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Technical Note

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Continuous Flow Synthesis of *n*-Alkyl Chlorides in a High-Temperature Microreactor Environment

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Supporting Information

ABSTRACT: Applying continuous flow processing in a high-temperature/high-pressure regime, *n*-alkyl chlorides can be prepared in high yields and selectivity by direct uncatalyzed chlorodehydroxylation of the corresponding *n*-alcohols with 30% aqueous hydrochloric acid. Optimum conditions for the preparation of *n*-butyl and *n*-hexyl chloride involve the use of a glass microreactor chip, a reaction temperature of 160−180 °C (20 bar backpressure) and a residence time of 15 min.

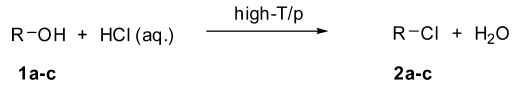
INTRODUCTION

The conversion of primary alcohols into their corresponding chlorides is an important and extensively used reaction in organic chemistry since alkyl chlorides are exceptionally useful building blocks for a wide variety of synthetic transformations. Traditionally, this substitution reaction is often performed using chlorination agents such as $SOCl_2$, PCl_3, or PCl_5, or even phosgene. The use of these reagents is neither atom economic, safe, or environmentally friendly and is therefore unsuitable for large industrial-scale preparations. Clearly, an almost ideal method would be the direct chlorodehydroxylation of the primary alcohol with hydrochloric acid—either gaseous or aqueous—involving a simple nucleophilic substitution (SN_2) process.[1−5] This method is inherently atom economic and avoids the formation of hazardous byproducts. However, especially for longer-chain alkyl chlorides, the direct chlorodehydroxylation process often requires the presence of a Lewis acid or phase-transfer catalyst, long reaction times and elevated temperature regimes.[1,2] Notably, Clark and co-workers have demonstrated that long-chain primary alcohols (C6−C12) can be converted into alkyl chlorides in good yields using sealed-vessel microwave processing (130−170 °C) on laboratory scale within a 10 min reaction time.[3] In most instances the use of a phase-transfer catalyst, aiding the transport of HCl into the nonaqueous reaction phase, was required in order to achieve high yields.[3] Building on these results we herewith introduce an experimentally simple and scalable high-temperature microreactor approach for the direct uncatalyzed chlorodehydroxylation of primary alcohols involving aqueous HCl. Previous continuous flow methods for the synthesis of alkyl chlorides from their respective alcohols have utilized hydrogen chloride gas in gas/liquid phase-transfer[4] or heterocyclic amine hydrochloride-based (e.g., quinoline, pyridine)[5] catalytic systems.

RESULTS AND DISCUSSION

Our interest in the direct chlorodehydroxylation of primary alcohols focused on a safe, efficient, and scalable generation of *n*-hexyl chloride from 1-hexanol. *n*-Hexyl chloride was chosen as a model substrate representing medium-chain *n*-alkyl chlorides (C4−C8) which are of significant industrial interest as alkylation agents and synthetic intermediates.[6] To widen the scope of our study, 1-butanol and 1-decanol were additionally included in our investigations (Scheme 1). While 1-butanol and concentrated aqueous HCl form a homogeneous phase at room temperature, 1-decanol is completely immiscible with aqueous HCl. 1-Hexanol is miscible with aqueous HCl to a very small extent at high temperature.

Scheme 1. Direct chlorodehydroxylation of primary alcohols to *n*-alkyl chlorides



a: R = n-butyl; **b:** R = n-hexyl; **c:** R = n-decyl

In order to provide a technically realizable and practical continuous flow protocol aqueous HCl of 30% (w/w) concentration was used for all experiments. As can be seen from the data shown in Table 1, the use of standard 37% (w/w) concentrated aqueous HCl would lead to exceedingly high autogenic pressures in an elevated temperature regime which would be difficult handle using commercially available flow reactors. For example, at a projected reaction temperature of

Table 1. Vapor pressure of aqueous hydrochloric acid[a]

temperature [°C]	pressure 30% (w/w) HCl [bar]	pressure 35% (w/w) HCl [bar]
160	11.00	28.51
180	17.69	41.22
200	27.34	57.85
220	40.77	79.06

[a]Data from ref 7.

