

Hydrogen Chloride Gas in Solvent-Free Continuous Conversion of Alcohols to Chlorides in Microflow

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S Supporting Information

ABSTRACT: Chlorides represent a class of valuable intermediates that are utilized in the preparation of bulk and fine chemicals. An earlier milestone to convert bulk alcohols to corresponding chlorides was reached when hydrochloric acid was used instead of toxic and wasteful chlorinating agents. This paper presents the development of an intensified solvent-free continuous process by using hydrogen chloride gas only. The handling of corrosive hydrogen chloride became effortless when the operating platform was split into dry and wet zones. The dry zone is used to deliver gas and prevent corrosion, while the wet zone is used to carry out the chemical transformation. The use of gas instead of hydrochloric acid allowed a decrease in hydrogen chloride equivalents from 3 to 1.2. In 20 min residence time, full conversion of benzyl alcohol yielded 96 wt % of benzyl chloride in the product stream. According to green chemistry and engineering principles, the developed process is of an exemplary type due to its truly continuous nature, no use of solvent and formation of water as a sole byproduct.

INTRODUCTION

Sustainable manufacturing of active pharmaceutical ingredients (APIs) encompasses several aspects such as continuous processing, process intensification, minimization of solvent use and advances in bioprocesses.¹ Currently, continuous processing is one aspect within process intensification, which targets the reduction of equipment size, costs, energy consumption, solvent utilization, and waste generation.² Microreactor technology is an actively studied platform aiming at implementing continuous processing, achieving process intensification and finally assisting in delivering sustainable processes for the production of APIs.³

In case of biologically active compound synthesis, the final target is constructed from intermediates. The quality of the final product and its cost are inevitably dependent on the manner intermediates are produced. Chlorides serve as good intermediates in the synthesis of APIs, usually in nucleophilic substitutions exemplified on Scheme 1, where a chloride atom is substituted by a nucleophile in the subsequent step.⁴ Due to

Scheme 1. Possible Scaffolds That Can Be Synthesized from Chloroalkanes



the lower molecular weight of chloride, when compared to other halogens, substitution of chloride generates less waste.⁵ Unfortunately, synthesis of chlorides from alcohols requires highly toxic and waste-intensive chlorinating agents such as thionyl chloride,⁶ phosphorus chlorides,⁷ pivaloyl chloride,⁸ Vilsmeier reagent,⁹ tosyl chloride,¹⁰ 2,4,6-trichloro-[1,3,5]triazine with DMF,¹¹ oxalyl chloride,¹² and phosgene.¹³ Mostly, chlorinating agents are used in stoichiometric or excessive amounts that lead to a high generation of waste.¹⁴

Therefore, the ideal process would involve conversion of neat alcohols to chlorides by hydrogen chloride (HCl). This will minimize waste generation since the sole byproduct is water. Kappe et al. showed utilization of 30 wt % aqueous hydrochloric acid in chlorination of 1-butanol, 1-hexanol, and 1-decanol within a microreactor.¹⁵ In 15 min residence time, with 3 equiv of 30 wt % aqueous HCl and at elevated temperatures quantitative yields were obtained. We recently realized a process utilizing 37 wt % aqueous HCl to afford a wider scope of aliphatic and benzylic substrates in the same time range.¹⁶ Furthermore, prepared chlorides were coupled with piperazine derivatives to synthesize cinnarizine, cyclizine, and buclizine derivatives in multistep continuous synthesis. The main drawback of both processes was the need for 3 equiv of hydrochloric acid to prevent synthesis of byproducts, such as ethers. In addition, continuity of the process was limited by the need to stop to refill the hydrochloric acid loop, which was used to circumvent corrosion of the pumps.

The limited solubility of hydrogen chloride in water leads to a limitation in its concentration. The maximum available concentration in hydrochloric acid is 37 wt %, meaning that in

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Figure 1. Hydrogen chloride gas delivery unit (top, dry zone) and chlorodehydroxylation rig (bottom, wet zones), where the reaction takes place.

the nucleophilic substitution case chloride competes with water as nucleophile. In order to maximize the concentration of hydrogen chloride within a medium, pure hydrogen chloride gas can be used. Using hydrogen chloride gas can also solve the problem of the aforementioned limited continuity and allows truly continuous processing. Large pressurized reaction vessels need to be under constant observation when such toxic and corrosive gases are used, requiring special precautions such as dedicated high-pressure facilities to avoid any leakages and allow moderate solubility of gaseous reagents in the reaction media. Gas-liquid reactions in large batch reactors are usually performed at lower temperatures to increase gas solubility and minimize associated risks. Finally, due to the low interfacial areas in batch reactors and low temperatures, reactions take place in extended times, which most of the times does not justify the effort.

