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Continuous Flow Multigram-Scale Synthesis of Cetylpyridinium Chloride

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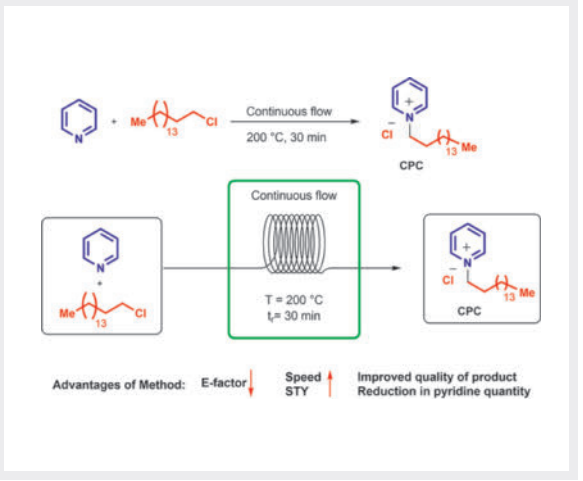
SIGNIFICANCE

- High-*T* and neat continuous flow synthesis of quaternary ammonium-based antimicrobial agent and disinfectant: cetylpyridinium chloride (CPC)
- Safe and efficient conversion within a smaller footprint with elements of sustainability designed for large-scale manufacturing
- A continuous flow protocol with >50-fold space-time-yield (STY) enhancement as compared to the conventional batch process



Keywords

Antimicrobial, Cetylpyridinium chloride, Continuous flow, High-*T*

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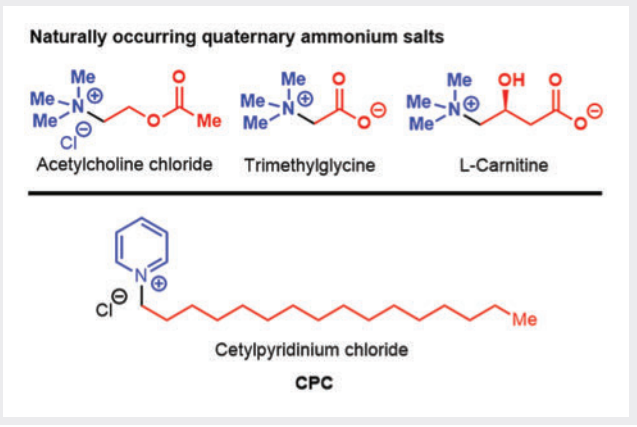
ABSTRACT

Cetylpyridinium chloride is popularly employed as an antimicrobial agent in high-volume commodity and consumer products. Given its high tonnage requirements annually, challenges in its synthesis using conventional batch manufacturing involving higher reaction temperatures at scale, lower yields and purity, and excessively long reaction times could be circumvented by adopting continuous flow as a safe and sustainable approach. We herein report a

facile, gram-scale continuous flow protocol for the synthesis of cetylpyridinium chloride (CPC) that reduces reaction time from ≥24 hours to 30 minutes with an isolated product yield of >90% and an HPLC purity of >99%.

Introduction

Quaternary alkyl pyridinium salts form a widely known utilitarian class of compounds as they exhibit promising antibacterial activity [1]. In particular, cetylpyridinium chloride (CPC) has wide application in FMCG (fast-moving consumer goods) products such as mouthwashes, toothpastes, throat and nasal sprays owing to its powerful antiseptic or antibacterial properties (▶ **Fig. 1**) [2–3]. Further surfactant properties of CPC have been utilized for the disinfection of poultry and medical devices [4].



▶ **Fig. 1** Biologically active quaternary ammonium salts.

CPC is projected as a multitonnage product globally, which makes it a product of major commercial significance. Since the first report in 1938 by Knight et al. [5] for the preparation of dodecylpyridinium chloride, several synthetic protocols based on this approach have emerged in literature discussing methods of improving the yield of quaternary alkyl pyridinium salts [6–7].

Given the importance and large-scale requirement of CPC, several patents have been filed [8–12], describing multiple approaches, namely (i) the synthesis with inexpensive cetyl chloride and pyridine at 110 °C for 80 h, (ii) synthesis under pressure using an autoclave followed by agitation at 180 °C, and (iii) synthesis in dry ethanol for reaction times around 40 h. Improved processes disclosed in recently filed patents did not necessarily address the relatively long reaction times as well as the requirement of a cumbersome and time-consuming purification procedure.

