Enhanced mixing of biphasic liquid-liquid systems for the synthesis of *gem*-dihalocyclopropanes using packed bed reactors

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Abstract

A continuous flow procedure for the *gem*-dichlorocyclopropanation of alkenes has been developed. The method is based on the generation of dichlorocarbene utilizing the classical biphasic aqueous sodium hydroxide/chloroform system. This reaction typically requires vigorous stirring for several hours in batch for completion. Tarry materials precipitate due to partial polymerization of dichlorocarbene and the process is difficult to scale. To overcome these problems and achieve very efficient mixing during the flow process a column reactor packed with PTFE beads as inert filling material has been used. PTFE beads have been found to be the optimal material to obtain fine dispersions of the aqueous phase in the organic solution. By heating the packed-bed reactor at 80 °C excellent conversions have been achieved after a residence time of only 4 min. The process has been applied for the synthesis of Ciprofibrate, a dichlorocyclopropane-containing drug used as treatment for several diseases associated with high lipid content in blood.

Keywords Dichlorocarbene · Phase-transfer catalysis · Packed-bed reactor · *gem*-dichlorocyclopropanation · Ciprofibrate · Continuous flow

Introduction

Biphasic liquid-liquid systems are very important in process chemistry and the pharmaceutical industry. Apart from multiphasic reactions, such as nitrations, saponifications and emulsion polymerizations, liquid-liquid systems are also involved in other processes like extractions [1–4]. The progress of these reactions is often limited by mass

transfer, which in turn depends on the surface contact area between the two phases [5, 6]. In batch reactors highly dispersed biphasic liquid-liquid mixtures can only be obtained by vigorous stirring and, accordingly, stirring speed is an important parameter contributing to the reaction performance [7, 8]. Scale-up of liquid-liquid systems in batch is therefore problematic, since high shear forces are required and a larger scale results in lower interfacial surface area to volume ratio. To enhance the mass transfer in biphasic systems phase transfer catalysts (PTC) are often used. A PTC is an additive that facilitates the migration of a reactant from one phase into another. To shuttle anionic reactants quaternary ammonium salts such as benzyltriethylammonium chloride or tetrabutylammonium bromide are often employed [9]. PTCs in general are considered to be advantageous towards the goal of sustainable chemical processing and green chemistry, since they enable the use of water as a reaction medium, reducing the consumption of organic solvents [10, 11].

Continuous flow and microreactor technology has been shown as a powerful tool to overcome the problems associated with poor mixing in multiphasic systems. A very high surface-area-to-volume ratio is typically achieved within the microchannels of a flow reactor, dramatically increasing the

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mass transfer that can be achieved [12, 13]. Liquid-liquid biphasic mixtures can produce several flow patterns in continuous flow reactors (Fig. 1) [4, 14–18]. To make the interfacial area as large as possible a turbulent flow regime is desired, which leads to an emulsion with highly dispersed droplets (Fig. 1a). Adequate turbulent flow even at low flow rates can be achieved by carefully designed mixing structures. Such microstructured devices have proven very useful for the generation of emulsions for very fast reactions involving biphasic systems [19, 20]. Slow reactions, in contrast, are highly problematic. Despite the very efficient mixing achieved in a micromixer, the immiscible phases tend to separate within the residence time unit for longer reactions. Formation of larger segments within minutes can stop the reaction progress. Thus, for longer reactions the mixing structure should ideally be extended throughout the whole reactor channel.

A classic example of a challenging biphasic liquid-liquid reaction is the generation of dichlorocarbene (DCC) utilizing the chloroform/aqueous hydroxide system. DCC is a versatile reagent utilized for the generation of *gem*-dichlorocyclopropanes from olefins. It has also been utilized for the Hofmann isonitrile synthesis and for the Reimer-Tiemann formylation (Scheme 1) [21, 22]. Dichlorocarbene is a highly reactive, short-lived intermediate [23]. It is usually generated in situ in the presence of the substrate. In a typical batch *gem*-dichlorocyclopropanation reaction, a solution of concentrated NaOH is added over a vigorously stirred solution of the alkene and a PTC in chloroform under reflux conditions for several hours [24]. Carbene molecules that are not rapidly trapped by the substrate tend to polymerize resulting in tarry materials, or to decompose in the presence of hydroxyl sources producing carbon monoxide, NaCl and water [25]. In addition to the NaCl produced as by-product during the DCC generation, the precipitation of tar further complicates appropriate mixing of the reaction.