Meanwhile, microreactors offer a great platform for gas– liquid reactions due to the formation of distinct, regular flow patterns with high periodicity or symmetry.¹⁷ These offer a high surface-to-volume ratio leading to high heat and mass transfer rates.¹⁸ Moreover, due to the low operating volumes of micro reactors only small volumes are pressurized at a time, while continuously performing the reaction. The higher safety associated with microreactors allows investigation of a wide range of process conditions, usually leading to process intensification. A number of examples utilizing gases as reagents within micro flow reactors, such as $CF_3I_1^{19} C_2H_2$,²⁰ C_2H_4 ,²¹ $CH_2O_2^{22} CH_2N_2^{23} Cl_2$,²⁴ $CO_2^{25} CO_2^{26} F_2$,²⁷ H_2 ,²⁸ NH_3 ,²⁹ O_2 ,³⁰ and O_3 ,³¹ have been published.

Herein, we report for the first time the use of hydrogen chloride gas as a reagent for a continuous synthesis of chloroalkanes in microflow. Highly corrosive in the presence of moisture, hydrogen chloride requires special precautions during the design of the process. We present related challenging aspects and corresponding solutions. Finally, the merit of the use of hydrogen chloride along with its limitations are presented.

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EXPERIMENTAL PLATFORM

In order to control the flow rate of hydrogen chloride, a gas mass flow controller is needed. In general, mass flow controllers are made of stainless steel and hastelloy, which are susceptible to corrosion. Hydrogen chloride in its pure state is harmless to stainless steel and hastelloy. However, the moment the moisture content rises above 10 ppm, severe corrosion starts to take place. Therefore, absolute dry conditions are needed to prevent the corrosion of the device. By splitting the experimental setup into two zones, dry and wet, first as a hydrogen chloride gas delivery unit and second as a reaction rig, the corrosion was circumvented.

Hydrogen Chloride Delivery Unit. Figure 1 (top) shows the assembly of the hydrogen chloride supply unit. In order to keep moisture out of the unit all connections were of VCR type from Swagelok. Moreover, due to the fact that polymer based tubing is permeable to moisture, stainless steel tubing of 1/4''size was used. One out of three nitrogen bottles was set to 40 bar for startups and shutdowns of the system. The other two were set to 15 bar pressure to be used in constant purging of the system in between experiments to prevent diffusion of moisture into the mass flow controller. Despite purging, a diffusion front is still present, which takes place in the direction opposite to the flowing nitrogen. Therefore, a stainless steel 2 m long "pig tail" with 250 μ m internal diameter was added following the last valve of the delivery unit. In our experience, inline nonmetallic check valves sometimes fail at high pressures and allow liquid to enter the gas stream. In case of such an unexpected failure, the liquid shall destroy the mass flow controller upon reaching it due to corrosion.

In order to visually verify if any liquid ever was moving toward the mass flow controller, transparent ethylene tetrafluoroethylene (ETFE) tubing of 250 μ m was added after stainless steel tubing. A polyether ether ketone (PEEK) valve was attached, which can be shut in case liquid flow was detected. Another 2 m of ETFE tubing of 750 μ m was added after, followed by an inline check valve.

In order to enhance desorption of water molecules from the surface of the tubing used in construction of the setup, a vacuum line was installed. A cyclic vacuum-purge procedure was applied before the start of the operation and before disassembling the setup. It is important to mention that in case of no vacuum, and sole purging, components of the setup corrode upon disassembly and exposure to air. A bypass around the mass flow controller was installed to assist vacuuming of the mass flow controller from both ends. Before introducing hydrogen chloride into the unit for the first time, a dew point transmitter was used to the measure moisture content. A moisture content of 0.8 ppm was typical for our system due to the dry nitrogen that was used for purging after purge-vacuum procedure. Pictures with a more detailed information regarding the setup are enclosed in the Supporting Information.

Chlorodehydroxylation Rig. Alcohols that are liquid under atmospheric conditions were pumped with a Knauer HPLC pump. A gas-liquid slug flow initiated in a Y-mixer and continued into the ETFE reactor as shown in Figure 1 (bottom). (NOTE: a T-mixer was not suitable due to the liquid slugs appearing on the gas feed line prior to the mixer. As a result, these penetrations brought about fluctuations in the gas flow rate observed on the mass flow controller.) The reactor was made of ETFE tubing of 762 μ m internal diameter. When 1 mm inner diameter tubing was used instead, escape of gas into the heating media upon operation was observed, due to the thinner wall thickness. A hot product stream was allowed to flow through 30 cm long tubing prior to entering the Equilibar back pressure regulator (BPR) to allow cooling. For present application, an Equilibar BPR demonstrated a unique ability to apply pressure and keep gas—liquid flows stable up to 16 bar pressure. Its use circumvented the need for gas—liquid separation prior to the pressurization unit. (NOTE: Inline cartridge based BPRs could not provide constant flow, and resulted rather in stop-flow behavior, which affected the operation of the mass flow controller, thus causing inaccuracy in the gas flow rate.) Table 1 demonstrates the window of operating conditions of the operating platform.

