Application Note 73:
Use of CSTR for biphasic reaction scale up

Produced by Stoli Chem and Vapourtec

Abstract

Vapourtec has teamed up with UK based reactor manufacturer Stoli Chem to demonstrate a new range of continuous stirred tank reactors for continuous flow applications.

In this application note we demonstrate how a biphasic reaction can be scaled up to kilos/day under very mild conditions using the SABRe reactor. The mixing provided by this reactor enabled a throughout of ~8 mol/day, equating to 1.4 kg/day.

For more details, please contact:
Vapourtec Application Support
application.support@vapourtec.com or call:
+44 (0) 1284 728659

Background

Continuous flow chemistry brings benefits of safer processes with a more consistent product quality. These benefits come fundamentally from much smaller flow reactors, giving a larger surface-to-volume ratio which improves mixing and temperature control. A typical inner diameter of a Vapourtec tubular reactor is 1 mm, compared to 20 mm for a batch reactor with comparable internal volume, improving heat and mass transfer.

One of the major limitations of small i.d. tubular reactors is scalability. This becomes critical with processes with challenging mixing behaviours, such as biphasic reactions.

One example of biphasic reactions explored in flow is the Stevens oxidation[1,2], highlighting the importance of good mixing. In this reaction, sodium hypochlorite is used to oxidise (in presence of an alcohol) aldehydes to esters.

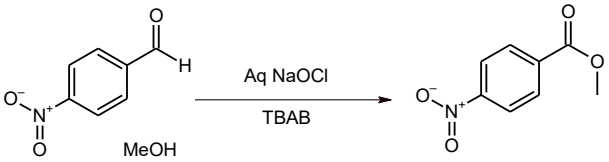

Figure 1 – Stevens oxidation of 4-nitrobenzaldehyde in ethyl acetate using an aqueous solution of sodium hypochlorite

Aqueous solutions of sodium hypochlorite are immiscible with the substrate's organic solution, requiring a phase transfer catalyst to ensure oxidant and substrate can react together.

In a non-mixing situation, the efficiency of the aqueous/organic phase transfer will dictate the kinetics of the reaction.

Continuously stirred tank reactors (CSTR) are a current alternative to scale up processes in flow. These reactors can be scalable towards cubic meter volume. Compared to tubular reactors, they typically offer a much slower mass transfer with poorer control of residence time.

Stoli Chem's Scalable Agitated Baffle Reactor (*SABRe*) reconciles the benefits of conventional flow tubular reactors with scalability and wide scope in conventional CSTRs.

Figure 2 – Detailed image of each individual CSTR with its internal agitator

The SABRe contains a series of 10 CSTRs inside a single vessel, with a total volume of 120 ml. This design provides excellent control of residence time for high throughput and product quality. Each CSTR is miniaturised, resulting in improved heat and mass transfer performance, comparable to that of plate reactors.

Figures 2 and 3 shows a detailed image of each individual CSTR and a cross section of the SABRe.

Figure 3 – Cross section of SABRe reactor

Setup

To achieve high flow rates, an acid resistant Vapourtec R-Series equipped with R2HF C pump module was chosen for this work. Reagents were pre-heated in tubular reactors using the R4 reactor heater module before entering the SABRe reactor.

The SABRe reactor was set on its standing platform inside the fume cabinet. A Huber chiller was connected to the SABRe's cooling/heating jacket. The chiller's temperature was controlled via the R-Series Software.

Figure 4 shows a schematic of the system used for this work.

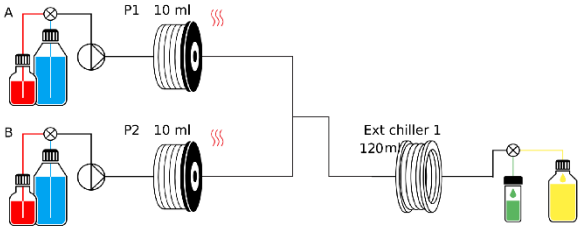

Figure 4 - Schematic of the R-Series used for this work

To use the concentration model built in the software, an *independent reactor* of 120 ml was selected to represent the SABRe. By selecting *external chiller 1*, the R-Series Software can control the reactor's temperature, even if it is not connected to the R4 heater module.

