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Improved efficiency of continuous conversion of alcohols to chlorides in flow microreactors with DESs/HCl via predictive fluid model

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ABSTRACT

The efficient and safe synthesis of chlorides is attractive in pharmaceutical chemicals yet presents challenges. Herein, a novel route has been developed for the conversion of alcohols into the corresponding alkyl chlorides in continuous flow microreactor. Meanwhile, the system utilizes deep eutectic solvents (DESs) hydrochloride solutions (DESs/HCl) as both solvents and catalysts for this reaction. The results suggest that the premixed mode continuous flow microreactor using DESs/HCl can significantly improve the harsh reaction conditions in the synthesis reaction of chlorides. Furthermore, tuning the HCl concentration under 383 K and 30 min conditions significantly increased the yields of *n*-Butanol chloride and Benzyl chloride to 86 % and 98 %, respectively. This work shows the great application potential of the continuous flow microreactor combined with DESs/HCl to convert alcohols into corresponding alkyl chlorides or aryl chlorides. Besides, the fluid model and HCl absorption kinetics were established based on the calculated diffusion coefficients (D_R), Damköhler number (Da), Bodenstein number (Bo), residence time (τ), and experimental results. The flow model of the mixture of DESs/HCl and alcohols in the microreactor was a plug flow, which is beneficial for improving the efficiency of this reaction.

1. Introduction

Alkyl chlorides serve as pivotal intermediates in the synthesis of various active pharmaceutical ingredients [1,2]. Traditionally, these compounds are synthesized through the chlorination of alcohols, a process that typically involves the use of hazardous chlorinating agents such as acetyl chloride, oxalyl chloride, thionyl chloride, phosphorus pentachloride, and phosgene [3–5]. However, this methodology stands in stark contrast to the principles of green chemistry, which advocate for improved atom economy, minimal waste production, and enhanced process safety [6,7]. Overall, the conventional synthesis of alkyl chlorides has significant disadvantages, such as poor atom economy, substantial waste generation, and diminished process safety. Therefore, it is necessary to develop sustainable synthetic methods that can overcome the above limitations.

Recently, the synthesis of alkyl chlorides via the reaction of alcohols with hydrochloric acid (HCl) or pure HCl gas has attracted attention due to its ability to reduce waste generation significantly [8]. For example, Li et al. catalyzed the reaction of *n*-Butanol with 37 % HCl in a stirred reactor at 353 K for 10 h and achieved a yield of chlorides of 15 % [9]. In contrast, the superior heat transfer efficiency and improved safety features of continuous flow microreactors can significantly increase chloride yields within a shorter reaction time [10]. Hessel et al. used pure HCl gas at 10 bar and increased the yield to 21 % within a reaction time of 20 min [1]. However, despite notable advances in the production efficiency of chlorides, these technologies still face challenges, such as the potential safety risks associated with high-pressure operations. Furthermore, current studies lack a detailed investigation of fluid dynamics and reaction kinetics. Therefore, the development of efficient and predictable green chemical synthesis techniques remains crucial for the high yield and safe production of alkyl chlorides.

In fact, deep eutectic solvents (DESs) have attracted considerable interest as environmentally friendly solvents and catalysts in applications ranging from gas capture to green catalysis [11–13]. Numerous

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studies have confirmed that DESs can act as solvents to absorb various toxic gases such as sulfur dioxide (SO_2), hydrogen sulfide (H_2S), and carbon monoxide (CO), while also acting as catalysts for converting them into useful chemicals [14–17]. The results suggest that DESs have significant potential for dissolving pure HCl gas and catalyzing its dehydrochlorination reactions with alcohols. This dual functionality of DESs not only increases the production of alkyl chlorides but also enhances the safety of the synthesis process. Furthermore, the study of the absorption and catalytic kinetics of HCl by DESs has facilitated the accurate estimation of the fluid model, kinetics and thermodynamic parameters. These parameters include diffusion coefficients (D_R), Damköhler (Da) number and the Bodenstein number (Bo) as well as activation energy, so on [18–20]. At the same time, the above parameters are crucial for screening the reaction conditions to be simplified and optimized for the synthesis of alkyl chlorides in continuous flow reactors. This advances both the synthesis efficiency and the economic viability of chlorides and related compounds. Therefore, establishing chemical models that are suitable for using DES/HCl as catalysts/solvents in continuous flow reactors can achieve the efficient synthesis of alkyl chlorides under mild conditions.

Herein, a kind of DESs choline chloride-glycerol (ChCl-Gly) was prepared by a simple mixture of ChCl and Gly with a molar ratio of 1:2. Then the combination of microflow reactor with dual solvent/catalyst DES ChCl-Gly (1:2) was studied for highly efficient dissolution of Cl gas and subsequent conversion of alcohols to corresponding alkyl chlorides in good to excellent yields. The diffusion coefficient and mixing time of alcohols in ChCl-Gly (1:2) were preferentially determined on the basis of Fick's law. Additionally, the premixed mode of the continuous flow reactor facilitates the formation of plug flow behavior with $Bo > 100$, which has a positive effect on improving chloride yield. Furthermore, the effects of residence time, reaction temperature, equivalents of HCl, and flow model on the yield of alkyl chlorides were investigated systematically. In addition, the applicability and recyclability of ChCl-Gly (1:2) in efficient continuous flow synthesis of alkyl chlorides were also explored.

2. Experimental

2.1. Materials

Hydrogen chloride (HCl, 99.99 v/v%) and glycerol (Gly, 99 %), Benzyl alcohol (BenOH, ≥99 %) were purchased from the Shanghai Macklin Biochemical Co., Ltd. Choline chloride (ChCl, 99 %), *n*-Butanol (*n*-BuOH, ≥99 %) were obtained from the Shanghai Adamas Reagent Co., Ltd. Nitrogen (N_2, 99.99 v/v%) was purchased from Jiangxi Huahong Special Gas Co., Ltd. The other chemicals were used without additional purification.

2.2. Synthesis of ChCl-based DESs

In this work, the ChCl-based DESs were synthesized using a combination method of hydrogen bond donor and hydrogen bond acceptor. Typically, ChCl (0.05 mol, 6.98 g) and Gly (0.1 mol, 9.21 g) are put into a glass container in a molar ratio of 1:2. The mixture is stirred at 450 rpm and 333 K until the solid dissolves completely and a homogeneous liquid is formed. Then, the homogeneous liquid was placed in a vacuum drying oven at 333 K overnight to obtain ChCl-based DESs, which were denoted as ChCl-Gly (1:2). Finally, the water content of the prepared the ChCl-based DESs was measured by a Mettler Toledo DL32 instrument, and the results showed that the water content of all DESs was less than 0.05 wt%.