 Table 1. Operating Parameters of Chlorodehydroxylation

 Flow Setup

parameter	range		
reactor volume	4 mL		
reactor internal diameter	762 μm		
gas mass flow rate	0.001–0.600 g/min (0.1–80 mL/min)		
reactant flow rate	0.09-0.15 mL/min		
temperature	25–120 °C		
pressure	16 bar		

RESULTS AND DISCUSSION

Benzyl chloride is used as an intermediate in the preparation of pharmaceuticals, flavorants, plasticizers, and perfumes. According to Gerrard et al., hydrogen chloride dissolves in benzyl alcohol under atmospheric pressure to a significant extent as shown in Figure 2.³² A significant absorption of gas, as shown



Figure 2. Solubility of hydrogen chloride gas in 1-butanol and benzyl alcohol (redrawn with permission from ref 32. Copyright 2007, John Wiley and Sons).

in Figure 3, was observed when benzyl alcohol and hydrogen chloride were mixed in the tubing prior to entering the reactor coil (at room temperature under 5 bar pressure). In theory, the solubility of gas in liquid increases with pressure and decreases with temperature. In addition, throughout the reactor the gas is consumed as the reaction progresses. With an increase in temperature, the extent of gas expansion, and thus residence time as well, are hard to quantify due to its substantial expansion and faster consumption. Therefore, the sole measure of success of a reaction was based on the yield of synthesized chloride, while residence time was estimated based on flow



Figure 3. Gas slug size with respect to the distance from the mixing point of gas and liquid, Y-mixer.

behavior. In-line absorption measurements to determine the residence time were avoided due to the corrosive nature of the product stream.

One of the goals in using gas was to minimize excess of HCl used, thus generated waste. In our previous investigations with 3 equiv hydrochloric acid, in 15 min residence time at 120 °C > 99% yield of benzyl chloride was obtained. Decreasing equivalents of HCl gas to 1 and allowing the same residence time resulted in 80 wt % at 60 °C and 89 wt % at 100 °C. Higher temperatures were not investigated due to a significant expansion of gas slugs, leading to significantly reduced residence time. Dibenzyl ether was formed as a sole side-product in 3 wt % at 60 °C and 5 wt % at 100 °C. Important to stress is that no gas slugs were observed at the inlet of BPR, and a minor amount of gas slugs was observed at the outlet.

To see whether benzyl ether formation could be minimized, while maximizing the yield of benzyl chloride, the effect of hydrogen chloride excess was studied. Gradually, increasing equivalents from 1.0 to 2.0 led to no change in side-product formation at 100 $^{\circ}$ C. We therefore decided to screen different reaction temperatures at 1.1 and 1.5 equiv. The results tabulated in Table 2 show that the selectivity does not improve

Table 2. Effect on Benzyl Chloride and Dibenzyl Ether Formation at Various Temperatures and Equivalents of Hydrogen Chloride

entry	eq HCl	T (°C)	BenzCl (wt %)	DBE (wt %)
1	1.1	80	89	3
2	1.1	90	92	5
3	1.1	100	95	5
4	1.5	80	87	3
5	1.5	90	96	4
6	1.5	100	95	5
7	2.0	100	95	5

with excess of hydrogen chloride. With the increase of equivalents, gas-hold up in the reactor increased, which led to a marginal decrease in residence time.

Assuming that dibenzyl ether is formed due to insufficient hydrogen chloride, prompted us to increase the system pressure to allow a higher concentration of hydrogen chloride within the liquid phase. Figure 4 shows the pressure effect on the reactant, product and side-product weight distribution at 80 °C. Benzyl chloride production increases with pressure from 79 wt % at 5



Figure 4. Pressure effect on weight distribution among benzyl chloride (red), benzyl alcohol (blue), and dibenzyl ether (green).

bar to 93 wt % at 16 bar, while the formation of byproduct stays the same and equal to 3-4 wt %. Thus, higher concentration of hydrogen chloride increased the conversion, while showing no effect on selectivity. No change in conversion was observed with increasing pressure at 90 and 100 °C. Dibenzyl either formed in 4 wt % at 90 °C with 92 wt % of benzyl chloride, and in 5 wt % at 100 °C with 95 wt % of benzyl chloride. We proceeded further with increasing equivalents at higher pressure (10, 12, 16 bar) at 100 °C. The minimum concentration of dibenzyl ether was 4% at 10 bar at 1.2 and more equivalents. Therefore, those conditions, i.e., 100 °C, 1.2 equiv, 20 min residence time, and 10 bar, were set as optimal, yielding full conversion and 96 wt % of benzyl chloride.