The output of the reactor was connected to the waste/collection valve, collecting the product in a single vessel.

The aqueous layer of the crude product was extracted with three washes of ethyl acetate. The organic phase was dried over magnesium sulphate and the solution was evaporated under vacuum.

All HPLC analysis was performed using an Agilent 1200 series, equipped with an Eclipse XBD-C18 column. All conversion values are reported as percentage area of HPLC, excluding areas of known solvent and catalyst peaks.

Reagents

All materials and reference samples were purchased from Fisher Scientific.

System Parameters

System solvent: Ethyl acetate (pump A) and deionised water (pump B)

Reagent A: 0.42 M solution of 4-nitrobenzaldehyde (4-NBA) in ethyl acetate, 10 equivalents of methanol, and 0.1 equivalents of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst.

Flowrate A: 13.10 – 32.60 ml/min

Reagent B: 14 % sodium hypochlorite solution (freshly supplied commercial solution).

Flowrate B: 10.90 – 27.40 ml/min

A:B molar ratio: 1:3

Reactor volume: 120 ml

Residence time: 5 ml

Stirring speed: 1100 RPM

Reactor temperature: 35 °C for both pre-heating reactors and SABRe reatcor

Back pressure regulator: None, atmospheric conditions

Results and Discussion

Work started by pumping both solvents to prime the reactors. The outlet of both pre-heating reactors was mixed at a Y-piece connector before entering the SABRe reactor.

Both pumps were set at the desired flowrate. Once the reactors were primed, the stirrer was set at 1100 RPM to provide mixing. The R-Series Software set the temperature of the reactors and chiller to 35 °C, and it automatically switched to pump reagents when the temperature equilibrated.

Different residence times were evaluated with the SABRe. With 5 minutes residence time, the Stevens oxidations yielded full conversion of 4-

nitrobenzaldehyde to methyl 4-nitrobenzoate, achieving a throughput of 60 g/h. Figure 5 and table 1 summarises the results of different residence times.

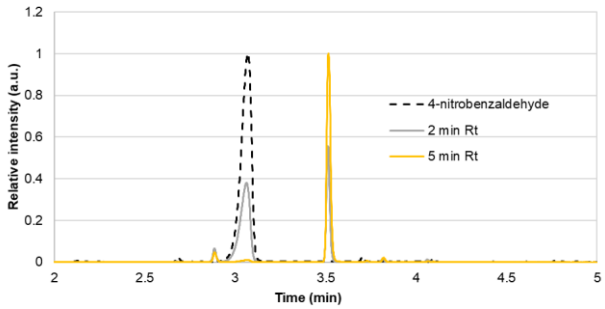

Figure 5 – HPLC chromatogram of crude products

Table 1 –Results of Stevens oxidation with different residence times

Rt	HPLC purity	
	4-nitrobenzaldehyde	Methyl 4-nitrobenzoate
2 min	64%	36%
5 min	0%	100%

Conclusion

The SABRe reactor has been used to perform the Stevens oxidation with full conversion. A CSTR type reactor enhances the reaction kinetics by improving reactant mixing, achieving a small scale throughput of 1.4 kg/day with just the footprint of a lab fume hood.

Acknowledgment

We wish to thank Stoli Catalysts Ltd for supplying the SABRe reactor used during this study, and for providing technical advice and support throughout. For further information regarding the reactor, please contact Stoli Chem: stolichem@Stolichem.com.

References

1. Leduc, A. B. & Jamison, T. F. Continuous Flow Oxidation of Alcohols and Aldehydes Utilizing Bleach and Catalytic Tetrabutylammonium Bromide. *Org. Process Res. Dev.* **16**, 1082–1089 (2012).
2. Vapourtec Ltd. *Application Note 50: Rapid Mixing Reactor for Biphasic Reaction Scale-up*. (2017).