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180 °C, the vapor pressure of 35% HCl is more than double the vapor pressure of a 30% solution (41.22 versus 17.69 bar).

Owing to the corrosiveness of HCl, process intensification using high-temperature/high-pressure conditions is a nontrivial affair, using either batch or continuous flow processing. The most common choice for processing highly corrosive concentrated HCl at elevated temperatures in industry are high performance Ni-based (Hastelloy C-276, Hastelloy B-3),[8] or Ta-based alloys (Ta, Ultra 76),[9] in addition to certain types of ceramic materials (for example SiC).[10] Since the chemical resistance of these materials toward aqueous concentrated HCl in an elevated temperature and pressure regime has not been fully documented,[8−10] and in addition since these materials are exceedingly expensive and difficult to manufacture, we have opted to use standard glass microreactors for our laboratory-scale investigations (see below).

As the starting point of our investigations, similar to the work by Clark and co-workers,[3] we have employed sealed-vessel microwave batch technology in order to rapidly evaluate the chlorodehydroxylation reactions shown in Scheme 1 in a high-temperature/high-pressure (high-T/p) process window. Experiments were carried out employing a Biotage Optimizer single-mode dedicated microwave reactor on a ∼2.1 mL scale in permanently crimped 5 mL Pyrex vessels, allowing controlled microwave processing of the corrosive reaction mixture at maximum temperature/pressure conditions of 250 °C/20 bar.[11] Our initial optimization study focused on the chlorodehydroxylation of *n*-hexanol by varying the reaction temperature (100−200 °C) and the HCl stoichiometry (1.0−5.0 equiv of 30% HCl) in such a way so that full conversion to the desired *n*-hexyl chloride in a reaction time suitable for subsequent continuous flow processing (≤15 min) was achieved. At the same time, the reaction conditions were carefully chosen in order not to exceed the pressure limit of both the microwave and microreactor equipment (p_{max} = 20 bar). As shown in Figure 1 an increase in temperature and/or equivalents of

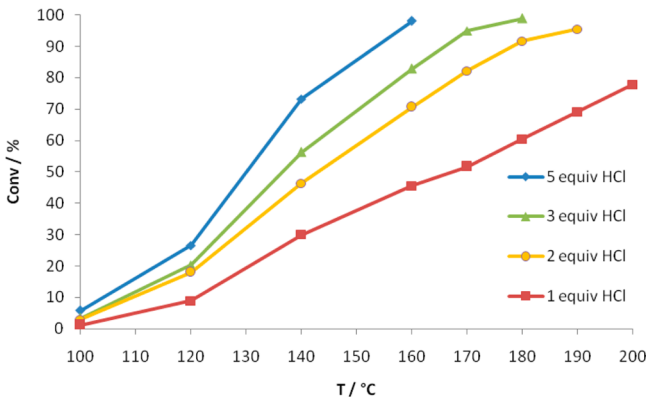

Figure 1. Reaction optimization for the chlorodehydroxylation of 1-hexanol using sealed-vessel microwave conditions (100−200 °C, 15 min reaction time, 1.0−5.0 equiv of 30% HCl). Conversions were determined by ^{1}H NMR and confirmed by GC-FID analysis.

aqueous HCl also increases the reaction rate. An optimum set of conditions for the chlorodehydroxylation was ultimately obtained by applying 3 equiv of 30% HCl, 15 min reaction time, and 180 °C reaction temperature (∼20 bar autogenic pressure). This set of conditions provided full conversion to the desired *n*-hexyl chloride in high selectivity (>98%).[12] After phase separation and drying in a desiccator an isolated 86% yield of *n*-hexyl chloride was obtained, which could further be purified by bulb-to-bulb microdistillation.