We were interested in the scale-up of the *gem*-dichlorocyclopropanation of alkenes with dichlorocarbene using the chloroform/aqueous NaOH system using continuous flow conditions. Challenged by the long reaction times required by the reaction, formation of solids, and the need for very efficient mixing during the whole process to avoid

separation of the phases within the channel, we have carried out a comparative study of several mixer/reactor combinations. It was found that packed bed reactors using PTFE beads as inert filling material provided the best performance. Herein, the results of our study, including optimization of the reaction setup and conditions, and their application to the synthesis of the *gem*-dichlorocyclopropane containing drug Ciprofibrate [26] are presented.

Results and discussion

Our investigation began with a series of preliminary batch experiments using sealed vessels with the goal of obtaining an initial set of reaction conditions for our flow experiments. The *gem*-dichlorocyclopropanation of cyclohexene **1**, providing 7,7-dichlorobicyclo[4.1.0]heptane **2** (Scheme 2), was chosen as a model reaction. Thus, in a 3 mL vial cyclohexene and 3 mol% benzyltriethylammonium chloride (BTEA-Cl) were dissolved in chloroform. An aqueous solution of sodium hydroxide 40 wt% was added and the mixture was vigorously stirred. Notably, the silicone septa ruptured (pressure ca. 6 bar) in most cases due to the formation of CO gas. The presence of this gas could be confirmed by approaching a CO detector to the reaction mixture. Under batch conditions, 97% conversion (GC-FID) to the desired product **2** was achieved after 1 h.

We then directly moved to continuous flow conditions. A simple continuous flow setup consisting of a Y-mixer (0.5 mm i.d.) and PFA tubing was initially tested. The setup consisted of three streams (Table 1). Aqueous NaOH (40 wt%) and the organic phase consisting of cyclohexene (1.95 M) and the PTC (3 mol%) in chloroform were pumped using a peristaltic and a syringe pump, respectively (see [Supporting Information](#)), and mixed using the Y-mixer. After the residence time coil (PFA tubing, 0.8 mm i.d.), the reaction was quenched with an aqueous stream, using a syringe pump. The system was pressurized at 5 bar. Utilizing this simple setup and mixer a segmented flow pattern was obtained. A series of phase transfer catalysts was examined at room temperature using a residence time of 10 min. Apart from the usual ammonium salts, secondary and tertiary amines were also evaluated as catalysts (Table 1). The use of amines as catalysts for dichlorocarbene reactions using the chloroform/aqueous hydroxide system, first reported by Isagawa et al [27], follows a different mechanism involving formation of ylides between the carbene and the amines in the aqueous phase [24, 28, 29]. Once the ylide is extracted to the organic phase it releases the carbene. Notably, conversions obtained using several inexpensive tertiary amines (Table 1, entries 2–8) were analogous to those for BTEA-Cl (entry 1). Other more bulky tertiary amines and secondary amines (entries 3, 6, and 9–11) gave poor results, in analogy to the reactivity described by Isagawa [27]. Best results were obtained using

Fig. 1 Common flow regimes for biphasic mixtures in microreactors (**a** emulsion, **b** slug flow, **c** laminar flow)

Scheme 1 Selected organic reactions involving dichlorocarbene as reactive intermediate

dimethylethylamine and diethylmethylamine (entries 4 and 5). Et₂MeN was selected as catalyst for subsequent experiments due to its low boiling point (63–65 °C) [30] which simplifies the reaction workup as it can be removed by simple evaporation. Monitoring of the reaction conversion after a series of flow experiments with increasing residence time (Fig. 2) at 40 °C revealed that, while the reaction is relatively fast during the initial 2–3 min, it then becomes exceedingly slow. Nearly 50% conversion was observed after 5 min residence time. Increase of the residence time to 10 min only produced an increase of conversion of 6%. This effect was ascribed to the above mentioned aggregation of the phases in the residence time PFA tube, producing longer segments of liquid and significantly decreasing the surface contact area between the immiscible liquids (Fig. 2). Temperature had a positive effect in the reaction outcome. Keeping the residence time constant at 1 min, the reaction temperature was gradually increased from room temperature to 80 °C. The conversion increased from <10% to 40% (Fig. 3). No side products were observed by GC or NMR analysis. However, a significant amount of tar was produced at higher temperatures, presumably due to the polymerization of the excess of carbene (the same tarry material was observed when running the reaction in the absence of cyclohexene). Tar precipitation eventually caused clogging of the reactor and irreproducible results [31]. Clogging could not be avoided by applying ultrasound.