2.3. Preparation of DESs/HCl solutions

DESs/HCl solutions (ChCl-Gly (1:2)/HCl) were obtained by the bubble absorption. The absorption device was purged with N_2 gas for 30 min to remove gas impurities before the HCl absorption test. Subsequently, HCl gas was introduced into the absorption device equipped with ChCl-based DESs at a flow rate of 30 mL min^{-1} at room temperature. The HCl content in ChCl-Gly (1:2) was measured using an electronic balance with a mass error of ±1 g. Next, the DES/HCl solutions were obtained after 20 min of bubble absorption.

2.4. Qualitative and quantitative analysis of alkyl chlorides

First, the reaction mixtures were dispersed into a receiving flask with water and ethyl acetate, and the organic phase was collected. For the qualitative and quantitative analysis of alkyl chlorides, the TRACE 1300 gas chromatography-mass spectrometry (GC–MS) and the TRACE 1310 gas chromatograph (GC) equipped with a TG-5HT chromatography column were used. The following procedures were used for the detection of aliphatic chloride: the temperature program was set to start at 303 K and hold it for 2 min. It then increased to 353 K at 5 K min^{-1} and held for 2 min. Finally, it increased to 493 K at 10 K min^{-1}. The detector temperature was set at 533 K and the injector temperature was set at 493 K. Alternatively, the process for detecting aromatic chlorides was as follows: the temperature program was set to start at 323 K and increase to 493 K at a rate of 10 K min^{-1}. The detector temperature and the injector temperature were consistent with the aliphatic chloride detection program. The results of the GC and GC–MS were quantitative by the area normalization method, and the yield and selectivity of the target products were calculated.

3. Results and discussion

3.1. Self-made integrated device and catalytic reaction process

This work presents the design of a device that integrates premix and continuous flow microreactors, as shown in Fig. 1. The purpose of this device is to achieve efficient, safe and controllable chemical reaction processes, particularly those requiring precise control over reaction conditions, rapid mixing, and heat exchange. The premix section consists of the outlets for HCl, alcohol and the inlets for the microreactor, which allow rapid and uniform mixing of reactants. Subsequently, the mixture is supplied directly into the conversion interface of the HCl absorber, thereby simplifying the reaction process. The continuous-flow microreactor system comprises an HPLC pump, a microreactor, a cooler, a back-pressure regulator (BPR), and a collector. This configuration ensures accurate reactant delivery, stable temperature control, consistent pressure regulation, and continuous product collection, thereby guaranteeing repeatability and scalability. The reaction pipeline of the microreactor is a polytetrafluoroethylene tube with an inner diameter of 0.8 mm and a volume of 2.5 mL, which has excellent corrosion resistance and thermal stability. The temperature and stirring controls are carried out by a constant temperature magnetic stirrer, which can perform reactions in broad range of temperatures. The other pipelines with an inner diameter of 1.6 mm, minimize the number of connections, dead volume, and pressure drops. This optimization enhances reaction efficiency and safety, reduces reactant and product losses, and improves operational efficiency and cost-effectiveness. The device is equipped with components supplied by Nanjing Ke Hang Experimental Instrument Co., Ltd., which have high reliability and versatility, and can be applied to various types of homogeneous catalytic systems.

The device was cleaned with flowing ethanol, and then N_2 was blown through it for 0.5 h to remove steam and other contaminants. The HPLC pump controlled the amount and residence time of the reactants in the microreactors, while the flow rate of the DESs/HCl solutions and alcohols varied between 0.042 and 0.167 mL min^{-1}. It was worth noting that the *n*-Butanol has boiling point of 391 K, meaning that too high temperature would cause the polytetrafluoroethylene reaction tube to soften, which would alter the reaction effect. Therefore, the reaction temperatures of the microreactors were controlled between 363–383 K.

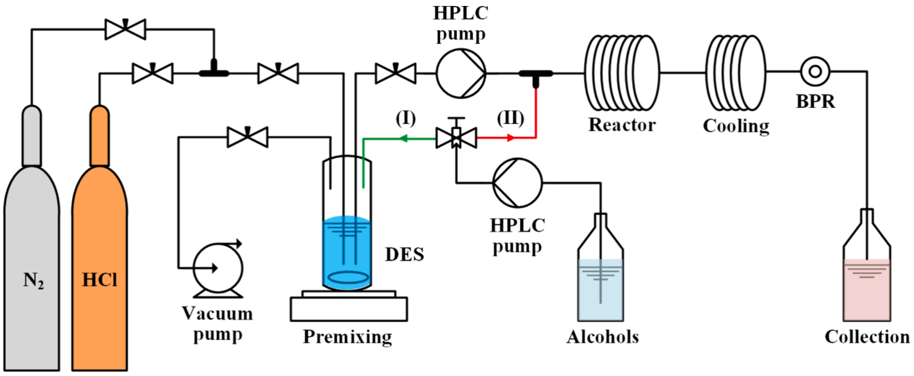

Fig. 1. Two mixed modes, (I) the Pre-mix and (II) T-mix of the continuous flow microreactor device.

The reaction mixtures with ChCl-Gly (1:2)/HCl solutions and alcohols were injected into the heated microreactor, but the gas column phenomenon occurred in the pipeline since no pressure was generated. At this point, we adjusted the BPR to reach a pressure of about 3 bar, which caused the gas column to disappear. Subsequently, the products were collected in a collection bottle with water and ethyl acetate, and the organic phase was separated for detection and analysis by GC.