A direct comparison of the chlorodehydroxylation of *n*-butanol, *n*-hexanol, and *n*-decanol (Scheme 1) under identical conditions demonstrates that the effective reaction rate is dependent on the alkyl chain length—the longer the alkyl chain the lower the reactivity (Figure 2). As already hypothesized by

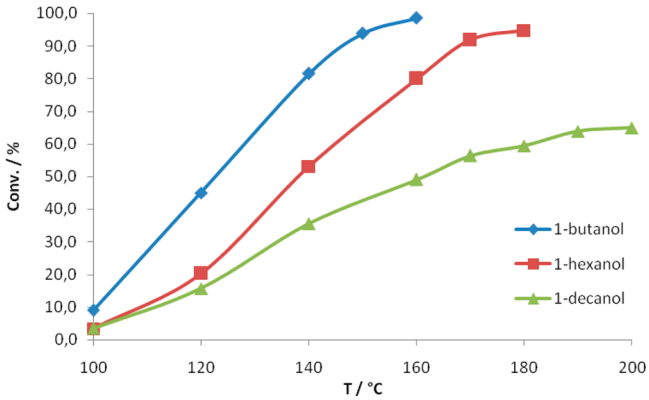

Figure 2. Comparison of reaction rates for the chlorodehydroxylation of 1-butanol, 1-hexanol, and 1-decanol using sealed-vessel microwave conditions (100−200 °C, 15 min reaction time, 3.0 equiv of 30% HCl). Conversions were determined by ^{1}H NMR and confirmed by GC-FID analysis.

Clark,[3] this effect is most likely connected to a decreased solubility of HCl in longer-chain alkyl alcohols.[13] For longer-chain alkyl alcohols (for example, 1-decanol) the transfer of HCl to the alcohol phase can thus be considered to be rate limiting. Since the maximum overall pressure in our reactor system is 20 bar, full conversion for 1-decanol could not be obtained. Higher conversions for this substrate in the absence of a phase-transfer catalyst could probably only be realized at significantly higher temperatures, higher concentrations and/or more equivalents of HCl reagent, and extended reaction times.

In order to validate this hypothesis and distinguish between a mass transfer and a kinetically limited reaction, we have additionally performed the chlorodehydroxylations of 1-hexanol and 1-decanol in the presence of phase transfer catalysts (see Tables S1 and S2 in the Supporting Information). It is a well-known fact,[14] that accessible phase transfer catalysts (such as $C_{16}H_{33}N(CH_3)_3^+Cl^-$) are able to lower the interfacial tension between the organic and the aqueous phase for mass transfer limited reactions and therefore may influence the reaction rate (by enhancing the transfer step). As shown in Table S2 in the Supporting Information, by using 5 mol % of $C_{16}H_{33}N(CH_3)_3^+Cl^-$ as a phase transfer catalyst the reaction rate for the chlorodehydroxylation of 1-decanol was enhanced from ∼50% to ∼80% under otherwise identical conditions (170 °C, 15 min), whereas it did not influence the 1-hexanol reaction. On the other hand, using large and bulky phase transfer catalysts (such as $Bu_4N^+Cl^-$) will provide the most "activation" of anions and thus are the best choice for slow kinetically controlled organic-phase reactions. Therefore, not surprisingly, there are no significant reaction rate enhancements for 1-decanol employing $Bu_4N^+Cl^-$, whereas this catalyst to some extent is able to increase the reaction rate for the chlorodehydroxylation of 1-hexanol (see Table S1 in the Supporting Information) We therefore assume that, under our experimental conditions, the chlorodehydroxylation of 1-decanol is mass transfer limited

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whereas the chlorodehydroxylation of 1-hexanol is intrinsically (kinetically) limited.[15]