To ensure active mixing during the complete residence time and avoid aggregation of the liquid phases, a glass reactor plate with an active mixing geometry was also evaluated. Unfortunately, appropriate mixing was only achieved at

Scheme 2 *gem*-Dichlorocyclopropanation of cyclohexene utilized as model reaction

relatively high flow rates (Fig. 4). Gradual increase of the flow rates of a biphasic water/chloroform mixture revealed that the desired dispersion is only achieved at a total flow rate of 1.5 mL/min. This resulted in a residence time for a 4 mL plate below 3 min and poor conversions were observed for the model reaction. Analogous problems were observed with a 3 mm inner diameter static Kenics type mixer.

We next turned our attention towards a packed bed reactor filled with inert material (beads). This strategy has previously been utilized to provide biphasic systems with excellent mixing even at low flow rates [16, 32–36]. Thus, an Omnifit glass column (12 mL) was utilized as reactor, and heated in a commercially available column heater (Syrris). Several inert materials, namely glass, stainless steel and PTFE beads, and particle sizes were tested as stationary phase for comparison. Pressure drop, reaction conversion and reactor dead volume were examined in all cases (Table 2). As expected, highest conversions were achieved when the smallest particles were utilized (entries 4–6), under otherwise analogous conditions. These results clearly demonstrate the importance of effective mixing for this reaction. The flow regime within the packed-bed reactor could not be visually inspected. This type of static mixers are known to produce droplet/dispersion regimes for biphasic liquid-liquid system [37–39]. Indeed, an excellent dispersion of the aqueous phase in the organic phase could be visually observed in the tubing at the mixer output by adding a dye to the water solution (Fig. 5c). PTFE particles provoked the lowest pressure drop in the system (entry 6) and, more importantly, a constant pressure profile over time even for long run reactions (> 4 h). In contrast, the system pressure gradually increased when using stainless steel and sand particles, probably due to the accumulation of polymeric material within the packed-bed. These results could be ascribed to the very low van-der-Waals forces characteristic of PTFE, which prevent materials to easily stick to its surface [40]. Moreover, this material is fully inert under most reaction conditions.

Table 1 Catalyst screening utilizing a PFA tubing reactor

Entry	Phase transfer catalyst	Conversion (%) ^a
1	BTEA-Cl	30%
2	Et ₃ N	27%
3	Bu ₃ N	15%
4	Me ₂ EtN	38%
5	Et ₂ MeN	39%
6	Benzyl dimethylamine	18%
7	<i>N</i> -Methyl piperidine	36%
8	<i>N</i> -Methyl pyrrolidine	35%
9	Hünig base	0%
10	Pyridine	0%
11	Secondary amines ^b	0%
12	No catalyst	0%

Reaction conditions are shown in the flow scheme

^a Determined by GC-FID peak area integration

^b Including: *i*Pr₂NH, *n*Pr₂NH, Et₂N, piperidine and pyrrolidine

PTFE was therefore selected as packing material for subsequent optimization studies.

Further optimization of the reaction conditions using the packed bed reactor was carried out by varying the catalyst loading, NaOH concentration, temperature and residence time

for the reaction (Table 3). Initially, a solution of 0.5 M cyclohexene in chloroform containing 3 mol% of catalyst was used. Increasing the amount of the catalyst up to 10 mol% improved the conversion significantly (Table 3, entries 1–3). Higher catalyst loading only showed minor improvement (entry 4).