3.2. The effects of diffusion coefficient and mixing time

The absorption and viscosity properties of homogeneous catalysts are important components of chemical engineering research [21,22]. Firstly, the HCl adsorption capacities, HCl adsorption rates, and the viscosity change during the absorption processes of ChCl-Gly (1:2) and Glycerol were determined. Secondly, changes in their ^{1}H NMR spectra (peak shifts and intensity) before and after HCl absorption were analyzed (see Fig. S1). Notably, ChCl-Gly (1:2) has superior adsorption capacity compared to Glycerol, and the absorption rate of HCl by ChCl-Gly (1:2) is considerably faster than that of Glycerol (see Fig. 2a). Specifically, ChCl-Gly (1:2) reaches saturation in about 19 min, while Glycerol takes about 138 min to reach adsorption equilibrium. Additionally, the change in viscosity during the absorption process proves to be a key factor as it affects the ability of catalysts/solvents to undergo homogeneous reactions. The results show that the viscosity of ChCl-Gly (1:2) decreased by 46.3 % after HCl absorption, in contrast to Glycerol, which showed an unexpected increase in viscosity of 66.7 % (see Fig. 2b). The viscosity decreases in ChCl-Gly (1:2) after HCl absorption is likely due to the disruption of the hydrogen bonding network, whereas the viscosity increase in Glycerol is attributed to the formation of stronger intermolecular interactions induced by HCl [23–25]. The significant change trend of solution viscosity could be one of the key factors contributing to the superior catalytic performance of ChCl-Gly (1:2) compared to Glycerol. Clearly, ChCl-Gly (1:2) demonstrates superior performance in HCl absorption compared to Glycerol, both in terms of adsorption capacity and adsorption rate. Therefore, ChCl-Gly (1:2) was selected to study the parameters of subsequent experiments, such as diffusion coefficients (D_R), mixing time (τ_{mix}), activation energies, and Henry's constants.

The lack of a stirrer in continuous-flow microreactor means that radial mixing within the tube relies on molecular diffusion between the fluids [26,27]. Therefore, understanding the diffusion coefficients of ChCl-Gly (1:2)/HCl solutions and alcohols is crucial to mastering the diffusion behavior of fluids in continuous flow microreactors and determining optimal operating conditions. This optimization enhances the performance of microreactors in chemical synthesis and catalysis. However, measuring the diffusion coefficient of reactants in ChCl-Gly (1:2) is a time-consuming and complex task. Fortunately, Abbott et al. successfully studied the self-diffusion coefficient of ChCl-Gly (1:2) using the pulsed field gradient (PFG) NMR technique [18]. Further, the diffusion coefficient of alcohols in ChCl-Gly (1:2) can be estimated using the Wilke-Chang equation (Eq. (1)) [28]:

$$D_R = 7.4 \times 10^{-15} \frac{T\sqrt{\varphi M_D}}{\eta_D V_R^{0.6}} \tag{1}$$

where D_R is the diffusion coefficient of alcohols in ChCl-Gly (1:2), T is the temperature in K, η_D is the viscosity in Pa•s, M_D is the molar mass of ChCl-Gly (1:2) in kg kmol^{-1} and φ is the association parameter of ChCl-Gly (1:2), respectively. And V_R is the molecular volume of the reactant at the normal boiling point in cm^3 mol^{-1}.

In the present work, we focus on measuring the D_R of *n*-Butanol, Benzyl alcohol and HCl, as well as estimating the influence of system temperature on the synthesis of alkyl chlorides. Moreover, we consider

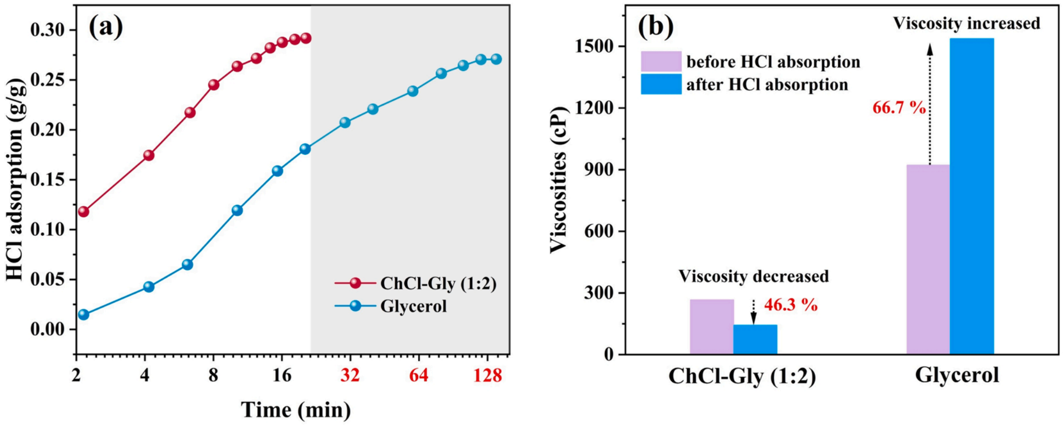

Fig. 2. (a) HCl absorption efficiency (b) the change trends of solution viscosity before and after HCl absorption under 298 K, 1 bar.

that the boiling point of *n*-Butanol is 391 K, while the product *n*-Butyl chloride has a lower boiling point than *n*-Butanol. Therefore, based on Eq. (1), we calculated the D_R of *n*-Butanol, Benzyl alcohol, and HCl in ChCl-Gly (1:2) catalyst/solvent at 363–383 K. The estimated D_R of the three species are summarized in Table 1. Obviously, the results show the temperature dependence of the three, and the D_R follows the order of HCl > *n*-Butanol > Benzyl alcohol. This may be attributed to the stronger resonance effec of the aliphatic alcohols and hydroxyl groups compared to aromatic alcohols, and without any exchange/interaction with other substances [29,30]. On the other hand, HCl may move as a whole molecule/ion, resulting in a significantly higher diffusion coefficient than the alcohol molecules. Furthermore, as the exchange/interaction between the hydroxyl hydrogen atoms of different molecules intensifies, a substantial disparity in the D_R values of aliphatic/aromatic protons and hydroxyl protons within the same molecule is anticipated.