Most of the processes disclosed for CPC operate using a batch reactor or a high-pressure autoclave and have major limitations such as (a) longer reaction times (>10 h up to 80 h), (b) lower product yields, (c) excessive usage of pyridine (several fold excess, typically >8 equivalents), (d) cumbersome work-up procedures, and (e) requirement of high pressures.

Despite these variations in classical batch processes that have catered to the global supply of CPC, there is a clear need to design an improved, efficient and sustainable synthesis of CPC.

We were, therefore, interested in developing an approach that would not only address the longer reaction times and tedious purification procedures but also ensure a robust process potentially less prone to scale-dependency factors while ensuring consistent yields and purities. We envisaged that continuous flow approach for synthesis of CPC could be advantageous in the context of using a smaller footprint that could be robustly translated from lab to manufacturing.

Over the past few years, advances in flow chemistry and continuous manufacturing have prompted a re-look of current batch processes and have increasingly addressed often encountered limitations therein [13–16]. Compared to the batch reactions, continuous flow processes provide major advantages, such as increased yield and selectivity, help create a safe working environment (safe handling of hazardous and reactive substrates), dramatic reduction in the process time, etc. The possibility of precise and instrument-intensive control of process parameters such as residence time, temperature, dosing, and pressure has imparted greater reproducibility and consistency in flow-based processes as compared to the classical batch reactions [13]. Advancements in flow technology (microreactor) have been driven by several research groups, namely, Ley [17], Kappe [18], Noel [19], Jamison [20], and Hilton [21].

There is a significant emphasis on improving the 'time-economy' of a chemical conversion [22]. Recently, Kapdi et al. have reported a Suzuki–Miyaura and Heck alkenylation reaction sequence in plug flow conditions, which greatly improved the conversion time for the cross-coupling of a series of C5-pyrimidine-substituted nucleosides [23]. As a part of ongoing interest on flow-based process development for large-volume ingredients, our recent efforts have focused on the high-*T* (high-temperature) regimen [24].

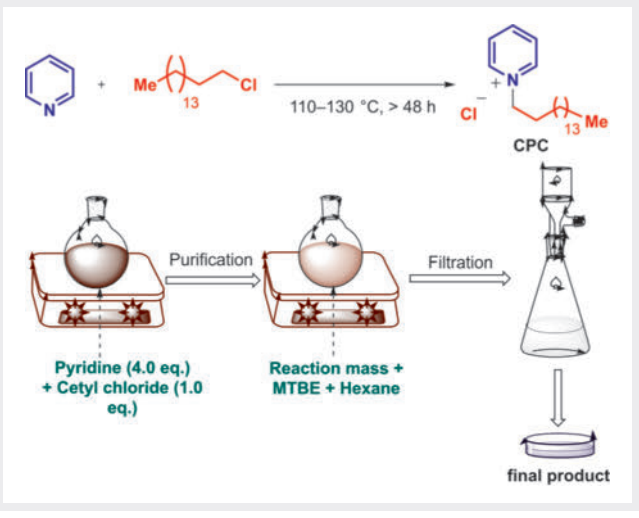
We herein report the development of a neat and high-temperature-mediated continuous flow process for the multigram-scale synthesis of CPC employing lower equivalents of pyridine and a significantly reduced conversion time.

Results and Discussion

As described earlier, an improved approach to address several operational problems such as long reaction times, excess requirement of pyridine, irreproducible yields, and variable purity (several purification steps required) is needed to transform current manufacturing of CPC to a more sustainable production. Our efforts were directed toward the identification of the key process parameters that could be potentially investigated for the development of a successful flow process for CPC. It should be mentioned at this point that long conversion

times (slower reaction kinetics) often preclude the development of a viable flow process owing to long residence times and inordinately slow flow rates.

As a first step toward preliminary screening and identification of the process parameters, we performed a batch reaction using pyridine and cetyl chloride on a gram-scale in a sealed-tube Radleys Carousel 12 Plus Reaction Station™ system at 100 °C. A schematic representation of the batch experimental protocol is depicted in ▶**Fig. 2**; the results thus obtained are tabulated in ▶**Table 1**. Although a high yield of ~94% was obtained, the time needed to facilitate a complete conversion was almost 2 days (▶**Table 1**, Entry-1). Furthermore, when the equivalents of pyridine were reduced from 4.0 equivalents to 2.0 equivalents, a significant reduction in the product yield was observed (▶**Table 1**, Entry-2). Subsequently, a 5 g batch was carried out under the same conditions (▶**Table 1**, Entry-3) to estimate the reproducibility of the process. In all the cases, the crude product isolated was yellowish brown in color. Post this initial batch screening, our efforts were directed toward development of an improved process capable of producing a high yield within lesser reaction times in an inherently safe and efficient manner.