Fig. 2 Effect of the residence time on the formation of **2** at 40 °C (left). The continuous flow setup depicted in Table 1 was used. Conversion was determined by GC-FID analysis. Image of the reaction mixture at the end of the residence time coil. Long liquid segments can be observed (right)

Fig. 3 Effect of the reaction temperature on the *gem*-dichlorocyclopropanation of cyclohexene. The reactor depicted in Table 1 was used. Conversion was determined by GC-FID analysis

Temperature had an important influence in the reaction outcome. While decreasing the temperature resulted in much lower conversions, increase to 90 °C provoked clogging of the reactor (entries 5 and 6). The conversion increased when higher concentrations of sodium hydroxide were applied (entry 7). This may be attributed to the fact that hydroxide anions are less solvated by water and therefore the reactivity increases

[41]. Increasing the concentration of the sodium hydroxide solution to 40 wt% led to clogging of the reactor (entry 8). The optimal concentration was 35 wt% of sodium hydroxide in water. To extend the residence time, an additional column was added to enlarge the reactor volume by 50%, providing a total volume of 6.9 mL. Excellent conversion could finally be achieved by gradually increasing the NaOH/CHCl₃ ratio (entries 10–11). Under optimal conditions 97% conversion of the substrate and >99% selectivity for the desired product **2** was obtained (entry 11).

The continuous flow procedure was then applied for the synthesis of Ciprofibrate, a *gem*-dichlorocyclopropane-containing drug used as lipid-lowering agent (Fig. 6) [42–45]. Precursor **3** was prepared according to the literature [46]. Using the optimized conditions (Table 3, entry 11) full conversion of **3** and complete selectivity for the desired Ciprofibrate **4** was observed by GC-FID analysis. Notably, the high purity with which **4** was obtained permitted a very simple workup consisting in extraction of the product with DCM/water and evaporation of the organic phase. Using this protocol, the reaction was run for 4 h. 18.8 g of

Fig. 4 Visual aspect of a biphasic water/chloroform system in a glass plate with active mixing geometry at (a) 0.5 mL/min and (b) 1.5 mL/min

Table 2 Comparison of packed bed reactors using different stationary phase materials

Entry	Stationary phase	Particle size [μm]	Dead volume [mL]	Conv. [%] ^a	Pressure drop [bar] ^b
1	Glass beads	2000	5.3	11	3.0
2	Glass beads	500–750	5.2	21	2.9
3	Glass beads	400–600	5.1	23	2.5
4	Stainless steel	60–125	4.9	29	3.4
5	Sand	40–100	4.7	30	3.3
6	PTFE	> 40	4.6	25	1.6

Conditions: Omnifit column packed with different stationary phase materials, 80 °C, organic stream: 0.5 M cyclohexene, 3 mol% Et₂MeN in chloroform, 530 μL/min; aqueous stream: 30 wt% NaOH, 1.07 mL/min; the two streams were combined prior the column via Y-mixer

^a Determined by GC-FID peak area integration

^b Pressure difference between the inlet and outlet of the column

Fig. 5 **a** Schematic view of the optimal continuous flow setup for the dichlorocarbene *gem*-dichlorocyclopropanation of alkenes utilizing a **(b)** column reactor packed with PTFE beads. **c** Visual aspect of the droplets of aqueous solutions in chloroform at the reactor output

Ciprofibrate **4** (98% yield) was isolated, corresponding to a productivity of ca. 5 g/h.

Conclusions

In summary, a continuous flow method for the *gem*-dichlorocyclopropanation of alkenes with in situ generated dichlorocarbene has been developed. The classical biphasic

aqueous NaOH/ CHCl_3 system has been utilized. The challenges associated with the very efficient mixing required by this process have been overcome on lab scale by using a packed-bed reactor filled with PTFE beads as inert material. This mixer enabled the generation of very fine dispersions of the aqueous solution in the organic phase even at relatively low flow rates, which was not achievable using other mixing elements. Moreover, using this strategy intense mixing is applied during all the residence time, avoiding aggregation of the

Table 3 Optimization of the reaction conditions for the *gem*-dichlorocyclopropanation of cyclohexene

Entry	Flow rate (aq./org. phase) [ml/min]	Catalyst loading [mol%]	NaOH _{aq.} conc. [wt%]	Temp.	Reaction volume [mL]	Conv. ^a [%]
1	0.80/0.80	3	30.0	80 °C	4.6	25
2	0.80/0.80	5	30.0	80 °C	4.6	36
3	0.80/0.80	10	30.0	80 °C	4.6	57
4	0.80/0.80	20	30.0	80 °C	4.6	62
5	0.80/0.80	10	30.0	60 °C	4.6	51
6 ^a	0.80/0.80	10	30.0	90 °C	4.6	—
7	0.80/0.80	10	35.0	80 °C	4.6	63
8 ^b	0.80/0.80	10	40.0	80 °C	4.6	—
9	0.80/0.80	10	35.0	80 °C	4.6 + 2.3	76
10	0.96/0.64	10	35.0	80 °C	4.6 + 2.3	90
11	1.07/0.53	10	35.0	80 °C	4.6 + 2.3	97