$$K(T) = K_0 exp\left(-\frac{Ea}{RT}\right) \tag{2}$$

Eq. (2) can be rewritten as:

$$D(T) = D_0 exp\left(-\frac{Ea}{RT}\right) \tag{3}$$

Furthermore, the activation energies of *n*-Butanol and Benzyl alcohol were calculated by using the Arrhenius equation at different temperatures, and the pre-exponential factors were obtained from the Arrhenius law [31]. Fig. 3 depicts the relationship between ln(D) and 1/T after a linear fit was made between the two variables. The results showed that all correlation coefficients R^2 were above 0.99, which means that the kinetic Eq. (1) could adequately describe the diffusion kinetics of alcohols in ChCl-Gly (1:2)/HCl solutions. In general, the activation energy of *n*-Butanol was 44.3 kJ mol^{-1}, and that of Benzyl alcohol was 43.9 kJ mol^{-1}. The results are close to the apparent activation energy of 48.37 kJ mol^{-1} reported in the related work for the reaction kinetics of *n*-Butanol with HCl [32]. This also indicates that the obtained diffusion coefficients have high reliability. Besides, Fig. S2 and Table S1 summarize the Henry's constants and $\ln(H_m/P^\theta)$ for HCl absorption in GhCl-Gly(1:2) at different temperatures. In general, hydrogen bonds are a non-covalent interaction with a binding energy of 10–20 kJ $mol{\cdot}K^{-1}$. In the interaction between ChCl-Gly (1:2) and HCl, the adsorption process involves both physical and chemical mechanisms. This hypothesis is supported by experimental data from adsorption isotherms (see Fig. 2a), which indicate that the interaction between ChCl-Gly (1:2) and HCl conforms to the expected adsorptive behavior. Further analysis reveals that during the absorption of HCl by ChCl-Gly (1:2), the change in Gibbs free energy (ΔG) ranges from −4 kJ $mol{\cdot}K^{-1}$ to −5 kJ $mol{\cdot}K^{-1}$, suggesting that this process is spontaneous absorption of HCl. Moreover, the ΔG values between ChCl-Gly (1:2) and Glycerol were compared in Table S2. The results indicated that ChCl-Gly (1:2) was slightly more favorable for the HCl absorption process, which was consistent with the results of the absorption experiment. Additionally, the ΔH values for both systems are very similar, suggesting that both processes release comparable amounts of heat. Meanwhile, it also means that the absorption heat of two absorbents may not significantly affect the HCl absorption capacity.

Table 1
D_R of reactant in ChCl-Gly (1:2) at different temperatures.

Temperature (K)	$D_R \times 10^{-10}$ ($m^2{\bullet}s^{-1}$)		
	n-Butanol	Benzyl alcohol	HCl
363	1.02	0.95	2.05
373	1.49	1.39	3.01
383	2.15	1.99	4.32

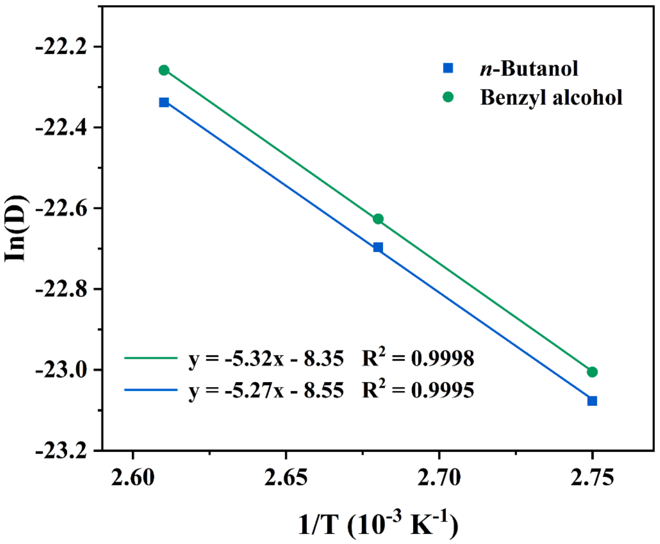

Fig. 3. Arrhenius plots for the diffusion coefficients of alcohols with ChCl-Gly (1:2)/HCl solutions.

3.3. *The effect of mixed modes*

To describe the physical τ_{mix} between different components in a fluid, Fick's law (Eq. (4)) is often used [20]. This law relates the large-scale average gradient to the small-scale diffusion mechanism, which is applicable to processes such as heat conduction or molecular diffusion. However, Fick's law neglects the possible chemical reactions that may occur in the system during the mixing process, which affects the estimation of τ_{mix}. Therefore, the Damköhler (*Da*) number (Eqs. (5) and (6)) needs to be introduced to correct the calculation of τ_{mix} [33]. The *Da* number indicates the relative rate of radial diffusion and reaction time. For example, the *Da* number greater than 1 signifies that within the system, the reaction kinetics markedly surpass the rate of radial diffusion [34]. In fact, this discrepancy results in a concentration gradient of the components within the microreactor. For homogeneous reactions, such heterogeneity in the concentration gradient can be problematic, increasing the formation of by-products and reducing both the conversion rate and selectivity of the reaction. Therefore, before using the microreactor to carry out the catalytic synthesis of alkyl chlorides, the reaction parameters should be adjusted according to the *Da* number estimation results to optimize the reaction performance.

$$\tau_{mix} = \frac{d^2}{4D_R} \tag{4}$$

$$Da = \frac{\chi d^2}{4\tau D_R} = \frac{\chi}{F_0} \tag{5}$$

$$F_0 = \frac{residencetime}{diffusiontime} = \frac{\tau}{\tau_{mix}} = \frac{4D_R\tau}{d^2} \tag{6}$$

$$X = \frac{X_R}{1 - X_R} \tag{7}$$

where τ is the residence time in the reactor, τ_{mix} is the physical mixing time between different components in a fluid, *X* is a coefficient that relates to the conversion rate by Eq. (7), F_0 is the Fourier number, X_R is the conversion rate of the reactant in the reactor.

Subsequently, we estimated the τ_{mix} of *n*-Butanol and Benzyl alcohol in ChCl-Gly (1:2) catalyst/solvent, and investigated their relationship with the D_R and the system temperature. For this analysis, we substituted the D_R data from Table 1 into the previously mentioned equation, thereby calculating τ_{mix} at various temperatures, as shown in

Table 2

τ_{mix} of *n*-Butanol and Benzyl alcohol in ChCl-Gly (1:2) at various temperatures in the microreactor.

Temperature (K)	τ_{mix} (s)	
	n-Butanol	Benzyl alcohol
363	1569	1684
373	1074	1151
383	744	804

Table 2. It could be seen that the τ_{mix} of Benzyl alcohol is marginally higher than that of the *n*-Butanol, with both significantly decreasing as temperature increases. The τ_{mix} of both reactants decreased by nearly 50 % when the temperature of the continuous flow microreactor was raised from 363 K to 383 K. The calculated results can be ascribed to the enhanced diffusion rates at higher temperatures, whiche improve the efficiency of the diffusion-controlled mixing process and in turn lead to lower τ_{mix} for the reactants in ChCl-Gly (1:2). Besides, this trend is consistent with the temperature dependency of D_R shown in Table 1, which suggests an inverse proportionality between τ_{mix} and D_R. It could be inferred that this was mainly due to the resonance effect and steric hindrance occurring between aliphatic alcohol and aromatic alcohol. In addition, based on the data in Table 1, since the D_R value of HCl was about twice that of alcohols, this part does not calculate its τ_{mix} in ChCl-Gly (1:2) DESs. Overall, within temperature range of 363–383 K, controlling the alcohol the τ_{mix} of alcohols at about 30 min in the microreactor is essential for uniformity of the reactant. However, given the complexity of the reaction, further study into the effect of the τ_{mix} on the synthesis of alkyl chlorides from alcohols and HCl using ChCl-Gly (1:2) as catalyst and solvent is warranted. This part will be evaluated and discussed in the next section.