Expansion of Scope. Optimized conditions for benzyl alcohol were applied to a range of aliphatic and benzylic alcohols. Scheme 2 shows corresponding yields at 100 °C, 1.2

Scheme 2. Prepared Chloroalkanes at Optimal for Benzyl Chloride Conditions^a



^{*a*}120 °C, 10 bar with 1.2 equiv of hydrogen chloride. Asterisks (*) indicate reactions carried out in a 10 mL reactor.

equiv, and 10 bar. When, aliphatic alcohols were used a significant decrease in gas solubility was observed that lead to large gas slugs both at the Y-mixer and at the BPR outlet. An increase in gas slugs drastically decreased the residence time to <5 min in the reactor (4 mL) used for benzyl alcohol. In order to have a similar residence time as for benzyl alcohol experiments, a 10 mL reactor was used instead, which led to residence time ranging from 15 to 20 min depending on the

substrate used. The difference in residence time is due to the different extent of gas absorption within the liquid phase.

The rate of nucleophilic substitution reactions depends on the type of nucleophile, electrophile, solvent, and leaving group. In order to assist nucleophilic substitution, either polar protic $(S_N 1)$ or aprotic $(S_N 2)$, solvents are used as solvents. One of the frequently used reaction systems in solvent-free nucleophilic substitutions is solvolysis, when the solvent is used as a nucleophile. The current investigation comprises a reverse system, where electrophile is a solvent. While the nucleophile is a chloride anion resulting from dissociation of hydrogen chloride.

Primary alkanes undergo S_N2 type of nucleophilic substitution, which occurs via a back-attack of an electrophile.³³ Due to insufficient polarity and relatively low hydrogen bonding in primary aliphatic alcohols, dissociation to release a free chloride anion as a nucleophile is not favorable. In contrast, due to the higher polarity and/or stronger hydrogen bonding present within pentanediol, both solubility of HCl gas and conversion of the alcohol were significantly increased. Conversion of pentanediol increased to 98%, resulting in the formation of 1,5-dichloro pentane as a sole side product. Secondary alkanes can react via S_N2 or S_N1 depending on the steric hindrance of an electrophilic carbon or stabilization of the cationic intermediate. Higher yields in isopropyl alcohol and cyclohexyl alcohol cases can be explained by this additional path being available. Among benzylic species 3-methoxy benzyl alcohol resulted in the largest gas consumption and the highest yield with no traces of a dibenzyl ether derivative forming. Conversion decreased when 2,6-difluorobenzyl alcohol was used, while no side product was formed. In case of 2phenylethanol absolutely no conversion was observed. These observations indicate that resonance stabilization of the benzyl cation is responsible for better yields when compared to aliphatic substrates and that $S_N 1$ is a main path for the reactions to take place.

In case with secondary and benzylic alcohols dissociation of protonated alcohols results in water and carbocation. As the reaction proceeds, more of the water is formed promoting dissociation of hydrogen chloride, increasing not only the absorption of HCl, but also the rate of S_N1 reactions. Looking back at the optimization of benzyl alcohol, it can be concluded that at the start of the reaction when limited water is formed as a byproduct, resulting in a limited amount of chloride anion, benzyl cation associates with both benzyl alcohol and chloride. Once a certain threshold concentration of water is reached, the chloride prevails in the reaction to combine with the benzyl cation. The S_N1 reaction pathway is also supported by the fact that no effect on the selectivity was observed when an excess of hydrogen chloride was used.

CONCLUSION

A continuous synthesis of chlorides from bulk alcohols via use of hydrogen chloride gas instead of toxic and wasteful chlorinating agents is demonstrated. The most challenging aspect of safe handling of this corrosive gas was its continuous controlled delivery into the reacting system. The elimination of moisture by continuous purging of the setup with dry nitrogen solved any corrosion issues.

The use of a microflow reactor allowed the application of process conditions that are beyond the limits of conventional batch technology. High temperature and pressure, easily applicable within the reacting system allowed reaching the initial objective of minimizing the excess of HCl used from 3 equiv to 1.2. However, the developed process is more beneficial for $S_N 1$ type reactions than $S_N 2$. As a result, further investigations are needed for the synthesis of specific target chloroalkanes. One of the possible steps is minimal addition of polar aprotic solvents to promote $S_N 2$. Based on green chemistry and engineering principles, a significant improvement is demonstrated due to the truly continuous nature of the process, no use of solvent and formation of only water as a byproduct.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00014.

Experimental procedure along with a more detailed description of operating platform (PDF)

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Notes

The authors declare no competing financial interest.

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