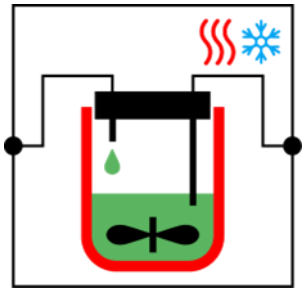

Application Note 74: Scale up of a S_NAr reaction to > 10 kg a day with CSTRs

Produced by Vapourtec

Abstract

In this application note, the first of a series dedicated to continuous stirred-tank reactors (CSTR), we demonstrate the application scope of CSTR for reaction scale up. The aromatic substitution of 3,4-difluoronitrobenzene with morpholine generates a poorly soluble product with equimolar amounts of fluoride salt, which can precipitate and block tubular reactors.

This application note describes:

- Full conversion of a S_NAr reaction with a cascade of CSTR.
- Ability to run in the presence of solids without blockages.
- > 0.5 kg/h of product synthesised with an R-Series.

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Background

Linezolid is a fully synthetic antibiotic used to treat severe bacterial infections where other antibiotics, such as penicillin, would not work. One of the strengths of this drug is that it can be orally administered while having 100 % bioavailability.

The first developed route to make linezolid, the UpJohn patent [1], starts with a nucleophilic aromatic substitution of morpholine with 3,4-difluoronitrobenzene, which builds half the molecule. This step is followed by a reduction of the nitro group to an amide to then form the oxazolidinone.

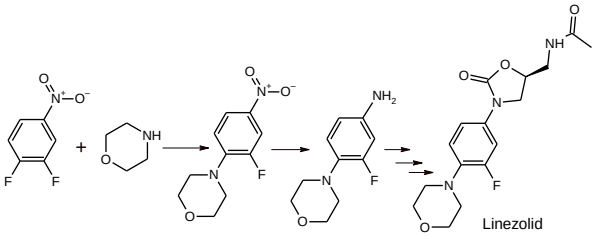

Figure 1 – Synthetic route to Linezolid

This S_NAr reaction presents two problems for a successful implementation in continuous flow, using microreactors:

1) An insoluble fluoride salt is formed in equimolar amounts as a byproduct.
2) The final product is solid and has limited solubility.

Previous publications showed successful results in performing this S_NAr reaction with diluted conditions and using excess morpholine to keep the salt soluble at temperatures ~ 100 °C [2–4]. Under these conditions, plug flow reactors (PFR) could be used without blocking.

Running at concentrations higher than 1.0 M poses the risk of product crystallization within the reactor, causing a blockage.

As the product melts at ~ 120-130 °C, this reaction could be performed at higher concentrations at temperatures over 130 °C. The main drawback of running at elevated temperatures is the potential decomposition of the solvent, DMF, into DMA and formic acid, increasing by-product formation.

To scale up this reaction in flow with minimum solvent consumption, it requires of a reactor that can handle precipitation without blocking.

In 2023, Vapourtec developed a continuous stirred tank reactor (CSTR) which can be integrated with existing Vapourtec's flow chemistry systems. The choice of wetted parts, PTFE, PFA, Kalrez and glass, make the CSTR a highly chemically inert reactor.

Figure 2 – Close-up image of CSTRs with safety screen

The Vapourtec CSTR is designed with the importance of safety as a core requirement. Each CSTR has a built-in burst disk that will safely release excess pressure within the CSTR body. It also comes with an optional safety screen.

A CSTR is a simple type of reactor; a vessel, that can be heated or cooled, equipped with a stirring mechanism, it provides active mixing. The weakness of this simple reactor design is that it suffers from back mixing and poor residence time distribution (RTD), making a single CSTR unsuitable for most continuous flow applications.

By connecting 3 or 4 CSTR in series, back mixing is reduced while RTD is much improved. Figure 3 shows the improvement in RTD when using one, four and eight CSTRs in series.