The design and operating parameters of microreactors have a significant impact on the efficiency of chemical conversion and product selectivity in the field of catalytic reactions in microreactors [35]. As a result, this study investigates several key factors that influence the operation of catalytic processes in microreactors, including the D_R, τ_{mix}, and the way the reaction components are mixed. It was found that optimization of the mixing processes in microreactor systems plays a crucial role in determining product selectivity and yield. In particular, for slower chemical reaction processes, the use of T-mixer or Y-mixer could suffice to achieve satisfactory mixing effect, enhancing diffusion and convection through the formation of fluid bifurcations and confluences, thereby promoting contact and reactions between reactants. However, in situations involving rapid reactions or rigorous reaction conditions, the presence of concentration gradients within the reaction system may facilitate the formation of byproducts while simultaneously inhibiting the desired target product [36]. For this reason, we employed an accurate comparison method to evaluate the effects of pre-mixer (Fig. 1 (I)) and T-mixer (Fig. 1 (II)) on the composition and yield of products in microreactors. The results showed that under identical reaction conditions (383 K for 30 min), the yield of *n*-Butyl chloride was similar for both mixing strategies, with 54 % and 55 %, respectively (see Fig. 4). Although the yields were similar, a slight increase in the byproduct of *n*-Butyl ether was noted with the use of the T-mixer. It is noteworthy that when the substrate was changed to Benzyl alcohol, the yield of Benzyl chloride in the pre-mixer reached up to 93 %, with only 3 % of *n*-Benzyl ether. In contrast, using the T-mixer, the yield of Benzyl chloride decreased to 83 %, with an increase in byproduct yield to 5 %.

The *Da* number quantifies the ratio of the reaction time to the D_R. Higher *Da* number imply that the reaction kinetics are the limiting factor. This suggests that the reaction environment in microreactors must be efficiently mixed and heated for fast reactions to occur. Conversely, lower *Da* indicates that the D_R exceeds the reaction rate, characteristic of slow reactions where the influence of mass transfer on the reaction is negligible [37]. For *n*-Butanol, the *Da* is in the range of 0.49, which is less than 1, signifying a reaction-limited state. In contrast, the *Da* for Benzyl alcohol ($6.3 > 1$), which implies that it works under a mixing-limited scenario. Therefore, determining the *Da* and estimating the τ_{mix} provide a method for the initial assessment of the need for enhanced mix or premix, offering an approximation of the operational conditions for optimal reactor performance. Overall, our study confirmed that employing a premix method for alkyl chloride synthesis on the self-made integrated device significantly improved the catalytic performance of ChCl-Gly (1:2), which was supported by the experimental results.

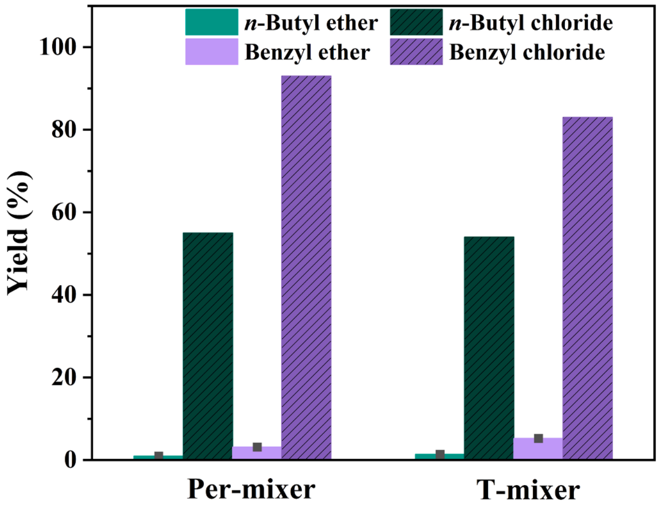

Fig. 4. The effect of two different mixer on the reaction of equimolar HCl (5 bar) with alcohol at 383 K, 30 min.

3.4. *The effect of Bodenstein number*

Fluid flow and reaction kinetics in microreactors are often considered plug flow reactors. However, axial diffusion plays an important role in mass transfer and reactions at low Reynolds (*Re*) numbers. The Bodenstein (*Bo*) number quantifies the deviation from and back mixing of ideal plug flow conditions (see Eq. (9)) [38]. Generally, $Bo > 100$ mean negligible deviation from plug flow, indicating that fluid flow mainly controls matter transfer with little effect from molecular diffusion. Under such conditions, the microreactors exhibit plug flow characteristics, with a minimal concentration gradient and a narrow distribution of residence times, which improves reaction efficiency and predictability. Conversely, $Bo < 100$ signify significant deviation from plug flow, implying that mass transfer is more dependent on molecular diffusion than fluid flow. This condition is akin to that of a completely mixed flow reactor, where mix and concentration are more uniform. However, the broader distribution of residence times leads to a wider product distribution and presents additional challenges in reaction control and predictability. In our experiment, the *Bo* of the ChCl-Gly (1:2)/HCl solution that catalyzed *n*-Butanol and Benzyl alcohol for 30 min at 383 K was calculated using Eq. (11), and $Bo > 100$ was found. The results confirm that the fluid flow within the microreactors closely approximates the plug flow model. Besides, the visually observed flow patterns in the pipes during operation in Fig. 5 support this assumption. Moreover, the *Bo* values are summarized in Table 3 and Table S3, which further confirms the plug flow behavior.

$$Bo = \frac{v_0 L}{D_{ax}} \tag{9}$$

In a circular pipe [39].

$$D_{ax} = D_R + \frac{v_0^2 d^2}{192 D_R} \cong \frac{v_0^2 d^2}{192 D_R} \qquad (1 < Re < 2000) \tag{10}$$

So combining Eqs. (7) and (8) can get Eq. (11)