Having a set of optimized batch microwave reaction conditions for the chlorodehydroxylation in hand, we then moved to continuous flow processing, following the "microwave-to-flow" paradigm.[16] All continuous high-T/p flow experiments were performed in a Syrris Asia 110 microreactor system (Figure 3), comprising (1) a pressurized solvent/reagent input store, (2) a corrosion-resistant dual pair syringe pump (one pair consists of a 50 μL and a 100 μL syringe), (3) a heater module, (4) a 1 mL internal volume borosilicate microreactor, (5) a 5 mL PTFE loop reagent injector, and (6) a corrosion-resistant backpressure regulator. The flow experiments were performed using a two-feed concept (aqueous feed A and organic feed B). Even though all parts of the dual glas syringe pumps which are in direct contact with chemicals, are made from corrosion-resistant Hastelloy or PTFE, we preferred to use the 5 mL PTFE loop reagent injector to store the strongly corrosive 30% HCl. Therefore, syringe pump A pumped water into the PTFE loop system to drive the aqueous 30% HCl into the 1 mL chip, whereas syringe pump B directly pumped the corresponding *n*-alcohol directly into the chip. The typical overall flow rate applied for this chlorodehydroxylation was ~70 μL/min, resulting in a residence time of ~15 min. After the reaction mixture left the microreactor, it was forced through the backpressure regulator and was subsequently collected for analysis.

Figure 3. Asia 110 microreactor system. 1: pressurized solvent/reagent input store; 2: corrosion-resistant dual pair syringe pump; 3: chip heater (T_{max} = 250 °C); 4: 1 mL internal volume borosilicate microreactor (channel length 1844 mm, channel width 391 μm, channel depth 1240 μm; p_{max} = 20 bar and T_{max} = 250 °C); 5: reagent injector (5 mL PTFE loop); part 6: backpressure regulator (1−25 bar). During operation the microreactor chip (inset, 4) is fitted inside the chip heater (3).

In Table 2 the results of the continuous flow chlorodehydroxylation experiments in an appropriate reaction temperature/residence time window producing optimum conversions are summarized. Notably, the conversions achieved in the microreactor show a near perfect correlation with the data obtained in the batch microwave protocols (Figure 4). For *n*-butanol full conversion and ≥98% selectivity for the formation of *n*-butyl chloride was achieved at 160 °C and 15 min residence time in the microreactor (≤2% di-*n*-butyl ether as byproduct). For *n*-hexanol 95% of *n*-hexyl chloride (~3% starting material, ≤2% di-*n*-hexyl ether) were obtained at 180 °C within 15 min. Isolation by phase separation provided product yields of 87% of *n*-butyl chloride and 85% of *n*-hexyl chloride, respectively (see Experimental Section for details). Only for the comparison of the 1-decanol substrate under

Table 2. Results of chlorodehydroxylation of primary alcohols with 30% aqueous HCl under microreactor conditions (Scheme 1)[a]

entry	substrate	temp. [°C]	^{1}H NMR conv. **2** [%][b]
1	1-butanol	150	96
2	1-butanol	160	99
3	1-hexanol	160	84
4	1-hexanol	170	93
5	1-hexanol	180	95
6	1-decanol	170	61
7	1-decanol	180	64
8	1-decanol	190	57

[a]Conditions: 3 equiv of (30%) HCl, 15 min residence time; total flow rate ~66.7 μL/min. The stated conversion values are the mean values of at least three experiments. [b]^{1}H NMR conversion/purity of the corresponding *n*-alkyl chlorides (confirmed by GC-FID); in all cases the formation of ~1−2% of the corresponding di-*n*-alkyl-ether byproducts was observed.

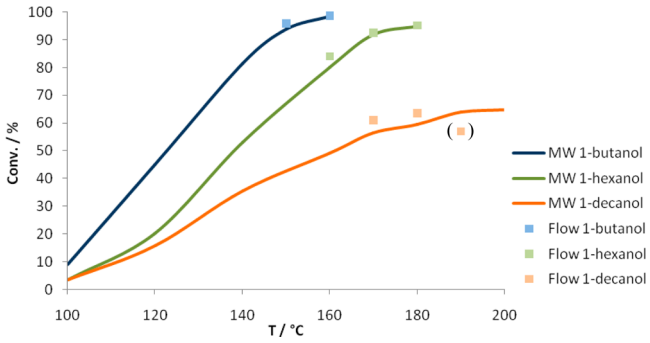

Figure 4. Comparison of chlorodehydroxylation of primary alcohols under flow and microwave (MW) conditions (Scheme 1). For conditions, see Figure 2 and Table 2.