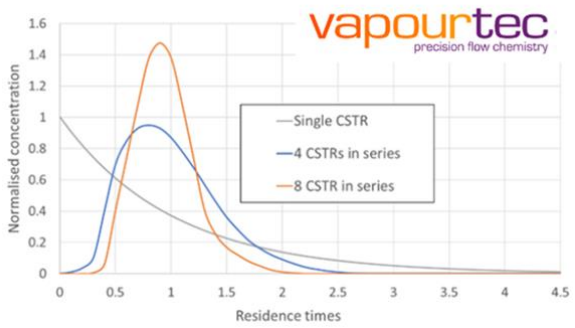

Figure 3 - RTD for CTRS in a series cascade

Changing the volume of each CSTR is relatively trivial. The aspiration tube determines the reactor's volume and by raising or lowering it, different volumes can be set, between 5 ml and 40 ml per reactor. The CSTR has stirrer speeds from 100 to 1200 rpm.

The key advantages of CSTR over PFR or microchip reactors are:

1) The ability to handle solids.
2) Separation of liquids and gases instead of using a membrane separator.
3) Access of long reaction times.
4) Active mixing.

In this application note we demonstrate how a CSTR is well suited to scale up reactions in which a solid is formed without affecting its performance.

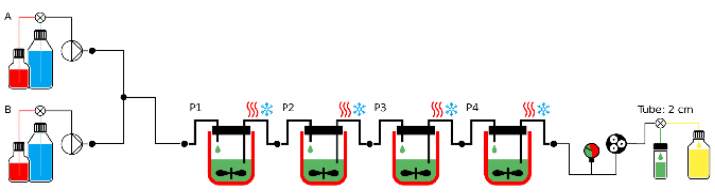

Figure 4 – Flow schematic of cascade of CSTRs

Setup

For this work, a Vapourtec RS-200 equipped with four CSTRs connected in series was used. The R4 reactor heater module kept the CSTRs at temperature and pumps A and B were used to deliver the reagent solutions.

System pressure was maintained at 2 bar throughout the experiments using an SF-10 pump as active BPR. In the R-Series software, the pressure limit was set to 4.5 bar and pressure loss detection was enabled. This will ensure if the system pressure increases over the limit or if the burst disc is activated, the software will stop pumping and heating.

System Parameters

System solvent: DMF

Solution A: 3,4-difluoronitrobenzene in DMF at 1.0, 2.0 and 4.0 M concentrations (limiting reagent)

Flow rate A: from 1.25 to 10 ml/min

Solution B: Morpholine in DMF at 2.0, 4.0 and 8.0 M concentrations

Flow rate B: from 1.25 to 10.00 ml/min

A:B molar ratio: 1:2

Residence time: 8 minutes

Reactor volume: 20 ml (4 x 5 ml CSTRs) at 600 rpm stirring speed and 160 ml (4 x 40 ml CSTRs) at 1000 rpm stirring speed

Reactor temperature: 100 °C

Back pressure regulator: 2 bar

Reagents

All materials were purchased from commercial suppliers.

Analysis

A portion of the steady state was collected automatically by the R-Series software. The crude solution was diluted 1/20 prior HPLC analysis. {Agilent 1200 series, equipped with an Eclipse XBD-C18 5 µm column at 40 °C, flow rate = 2 ml/min, the column was eluted using a linear gradient from 5 % to 95 % ACN over 7 minutes}.

All conversion values are reported as percentage area of HPLC, excluding areas of known solvent peaks.

Results and Discussion

As starting point, we replicated the reaction conditions as reported in Application Note 2[4], 8 minutes Rt, 100 °C and 3,4-difluoronitrobenzene at 1.0 M concentration. The total reactor volume was 20 ml, and full conversion was observed, indicating the performance of a cascade of 4 CSTR was similar to a 10 ml tubular reactor.

To increase the throughput, the concentration of the stock solutions was increased while maintaining the same reaction parameters. Table 1 compiles the results and throughputs of the experiments done at different concentrations and reactor volumes.

When doubling the concentration of starting material, the reaction yielded full conversion with the same residence time.

Exp i.i	Concentration of 3,4-difluoronitrobenzene	Reactor volume	Residence time	Throughput
1	1.0 M	4x5 ml	8 min	16.5 g/h
2	2.0 M	4x5 ml	8 min	33 g/h
3	4.0 M	4x5 ml	8 min	66 g/h
4	**4.0 M**	**4x40 ml**	**8 min**	**526 g/h**

Table 1 – Summary of reaction conditions

Further increment of the concentration of starting materials to 4.0 M for 3,4-difluoronitrobenzene still drove reaction to completion, but the throughput increased to 1.6 kg/day.