▶**Fig. 2** Batch process for the synthesis of CPC.

Against this background, we contemplated the use of continuous flow chemistry approach to CPC and exploit the intrinsic advantages of flow. In particular, we wanted to investigate whether high surface-to-volume ratio, enhanced heat and mass transfer, better intermixing of reactants, and the ability to safely explore temperatures higher than the boiling points of the reactants will bring about an improvement in the current batch process. With this knowledge, we set forth to conduct a few flow chemical trials to facilitate a deeper insight into the nature of conversion and identify a set of reaction conditions where conversion is complete within a reduced reaction time without compromising on the yield of the compound.

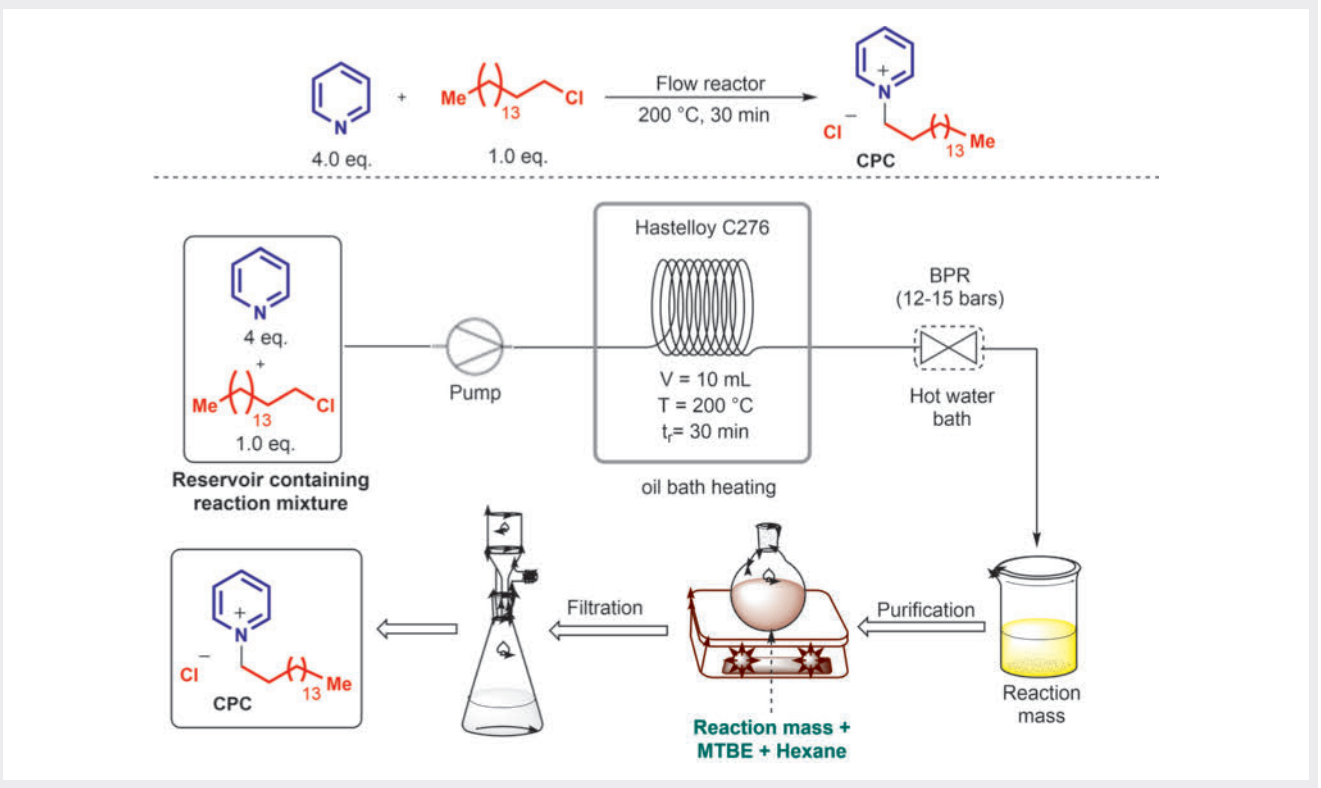
A flow-based setup, comprising a 10-mL Hastelloy coil reactor (1/8″ OD) coupled to a peristaltic or HPLC pump, was configured in-house (▶**Fig. 3A**) and various flow conditions were screened as part of optimization trials (▶**Fig. 4** and ▶**Table 2**). It was observed that temperature in excess of 180 °C was typically required to ensure complete consumption of cetyl chloride with a residence time less than 1 h. All the runs carried out at 180 °C and 200 °C afforded CPC as an off-white to white solid after work-up and isolation (▶**Fig. 3C**). Indeed, the best results were observed when the quaternization reaction was carried out with 4.0 eq. of pyridine and 1.0 eq. of cetyl chloride at a temperature of 200 °C with a residence time of 30 min to obtain CPC with an isolated yield of 96% and HPLC purity of >99% (▶**Table 2**, Entry-4).