microwave and continuous flow conditions were small differences observed: at temperatures of 170 and 180 °C, the obtained ^{1}H NMR and GC-FID conversions for the continuous-flow experiments were 3−5% higher than in the microwave batch experiments. This may be due to the higher interfacial areas under microreactor conditions (see Supporting Information), resulting in higher diffusion rates compared to the conventional batch conditions. As mentioned above, for water insoluble alcohols, the diffusion rate of HCl into the organic layer presumably is rate limiting. Notably, at 190 °C the conversion compared to the microwave experiments was ~7% lower. This is simply caused by the pressure limitations of the used flow equipment. The backpressure p_{max} is set to 18 bar (to maintain a maximum system pressure of 20 bar) and is therefore lower than the vapor pressure at 190 °C for 30% aqueous HCl (Table 1) As a consequence, the formation of gaseous slugs at 190 °C was observed, which reduced the effective residence time and therefore lowered the overall conversion. Notwithstanding this experimental artifact, the microwave batch and (conventionally heated) microreactor results for the chlorodehydroxylation of the primary alcohols studied herein do not show any significant differences in conversion or selectivity, confirming the validity of the "microwave-to-flow" concept.[16]

An image of a processed reaction mixture in the glass microreactor clearly indicates the distribution of aqueous and organic segments in a segmented flow regime (Figure 5, see Supporting Information for more details). Since the results

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Figure 5. (a) 1000 μL microreactor chip while processing the reaction mixture of (18.8 μL/min) 1-hexanol and (47.9 μL/min) aqueous 30% HCl at room temperature. (b) Enlarged part of residence time area of the microreactor showing aqueous segments (graphically enhanced for clarity).

obtained for longer-chain alcohols (*n*-hexanol, *n*-decanol) under batch microwave and microreactor conditions are virtually identical, we assume that the mixing quality for biphasic reaction mixtures of this type in a strongly agitated, sealed-vessel microwave vial (~2.1 mL reaction volume) can match the generated interfacial area under segmented flow conditions in a microreactor (Figure 5). Clearly, the main advantage of the continuous flow approach is the direct scalability, as the batch microwave method will be impossible to scale to an industrially relevant volume.[16]

■ CONCLUSION

In conclusion, we have demonstrated that primary alcohols (*n*-butanol, *n*-hexanol) can undergo efficient chlorodehydroxylation with 30% aqueous HCl in a high-temperature/high-pressure process window to provide the corresponding *n*-alkyl chlorides in high yield and selectivity. Employing microwave batch technology as an optimization tool, the optimum reaction conditions were rapidly identified and subsequently translated into a continuous flow protocol. Typical reaction conditions involved 160−180 °C at 20 bar backpressure and a 15 min residence time inside a conventional glass microreactor chip. This catalyst- and solvent-free protocol represents an atom-efficient and safe method for the direct and "green" synthesis of *n*-alkyl chlorides from primary alcohols. Most importantly, the successful translation from batch to continuous flow has opened up a way to scale this high-temperature/high-pressure protocol to an industrially relevant scale. Avenues along these lines are currently considered in our laboratory.

■ EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (d) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. GC FID analysis (to validate the ^{1}H NMR results) was performed on a Trace-GC (ThermoFisher) with a flame ionization detector using a HP5 column (30 m × 0.250 mm ×0.025 μm). After 10 min at 50 °C the temperature was increased in 10 °C/min steps up to 150 °C and kept at 150 °C for 4 min; afterwards the temperature was increased in 25 °C/min steps up to 300 °C. The detector gas for the flame ionization was H_2 and compressed air (5.0 quality). All solvents and reagents were obtained from standard commercial vendors and were used without further purification. Samples of 30% concentrated aqueous HCl were prepared by dilution of 37% conc. HCl under ice-bath cooling.