There was no noticeable precipitation nor solid build up in the CSTR reactors.

To further increase the throughput, the volume of the CSTRs was raised from 5 ml to 40 ml each, giving a total reactor volume of 160 ml.

To maintain 8 minutes Rt pumps A and B were set at 10 ml/min each and the stirring speed of the CSTRs was increased to 1000 rpm. The performance of the CTSR at its maximum volume vs at its lowest volume was identical. There were no traces of 3,4-difluoronitrobencene in the samples analysed by HPLC, but the throughput was

increased to over 0.5 kg/h, equating to 12,6 kg/day with the same purity profile.

Conclusion

CSTR reactors have been used to perform a S_NAr at high concentrations without performance issues. The reaction conditions, initially optimised in tubular reactors, were directly transposed to the CSTRs, and more concentrated stock solutions enabled the increase of throughput of a RS-200 flow chemistry system to 12,6 kg/day.

Supporting information

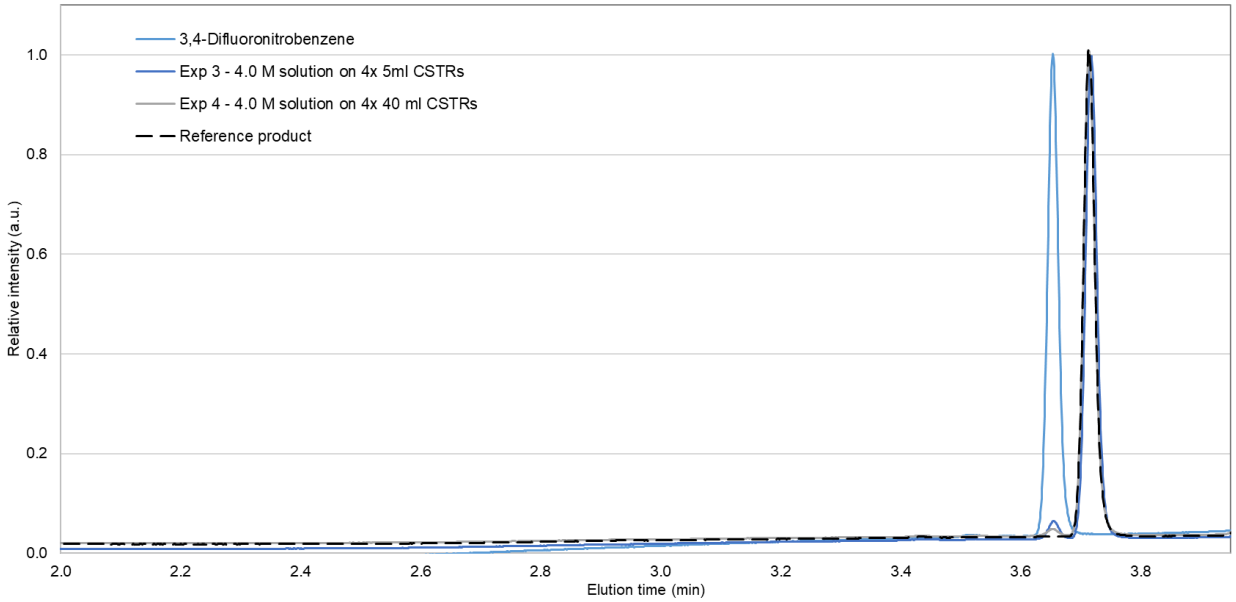

Figure S1 – HPLC traces of reference samples and scale up experiments using a 4.0 M solution of 3,4-difluoronitrobencene

References

1. Bartl, J. Patent WO2014071990A1 - Process for making linezolid. 29 (2014).
2. Russell, M. G. & Jamison, T. F. Seven-Step Continuous Flow Synthesis of Linezolid Without Intermediate Purification. *Angew. Chemie Int. Ed.* **58**, 7678–7681 (2019).
3. O'Brien, A. G. *et al.* Continuous Synthesis and Purification by Direct Coupling of a Flow Reactor with Simulated Moving-Bed Chromatography. *Angew. Chemie Int. Ed.* **51**, 7028–7030 (2012).
4. Vapourtec Ltd. *Application Note 2 – Optimisation of Step 1 in the Synthesis of Linezolid using a 'Dual-Core™' Tubing Reactor*. (2006).