▶**Fig. 3** (**A**) Continuous flow setup for the synthesis of CPC; (**B**) Hastelloy coil reactor (1/8″ OD, 10 mL internal volume capacity) used for conducting the experiments; (**C**) in-house CPC synthesized through continuous flow.

▶**Table 1** Batch process parameters for the synthesis of CPC.

No.	Stoichiometric equivalents		Temperature (°C)	Time (h)	Isolated yield (%)
	Cetyl chloride	Pyridine			
1	1.0[a]	4.0	100	48	94
2	1.0[a]	2.0	100	74	66
3	1.0[b]	4.0	100	54	89

[a]Reaction was carried out on a 1.5 g scale
[b]Reaction was carried out on a 5 g scale



▶ **Fig. 4** Continuous flow setup and purification protocol for the synthesis of CPC.

▶ **Table 2** Optimization studies for continuous flow synthesis of CPC.

No.	Stoichiometric equivalents		Temperature (°C)	Time (min)	Yield (%)	HPLC purity (%)	Moisture content (%)
	Cetyl chloride (1)	Pyridine (2)					
1	1.0	2.0	160	30	39	98.71[b]	5.6
2	1.0	4.0	180	30	70	99.30[b]	5.6
3	1.0	4.0	200	15	78	99.28[b]	5.8
4	1.0	4.0	200	30[a]	96	99.23[b]	6.1
5	1.0	4.0	200	60	91	98.99	5.3

[a]Similar conversion observed for a residence time of 45 min.
[b]Off-white to white colored solid.

Compared to the batch reaction, the continuous flow process has thus provided us with notable advantages: (a) short residence time <1.0 h for complete consumption of the limiting reactant, namely, cetyl chloride (compared to 48 h for a batch process); (b) very high yields, viz. >95%; (c) excellent HPLC purity (>99%) with adherence to the physical appearance and nature of the product as per standard specifications obtained via a simple work-up procedure; and (d) smaller footprint thereby enabling a more efficient production-scale adaptability in comparison with a batch process (▶ **Fig. 3A and 3B** show the setup). Most importantly, the flow conditions identified would help preclude any impact of scale on the successful outcome of the reaction and meeting critical quality attributes of the final product.

A meaningful implication of the current flow process in a manufacturing scenario can be correlated with an assumed production capacity and throughput of CPC (approximated extrapolation from the data reported in Ref. [12]). In a batch scenario, 1.0–1.2 MT (metric tons) per week would require a minimum of three batch cycles involving a 2 kL batch reactor operating at 120–130 °C with 60% volume occupancy for a 24 h conversion time. In contrast, extrapolating our current findings and 30 min residence time in a flow process involving a rig equipped with a 20 L flow reactor can potentially

▶ **Table 3** Comparison of space-time-yield (STY) for synthesis of CPC in batch versus flow

No.	Parameter	Batch[a]	Flow[b]
1	STY ($g.L^{-1}$ h^{-1})	8	1050
2	RME (%)	33	57

[a]Approximated extrapolation from the data reported in the patent considering a non-catalyzed process [12].
[b]Extrapolated from in-house experiments conducted in flow.

generate 3.0–3.5 MT of CPC per week (see ▶ **Table 3** for a comparison between derived process metrics of batch vs flow). Given that the batch reactions are typically performed at or slightly above the boiling points of pyridine, the safety risk and energy efficiency would directly correlate with the reactor footprint. Clearly, a continuous flow manufacturing approach of CPC would be sustainable in the long term.