Microwave and Continuous Flow Instrumentation. Microwave-assisted reactions were carried out in an Emrys Optimizer EXP (Biotage AB, Uppsala, Sweden) single-mode microwave instrument producing controlled irradiation at 2.45 GHz in 2−5 mL cylindrical Pyrex microwave reaction vials using isochoric conditions (all microwave experiments were run with a total reaction volume of ~2.1 mL). Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel. All microwave experiments were carried out using magnetic stirring at a rate of 720 rpm (15 s stirring prior to the heating).

Flow experiments have been performed in an Asia 110 series microreactor (Syrris Ltd., Royston, UK), employing a two-feed microreactor glass chip (1000 μL internal volume: 107 μL mixing volume, 894 μL reaction volume; part number 2100145; see Figure 3).

Reaction Optimization and Determination of Conversion in Batch and Flow Experiments. The conversions and selectivities for all transformations have been determined by ^{1}H NMR and confirmed by GC-FID analysis. ^{1}H NMR and GC samples (~20 μL) for the continuous flow experiments were taken after reaching steady-state conditions at three different time intervals during the collection of the reaction mixture (Table 2). ^{1}H NMR and GC samples for the microwave experiments were taken at different time intervals after completion of each experiment (Figures 1 and 2). Batch and flow results gave identical ^{1}H NMR and GC-FID signal patterns. The ^{1}H NMR conversion was determined by integration of specific ^{1}H NMR signals (all in the range of 3.35−3.65) of the corresponding alcohol (2H, $-CH_2-OH$), alkyl chloride (2H, $-CH_2-Cl$), and dialkyl ether species (2H, $-CH_2-O-CH_2-$). The mean values have been determined from at least two samples of three independent experiments. GC-FID data reflect peak area percentage values. Standard deviations have not been stated as the results are rather similar.

1-Hexanol. Five microliter aliquots have been taken from the organic phase for GC-FID and ^{1}H NMR analysis (*n*-hexanol is virtually insoluble, and *n*-hexyl chloride is completely insoluble in 30% HCl). For the 1-hexanol case traces of 1-hexene (<0.5%) could be identified by GC analysis (no olefinic protons were seen in the ^{1}H NMR, however).

1-Decanol. Five microliter aliquots have been taken from the organic phase for GC-FID and ^{1}H NMR analysis (*n*-decanol and *n*-decyl chloride are insoluble in 30% HCl).

1-Butanol. For taking representative samples from the biphasic liquid−liquid mixture of the microwave samples, the reaction mixture was stirred intensely for ~5 min at high stirring rates (>1000 rpm) to generate an emulsion (*n*-butanol

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is soluble in 30% HCl, *n*-butyl chloride is insoluble). Subsequently 20 μL aliquots were taken for ^{1}H NMR (d_6-acetone) analysis.

Synthesis of *n*-Hexyl Chloride under Microwave Batch Conditions (Figure 2). Into a 2−5 mL cylindrical microwave Pyrex process vial equipped with a magnetic stir bar were placed 592 μL (485.4 mg, ∼4.75 mmol) of *n*-hexanol and 1508 μL (∼14.25 mmol) of 30% (w/w, ∼9.5 M) aqueous HCl. The vial was sealed by capping with a Teflon septum fitted in an aluminum crimp top and the sample heated in the microwave reactor for 15 min (fixed hold time) at 180 °C (20 bar). After the reaction time had elapsed, the mixture was cooled to 45 °C by gas jet cooling. The organic layer was separated from the aqueous phase and dried in a desiccator over $CaCl_2$(s) to provide 495 mg (86%) of *n*-hexyl chloride of >95% purity (^{1}H NMR, GC-FID). This sample could be further purified by bulb-to-bulb microdistillation to provide 71% of pure product as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89−0.94 (t, J = 15 Hz, 3H), 1.28−1.47 (m, 6H), 1.74−1.83 (m, 2H), 3.53−3.58 (t, J = 15 Hz, 2H).