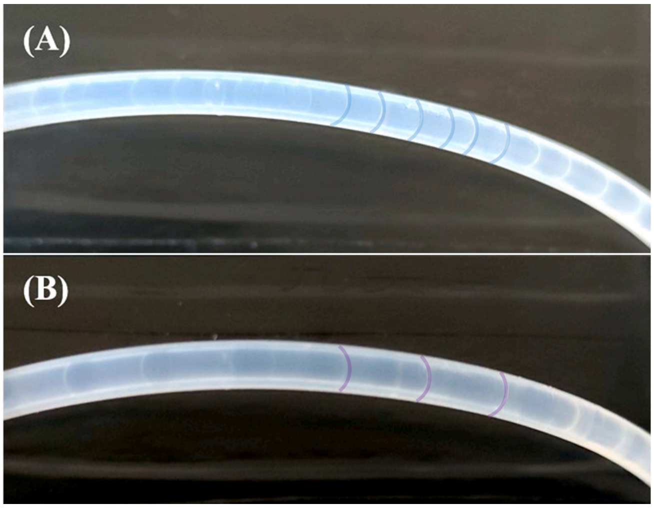

Fig. 5. (A) Photograph of *n*-Butanol converted to *n*-Butyl chloride; (B) Photograph of Benzyl alcohol converted to Benzyl chloride at 383 K and 30 min.

Table 3
Bo number variation in microflow reactors at different temperatures during ChCl-Gly (1:2)/HCl dissolution with *n*-Butanol and Benzyl alcohol.

Temperature (K)	*Bo* numbers	
	n-Butanol	Benzyl alcohol
363	55.1	51.3
373	80.5	75.1
383	116.1	107.5

$$Bo = 192 \bullet \frac{D_R \tau}{d^2} \tag{11}$$

where v_0 is the cross-sectionally averaged axial flow velocity, L is the length of the pipe in microreactors, D_{ax} is the taylor dispersion coefficient, d is the characteristic width of the pipe in microreactors, Re is reynolds number.

3.5. Validation of the model and the effect of reaction conditions

The effects of temperatures, HCl molar equivalents, residence times, and solvents on the conversion of alcohols to chlorides were studied using ChCl-Gly (1:2)/HCl as catalyst and solvent in a self-made integrated device. The yields of the corresponding chlorides were examined by premix equimolar amounts of HCl and alcohols in microreactors at 363–383 K for 30 min (see Fig. 6a). The results indicated that with an increase in reaction temperature, the yield of *n*-Butyl chloride rose from 22 % to 55 %, and that of Benzyl chloride from 87 % to 93 %, demonstrating a positive impact of temperature on the conversion of alcohols to alkyl chlorides. The fluid temperature of 383 K proved more favorable for this reaction in a plug flow mode, which is consistent with the predictions based on the *Bo*. However, elevated temperatures also led to byproduct formation, with the rates of *n*-Butyl ether and Benzyl ether increased from 0.4 % and 2.3 % to 1.1 % and 3.4 %, respectively. Thus, this reduced the purity and selectivity of alkyl chlorides, so the reaction temperature cannot increase further. To delve deeper into these observations and maximize the yield of alkyl chlorides, subsequent experiments involved augmenting HCl dosage, as shown in Fig. 6b. Interestingly, while an excess of HCl did not significantly improve the selectivity of the two alcohols towards alkyl chlorides, increasing the HCl concentration from equimolar to twice the amount led to a marked rise in the yield of *n*-Butyl chloride, from 55 % to 86 %. The yield of Benzyl chloride also experienced a modest increase, from 93 % to 98 %. These findings suggest that the heightened concentration of HCl facilitates the accelerated formation of *n*-Butyl chloride, attributed to the more efficient contact between excess HCl and *n*-Butanol in the microreactors. This also confirms the slower reaction rate between *n*-Butanol and HCl. Furthermore, the relationship between the yield of alkyl chlorides from HCl and alcohols and the residence time was also studied (see Fig. 6c). The yield of n-Butyl chloride gradually increased with residence time at 383 K, rising from 38 % for 15 min to 69 % for 60 min. The yield of Benzyl chloride reached a peak of 93 % after 30 min and remained unaffected by further increases in residence time. This is contrary to previous literature which suggested an increase in byproduct formation over time, thereby underscoring the potential of the pre-mix method to improve the τ_{mix} of microreactors. Additionally, these results emphasize that the conversion of *n*-Butanol to *n*-Butyl chloride proceeds at a slower rate compared to the conversion of Benzyl alcohol to Benzyl chloride.

Finally, a comparative analysis was conducted on the effects of DESs and single components. The catalytic efficacy of various systems in the conversion of alkyl alcohols to alkyl chlorides was investigated, utilizing ChCl-Gly (1:2) and Glycerol as the catalyst and solvent, respectively. Reactions were carried out under equimolar conditions with HCl and *n*-Butanol at 383 K and 5 bar for a duration of 30 min. As shown in Fig. 6d, the yield of *n*-butyl chloride yield in Glycerol was significantly lower at 36 %, compared to 55 % in ChCl-Gly (1:2). This enhanced reactivity in ChCl-Gly (1:2) can be attributed to rich hydrogen bond network of the solvent, which potentially increases the nucleophilicity of the alcohol oxygen atom [40]. The propensity of ChCl-Gly (1:2) to release free chloride ions that act as effective nucleophiles expedites the reaction process. Therefore, ChCl-Gly (1:2) is demonstrated to be a more effective catalyst in the synthesis of alkyl chlorides. Furthermore, we conducted a comparative analysis of the impact of reactor types on the efficiency of this reaction, and the results are shown in Table S4. It was found that the continuous flow microreactor demonstrated superior performance compared to the stirred tank reactor in this conversion process. This disparity can be attributed to the strong back-mixing effects and lower heat transfer efficiency in the stirred tank reactor, which lead to a wider residence time distribution and consequently lower chloride yields. In contrast, the continuous flow microreactor facilitates more efficient conversion due to the plug flow along the axial direction and the narrower residence time distribution, ultimately leading to higher product yields.