Conclusions

We herein report an efficient and sustainable approach for the synthesis of CPC using a continuous flow process in the high-*T* regimen. This approach addresses several shortcomings in the known route of synthesis, including stoichiometric excess of pyridine, longer reaction times, and lower yields.

Experimental Section

Materials and Methods

1-Chlorohexadecane (cetyl chloride, 98% pure) was procured from BLD Pharmatech (India) Pvt. Ltd. Pyridine (99% pure) was purchased from Avra Synthesis Pvt. Ltd. All solvents procured from commercial sources were used without further purification. Melting point was recorded on a POLMON melting point apparatus (Model Number: MP96). ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. Chemical shifts (δ) in ppm are reported relative to Me_4Si (= 0 ppm) by using residual solvent signals as internal reference [$CDCl_3$: δ = 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR)]. HPLC was performed on an X-Bridge C18 150*4.6 mm 5 µm column with a mobile phase of 0.1 % TFA in water and acetonitrile. Mass data were recorded on an Agilent 1200 Series liquid chromatography module hyphenated to a 6430 Triple Quad LC/MS system.

General procedure for the synthesis of CPC through conventional batch techniques

All batch experiments were carried out in a sealed tube or a Radleys Carousel 12 Plus Reaction Station™ under inert atmosphere. Into a round bottom flask, a mixture of cetyl chloride and pyridine at the specified equivalents was heated and maintained under stirring for the specified reaction temperature and duration. Subsequently, the reaction mixture was cooled to room temperature to yield a dense brown liquid. This was dissolved in methyl tert-butyl ether MTBE (15 volumes) into which hexane (10 volumes) was further added. The resultant mixture was stirred for 1 h and the supernatant liquid was decanted, following which a further amount of hexane (20 volumes) was added to the residue. The resultant mixture was stirred for 1 h. The suspension thus obtained was filtered and the resultant solid was dried under reduced pressure to provide a yellowish-brown solid (CPC).

Typical procedure for the synthesis of CPC through a continuous flow Hastelloy reactor

All continuous flow experiments were performed in a Hastelloy coil reactor (AmAr Equipment Pvt. Ltd., India, 1/8″ OD, 10 mL) maintained at desired temperatures using a silicone high-temperature oil bath. A mixture of cetyl chloride (25.06 g, 29.0 mL, 0.096 moles) and pyridine (30.46 g, 31 mL, 0.385 moles) was sparged with Argon under stirring at 55–60 °C for 1 h. The reactant mixture was pumped using an HPLC piston pump (Waters) at a flow rate of 0.333 mL/min to afford a residence time (RT) of 30 min. Initially, about two reactor volumes (20 mL) were discarded to let the reaction attain steady state, following which about one reactor volume (10 mL) was collected. Once the collection was complete, the reaction mass was worked-up and purified as followed in the procedure described above to obtain a white to off-white solid (CPC; ▶ **Fig. 3C**).

Melting point: 80-84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.53 (d, *J* = 5.2 Hz, 2 H, Ar-*H*), 8.60-8.40 (m, 1 H, Ar-*H*), 8.25-8.00 (m, 2 H, Ar-*H*), 5.01 (t, *J* = 6.8 Hz, 2 H, *N*-$C\underline{H_2}$-CH_2-), 2.55-2.10 (br s, 2 H, H_2O), 2.10-1.92 (m, 2 H, *N*-$\bar{C}H_2C\underline{H_2}$-), 1.5-1.05 (m, 26 H, *N*-$CH_2CH_2(\underline{CH_2})_{13}CH_3$), 0.86 (t, *J* = 6.4 Hz, 3 H, *N*-$CH_2CH_2(CH_2)_{13}\underline{CH_3}$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.20 (CH), 145.03 (CH), 128.45 (CH), 62.10 (CH_2), 31.93 (CH_2), 31.83 (CH_2), 29.60 (CH_2), 29.56 (CH_2), 29.52 (CH_2), 29.44 (CH_2), 29.29 (CH_2), 29.27 (CH_2), 29.02 (CH_2), 26.04 (CH_2), 22.59 (CH_2), 14.02 (CH_3). Mass [m/z] calculated for $[C_{21}H_{38}N]^{+}$: 304; found: 304.

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Contributors' Statement

All the authors have contributed equally.

Conflict of Interest

The authors declare no conflict of interest.

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