Synthesis of *n*-Butyl Chloride under Microwave Batch Conditions (Figure 2). Into a 2−5 mL cylindrical microwave Pyrex process vial equipped with a magnetic stir bar were placed 470 μL (337.8 mg, ∼4.56 mmol) of *n*-butanol and 1630 μL (∼15.40 mmol) of 30% (w/w, ∼9.5 M) aqueous HCl. The vial was sealed by capping with a Teflon septum fitted in an aluminum crimp top and the sample heated in the microwave reactor for 15 min (fixed hold time) at 180 °C (20 bar). After the reaction time had elapsed, the mixture was cooled to 45 °C by gas jet cooling. The organic layer was separated from the aqueous phase and briefly dried in a desiccator over $CaCl_2$(s) to provide 417 mg (88%) of *n*-butyl chloride of >98% purity (^{1}H NMR, GC-FID). (^{1}H NMR $CDCl_3$: δ = 0.89−0.94 (t, J = 15 Hz, 3H), 1.28−1.47 (m, 6H), 1.74−1.83 (m, 2H), 3.53−3.58 (t, J = 15 Hz, 2H).

Synthesis of *n*-Hexyl Chloride under Continuous Flow Conditions (Table 2). Five milliliters of 30% aqueous HCl were loaded into the PTFE loop module (Figure 3). By pumping water (flow rate feed A: 47.9 μL/min) into the loop the conc. aq HCl was driven into the microreactor, while feed B (*n*-hexanol flow rate 18.8 μL/min) was directly pumped into the two-feed glass microreactor. The 1 mL glass microreactor chip was heated to 180 °C in the chip heater, and the reaction mixture was pumped through the reactor (overall flow rate 66.67 μL/min) and left the microreactor after 15 min of reaction time by passing through a dynamic backpressure regulator (p_{max} set to 18−19 bar) into the collection vial. After 30 min a total volume of 4 mL (1.128 mL of 1-hexanol and 2.874 mL of 30% HCl) was processed. *n*-Hexyl chloride was isolated by phase separation from the aqueous phase and dried in a desiccator over $CaCl_2$(s) to provide 927 mg (85%) in >95% purity; ^{1}H NMR ($CDCl_3$): δ = 0.89−0.93 (t, J = 12 Hz, 3H), 1.32−1.46 (m, 6H), 1.74−1.83 (m, 2H), 3.53−3.57 (t, J = 15 Hz, 2H).

Synthesis of *n*-Butyl Chloride under Continuous Flow Conditions (Table 2). Five milliliters of 30% aqueous HCl were loaded into the PTFE loop module (Figure 3). By pumping water (flow rate feed A: 51.7 μL/min) into the loop the conc. aq HCl was driven into the microreactor, while feed B (*n*-butanol, flow rate 14.9 μL/min) was directly pumped into the two-feed glass microreactor. The 1 mL glass microreactor chip was heated to 180 °C in the chip heater and the reaction mixture was pumped through the reactor (overall flow rate 66.67 μL/min) and left the microreactor after 15 min of reaction time by passing through a dynamic backpressure regulator (p_{max} set to 18 bar) into the collection vial. After 30 min a total volume of 4 mL (0.894 mL of 1-butanol and 3.102 mL of 30% HCl) was processed. *n*-Butyl chloride was isolated by phase separation from the aqueous phase and briefly dried in a desiccator over (s) $CaCl_2$ to provide 787 mg (87%) in >98% purity; ^{1}H NMR (d_6-acetone): δ = 0.89−0.94 (t, J = 15 Hz, 3H), 1.39−1.51 (m, 2H), 1.69−1.78 (m, 2H), 3.59−3.63 (t, J = 12 Hz, 2H, 2H).

■ ASSOCIATED CONTENT

Supporting Information

Determination of interfacial areas in the microreactor. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Online videos of a stirred biphasic hexanol/water mixture under sealed-vessel microwave batch conditions at 180 °C demonstrate the effect of boiling/agitation on the interfacial area. Under these experimental conditions similar high mass transfer rates as in a microreactor environment are probably obtained. See Figure S2 in the Supporting Information for more details.

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