3.6. Comparison with the previous reptored results

The performance of ChCl-Gly (1:2) as catalysts/solvents and microreactors were compared with other catalysts and reactors reported in the literature for the synthesis of chlorides (see Table 4). The results showed that although a stirred was used as the reactor (Table 4, entry 1), 1 e q. of HCl could induce the synthesis of Benzyl chloride. However, the reaction time extended up 600 min, and the yield of Benzyl chloride was only maintained at 15 %. In addition, it was difficult to convert Benzyl alcohol to Benzyl chloride with high yield using microreactor without catalyst as the reactor (Table 4, entries 2, 3). Overall, these results were mostly lower than the catalytic performance of ChCl-Gly (1:2), and a yield of 86 % was obtained when the amount of HCl was adjusted to 2 eq. (Table 4, entry 5). Therefore, compared with the catalytic systems reported in the literature, ChCl-Gly (1:2) catalysts/solvents can efficiently catalyze Benzyl alcohol under milder conditions, and achieve high selectivity and excellent yield of Benzyl chloride.

3.7. Applicability and reusability

The applicability of ChCl-Gly (1:2) for the catalysis of different alcohols was investigated under the optimal reaction conditions (383 K, 5 bar, 30 min), and the results are summarized in Fig. 7. It was observed that various alcohols could be converted into the corresponding products with relatively good yields. For example, 1-chlorohexane was

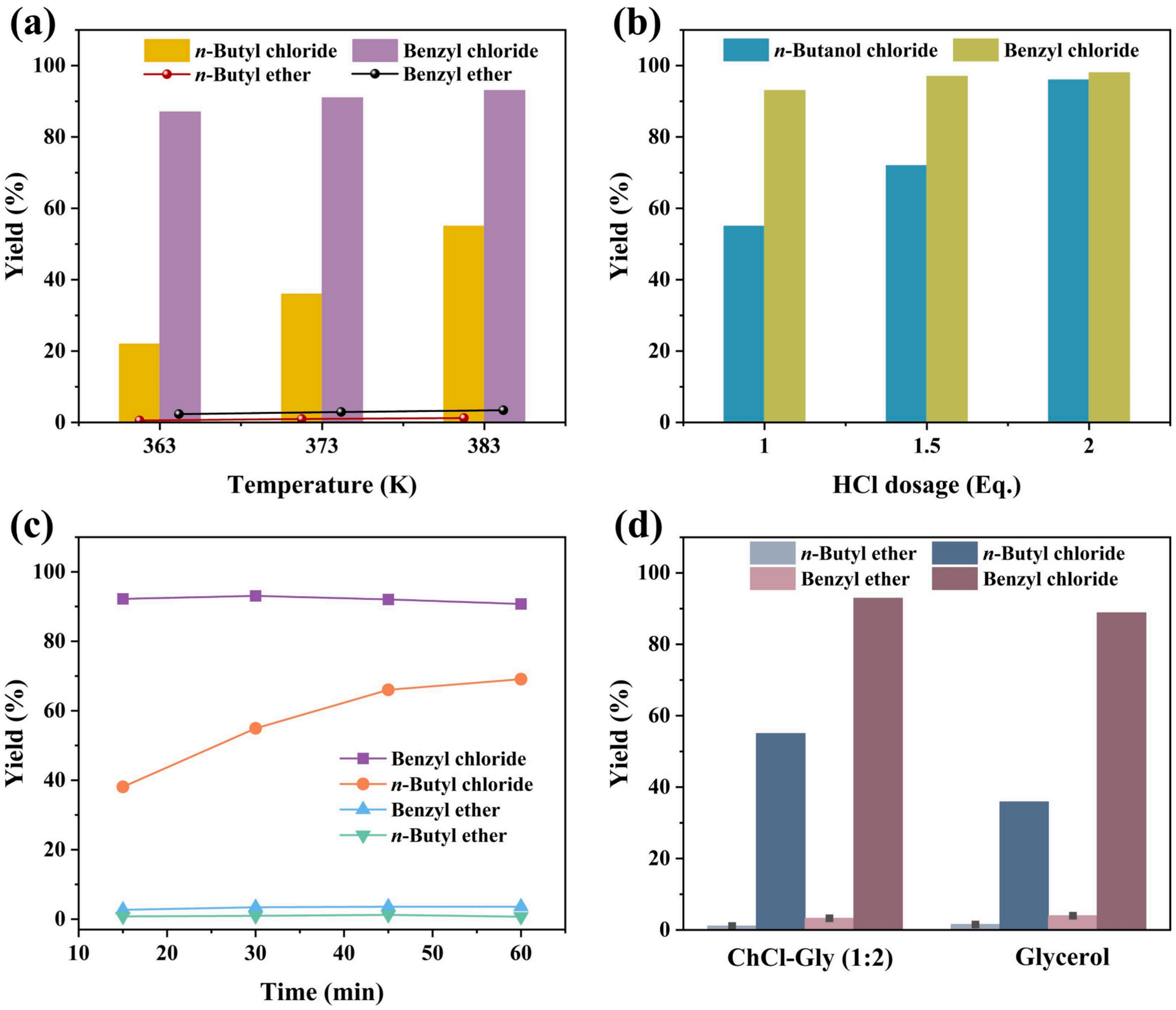

Fig. 6. The effect of (a) temperature on synthesize alkyl chloride from HCl (5 bar) and alcohol over 30 min, (b) equivalents of HCl on yield over 30 min at 383 K, 5 bar, (c) residence times on the formation of the main product and byproduct at 383 K, and (d) the comparative yields of alkyl chlorides using ChCl-Gly (1:2) and Glycerol as solvents over 30 min at 383 K, 5 bar.

Table 4
Comparison of the synthesis of Butyl chloride by other catalytic systems in different reactors.

Entry	Reactors	Catalysts/Solvents	HCl reagent	HCl (eq.)	T. (K)	P. (bar)	Time (min)	Yield (%)	Ref.
1	Stirred reactor	[Hmim]Cl	37 wt% HCl	1	353	1	600	15	[9]
2	Microflow reactor	–	30 wt% HCl	3	373	20	15	10	[41]
3	Microflow reactor	–	pure HCl gas	1.2	393	10	20	21	[1]
4	Microflow reactor	ChCl-Gly (1:2)	pure HCl gas	1	383	5	30	55	This work
5	Microflow reactor	ChCl-Gly (1:2)	pure HCl gas	2	383	5	30	86	This work

