next 30%	105	10.5
last 50%	125	8.5

With a protocol established to control the heat flow generated by iodine oxidation, additional control elements were still required—especially with respect to gas production. Treatment of the off-gas using a sodium hydroxide scrubber allowed for effective neutralization of corrosive gaseous byproducts, HCl and SO_2. The off-gas rate during the reaction phase is not addition controlled.[16] Since the initial reaction rate is high, a staged temperature increase was used to control the off-gas rate. On larger scale a similar gas treatment strategy would need to be utilized with reactors that are properly sized to prevent over pressurization.

In conclusion, we have developed a new and high-yielding procedure for the preparation of CMCS from chloroiodomethane and chlorosulfonic acid. Key insights were leveraged to drive the reaction to completion through HI oxidation and to deplete the water generated *in situ* by using thionyl chloride, leading to significant increases in both quality and yield. An innovative oxidative quench protocol was developed to remove the iodine while avoiding iodide formation. Critical RC1 data was utilized to develop a portion wise cubic-addition based quench protocol, providing a fundamental basis of safety for this new procedure. The process described herein affords an efficient and scalable protocol for the preparation of high-quality CMCS.

EXPERIMENTAL SECTION

General. The reactions were performed under a nitrogen atmosphere. Reagents were used as received. In-line Raman, GC or Proton NMR was used to monitor the reaction progress. Details for the Raman and GC methods are listed in the Supporting Information. Quoted yields are calculated solution yields based on quantitative analysis of proton NMR with 1,4-dichlorobutane as an external reference standard. NMR analysis was performed on a Bruker DRX-500 instrument.

In a typical experiment: A 5-L reactor was equipped with a temperature probe, an agitator and a condenser that was connected to a scrubber filled with aqueous NaOH solution. A nitrogen inlet was attached between the condenser and the scrubber. After the reactor was inert with nitrogen, DCM (1.44 L), chlorosulfonic acid (170.9 g, 1.47 mol, 1.65 equiv), and thionyl chloride (84.6 g, 0.711 mol, 0.8 equiv) were charged at 20 °C, followed by chloroiodomethane (160 g, 0.889 mol, 1.0 equiv). The batch temperature increased to 25 °C after the addition of chloroiodomethane. Gas evolution commenced after ∼5 min and the mixture became a dark red color. After being agitated for 1 h at 20−25 °C, the mixture was heated to 35 °C over 30 min and stirred until reaction completion (chloroiodomethane <5% by in-line Raman and confirmed by GC or proton NMR, ∼6 h). The reaction mixture was then cooled to 0 °C, and quenched by a cubic addition (addition of 1.5%, 3.5%, 5%, 10%, 30%, 50% in portions) of a cold 10 wt % bleach solution (0 °C; 1.72 kg, 2.31 mol, 2.6 equiv). After the bleach addition the resulting mixture was agitated for 0.5 h prior to the phase split. The rich bottom organic layer was washed with a 0.25% bleach solution (800 mL), affording a colorless CMCS solution in DCM (1.98 kg, 6.82 wt %, 92% solution yield). A sample of the CMCS solution was concentrated to provide neat CMCS as a dense colorless liquid with spectra identical to that in literature.[9a]

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

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(11) DCM appeared to be the optimal solvent for the preparation. Other common solvents were either disfavored (e.g., 1,2-dichloroethane), or incompatible (toluene, THF, DMF), or poorly performed (heptanes).

(12) For the reactions of sulfonyl chlorides with iodide, see: Buncel, E. *Chem. Rev.* **1970**, *70*, 323.

(13) CMCS solution in DCM was relatively stable to water. On the basis of these observations, pathway 3 or 5 is likely to dominate the decomposition pathway in the presence of iodide aqueous solution.

(14) Trapping the iodine with an olefin or alkyne (fumaric acid, dimethyl acetylene dicarboxylate) was unsuccessful.

(15) The late peaks in Figure 1 could be due to the secondary reactions (for detail, see in the Supporting Information), for example, hydrolysis of thionyl chloride, which proceeded faster at higher pH when more basic bleach was added. Subsequently, the oxidation of the resulting sulfite from the hydrolysis to sulfate could also take place.

(16) A delayed off-gas was observed (10−15 min after initial addition of the substrate). The off-gas rate may depend on the batch temperature and the agitation speed.