Conditions: Omnifit column packed with PTFE particles (>40 μm), diethylmethylamine was used as catalyst, organic stream: 0.5 M cyclohexene + catalyst premixed in chloroform; the organic and aqueous streams were combined before the first column via Y-mixer

^a Determined by GC-FID peak area integration

^b Reactor clogged under these conditions

Fig. 6 Continuous flow synthesis of Ciprofibrate **4** via *gem*-dichlorocyclopropanation of **3** with in situ generated dichlorocarbene

liquid droplets. *N,N*-diethylmethylamine, was found as the best catalyst for the transformation. Notably, utilization of amines instead of quaternary ammonium salts significantly simplified the reaction work-up. Under optimal conditions at 80 °C and a 2:1 aqueous (NaOH 35 wt%)/CHCl₃ ratio, excellent conversion and selectivity for the desired *gem*-dichlorocyclopropane was obtained, in a readily scalable protocol. The process was stable for at least 4 h, producing 19 g of the target compound.

Experimental section

General remarks ¹H NMR spectra were recorded on a Bruker 300 MHz instrument. ¹³C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet. GC-FID analysis was performed on a ThermoFisher Focus GC with a flame ionization detector, using a TR-5MS column (30 m × 0.25 mm ID × 0.25 μm) and helium as carrier gas (1 mL min⁻¹ constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C min⁻¹ to 300 °C and kept constant at 300 °C for 4 min. The detector gases for flame ionization were hydrogen and synthetic air (5.0 quality). GC-MS spectra were recorded using a ThermoFisher Focus GC coupled with a DSQ II (EI, 70 eV). A TR-5MS column (30 m × 0.25 mm × 0.25 μm) was used, with helium as carrier gas (1 mL min⁻¹ constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C min⁻¹ to 300 °C and kept at 300 °C for 3 min. All chemicals were purchased from standard commercial vendors and utilized without further purification.

Representative procedure for the continuous flow synthesis of *gem*-dichlorocyclopropanes Flow experiments were performed using the continuous flow setup described in the Fig. S1 in the [Supporting Information](#). The organic feed contained 0.5 M of the olefin and 3 mol% of diethylmethylamine in chloroform. The aqueous solution feed consisted of 35 wt% NaOH in water. The organic solution was pumped by using a Syrris® Asia syringe pump and the alkaline aqueous solution was pumped using a Vapourtec® SF-10 peristaltic pump. Both streams were combined in a Y-mixer before entering an Omnifit® packed-bed reactor filled with PTFE particles (>40 μm). To extend the reactor volume, a second packed-bed was connected in series to give a total reaction volume of 6.9 mL. Both columns were arranged in a vertical orientation and the reaction mixture was passed through them from the bottom upwards. The columns were heated to 80 °C using a Syrris® column heater. After the column reactors the reaction mixture was diluted inline with water. A 5 bar back-pressure-regulator was installed in the reaction output. The crude reaction mixture collected from the reactor outlet was extracted with DCM. The organic layer was dried over MgSO₄ and concentrated under reduced pressure yielding the desired *gem*-dichlorocyclopropane.

Ciprofibrate methylester (4) 18.8 g (98% yield), ¹H-NMR (300 MHz, CDCl₃): δ = 7.13 (2H, d, ³J = 8.3 Hz), 6.82 (1H, d, ³J = 8.3 Hz), 3.78 (3H, s), 2.90–2.77 (1H, m), 1.94 (1H, dt, ²J = 15.8 Hz, ³J = 7.9 Hz), 1.87–1.74 (1H, m), 1.61 (6H, s). ¹³C-NMR (75 MHz, CDCl₃): δ = 174.7, 154.8, 129.7, 128.3, 79.2, 60.9, 52.5, 34.8, 25.8, 25.4.

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