obtained from 1-hexanol catalyzed by ChCl-Gly (1:2) with a yield of 54 % (Fig. 7, entry 1). Similarly, 1-octaxinol and 1,5-pentanediol were converted into the target products with yields of 43 % and 89 %, respectively (Fig. 7, entries 2, 3). Notably, when the HCl conditions were tuned to 2 eq., the yields of 1-chlorooctane and 1-chlorohexane increased to 75 % and 83 %, respectively (Fig. 7, entries 1, 2, yields in brackets). Cyclopentanol and cyclohexanol given cyclopentyl chloride and chlorocyclohexane with yields of 98 % and 64 %, respectively (Fig. 7, entries 4, 5). In addition, aromatic alcohols provided excellent aromatic chlorides with yields of 85–97 % (Fig. 7, entries 6–9). However, it is still important to note that the electron-withdrawing group in p-fluorobenzyl alcohol exerts a detrimental impact on the reaction efficiency (Fig. 7, entry 9). As a result, while the conversion is still efficient, the presence of the electron-withdrawing group leads to a lower yield of p-fluorobenzyl chloride compared to other aromatic chlorides. Overall, ChCl-Gly (1:2) are easily applicable for the synthesis of various chlorides in microreactors, thus representing a potentially valuable solution for active pharmaceutical ingredients.

Fig. 8 shows the reusability of the ChCl-Gly (1:2) for the synthesis of Benzyl chloride within a microreactor. It is observed that the limited solubility of chlorides in the ChCl-Gly (1:2) medium facilitates the facile separation of the reaction mixture upon collection. This separation notably aids in the subsequent recovery of ChCl-Gly (1:2). Next, the removal of water and residual reactants from the ChCl-Gly (1:2) via a vacuum drying oven at 353 K allows for the direct reuse of ChCl-Gly (1:2) in subsequent work. Moreover, the ChCl-Gly (1:2) has demonstrated commendable catalytic efficacy and reusability across five successive Benzyl chloride synthesis reactions, which means that it

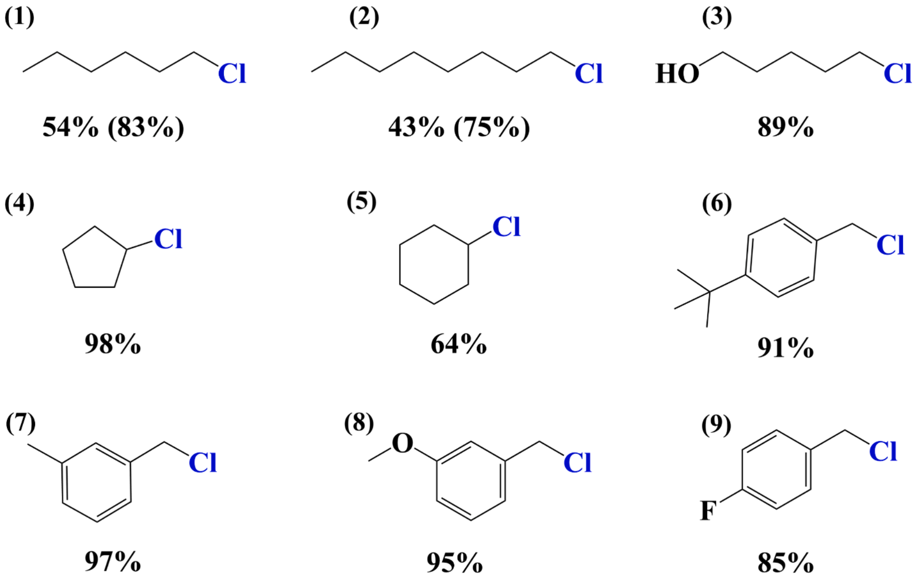

Fig. 7. Synthesis of other types of chlorides using ChCl-Gly (1:2)/HCl catalysts/solvents in microreactor, and the yields in brackets is 2 eq. HCl.

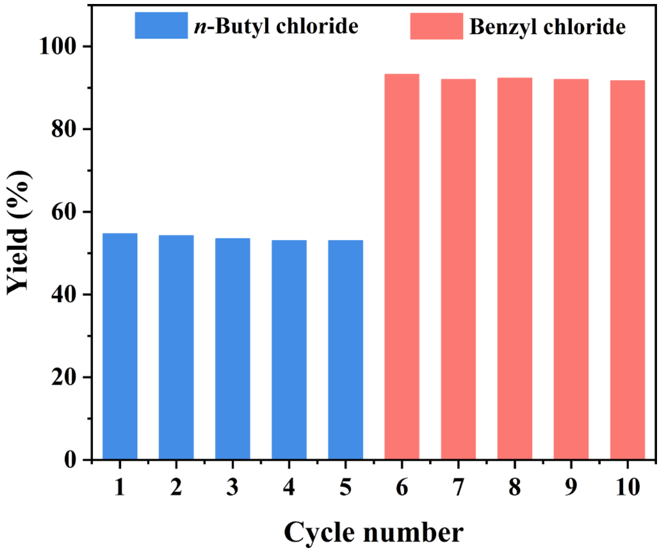

Fig. 8. The recovered ChCl-Gly (1:2) for the conversion of alcohols to chloride in the microreactor at 383 K and 1 eq. HCl for 30 min.

maintains catalytic activity. Consequently, the ChCl-Gly (1:2) embodies the principles of high efficiency, eco-friendliness, and sustainable chemical processes and has potential application value in the field of pharmaceutical intermediates synthesis.

4. Conclusion

In summary, we have successfully developed a continuous flow microreactor system that utilizes DESs saturated absorption HCl gas to form DES/HCl solutions for converting alcohols into their corresponding chlorides. This method significantly reduces the reaction pressure and mitigates the risks associated with HCl gas leakage. Furthermore, we established fluid model by calculating the mixing time and other fluid dynamics parameters of the DESs/HCl solution with alcohols in the microreactor, which enabled the creation of a fluid model that allows us to pre-determine the necessity of premixing or enhanced mixing. As a result, the continuous flow microreactor with DESs/HCl catalytic system efficiently produces alkyl chlorides from the reaction of HCl with alcohols under relatively mild conditions. Thus, continuous flow microreactors with DESs/HCl for alcohol conversion present an effective and safer method for the synthesis of alkyl chlorides.

CRediT authorship contribution statement

Shu-Yi Huang: Investigation, Formal analysis. **Yan Zhou:** Resources, Methodology. **Yu-Xuan Huang:** Investigation. **Nan Wang:** Visualization. **Zi-Teng Gao:** Visualization. **Ming-Shuai Sun:** Validation. **Wei Hui:** Writing – original draft, Supervision, Methodology. **Duan-Jian Tao:** Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2024.126041.

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