Application Note 50:

Rapid Mixing Reactor for Biphasic Reaction Scale-up

Produced by Vapourtec

Abstract

This application note describes:

- Vapourtec Reactors for Rapid Mixing and High Flow rate pump module
- Greater than 99.9% conversion at a 58 s residence time in a 60 ml reactor
- Over 4.5 kg/day production with just the footprint of a Vapourtec R-Series

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Background

The scale-up of a successful reaction is an important stage in process development, and one that is ideally suited to continuous flow chemistry. Achieving a high throughput of material, with high output of the desired product is very dependent on reaction kinetics; the faster the reaction, the more product can be produced in a certain time. Good mixing is critical to ensuring the reaction proceeds as fast as possible, and is an important feature of reaction scale-up. The Vapourtec large diameter PFA Reactors for Rapid Mixing contain static mixers throughout their length to increase a much more dynamic mixing environment than a standard tubular reactor, and are ideal for high throughput applications.

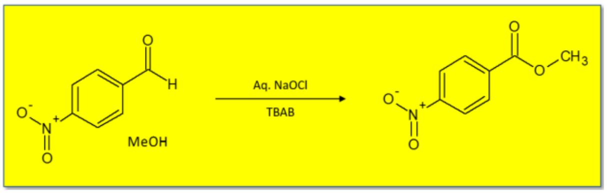

Figure 1 Example synthesis of a methyl ester using a Steven's oxidation, with sodium hypochlorite. Tetrabutylammonium bromide (TBAB) acts as a phase-transfer catalyst, shuttling the reactants in and out of the two phases.

One example of a reaction with a challenging mixing behavior is an ester synthesis via a Steven's oxidation, which uses aqueous sodium hypochlorite to oxidize an aldehyde to an ester in the presence of an alcohol, allowing the direct synthesis of the ester from the aldehyde. The aldehyde is insoluble in the aqueous mix, and so is in an organic solvent, which results in a biphasic reaction solution. To facilitate the reaction, a phase-transfer catalyst is employed to shuttle the reactants between phases, Figure 1. In a non-mixing environment, the kinetics of this reaction are dependent on the efficiency of the phase-transfer. In this application, the Vapourtec Reactors for Rapid Mixing are used to scale up this biphasic reaction to over 4.5 kg per day.

Setup

All reactions were performed using a Vapourtec R-Series, equipped with a High Flow pump module. Reagent bottle A contained 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. Reagent bottle B contained 15% sodium hypochlorite solution (freshly supplied commercial solution). Pump A solvent was ethyl acetate and pump B solvent was deionized water. The reagent stream mixed at a Y-piece connector before passing into the reactor. Different reactors were used for specific aspects of the investigation: a Vapourtec standard 10 ml PFA reactor, a Vapourtec 20 ml large diameter PFA Reactor for Rapid Mixing, and a Vapourtec 60 ml large diameter PFA reactor for rapid mixing. Both large reactors contain static mixers. The reactor outflow passed to a Vapourtec variable back pressure regulator (BPR) and to a Gilson fraction collector, Figure 2. The reactor system and fraction collector were controlled using flow control software. 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.

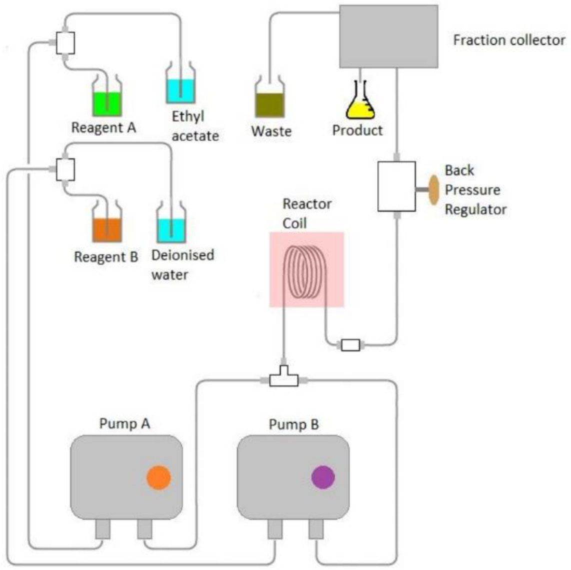

Figure 2: General configuration of the Vapourtec R-Series used for reaction scale-up, using a Vapourtec High Flow rate pump module, and the different reactors, a Vapourtec 10 ml standard reactor and a Vapourtec 20 or 60 ml large diameter Reactor for Rapid Mixing.

Synthesis of 3-Phenyl Pyridine

The synthesis of methyl 4-nitrobenzoate from 4NBA is a known application to Vapourtec,[1] and previously determined conditions were chosen as a reference point, Table 1, row 1. These conditions had not previously been optimized for maximum throughput, and so were varied until a loss of conversion was observed. The conditions that permitted the highest throughput of 25 mmolh^{-1}/4.5 gh^{-1} at 25 °C while retaining a high conversion is reported, Table 1, row 3.

Table 1: Effect of increasing total flow through a Vapourtec standard 10 ml PFA reactor. It is clear that below a residence time of 5 min, conversion begins to drop. [a] Conditions at which 25 mmolh^{-1} was achieved.

Reactor	Temperature/°C	Residence Time/Min	Conversion/%
10 ml	25	10	99.99
10 ml	25	6:40	99.99
10 ml	25	5	97.30[a]
10 ml	25	4	71.40

This model synthesis was used for the remainder of the experimentation in the larger scale reactors, so that a comparison to the standard non-mixer reactor could be made.

Reaction Scale-up

To achieve a scale up of this reaction using the Vapourtec Reactors for Rapid Mixing, there are three parameters than can be varied in an effort to increase the throughput of 4NBA: Increasing the concentration of the 4NBA; increasing reaction temperature to accelerate reaction kinetics; decrease the residence time, so that more substrate passes through the reactor within a given time.

Residence Time

Using the reactor setup described above, experiments were programmed using the flow control software to determine the effect of residence time within the Vapourtec 20 ml reactor for rapid mixing on the conversion of 4NBA, Table 2. It is clear that the enhanced mixing alone permits a reduction of residence time from 5 min to 2 min while retaining conversion greater than 90 %, resulting in an increase of throughput to 130 mmolh^{-1} (22.6 gh^{-1}). Below a residence time of 2 min, it is clear that the conversion begins to drop.

Table 2: The effect of decreasing residence time on conversion of 4NBA with a Vapourtec 20 ml Reactor for Rapid Mixing. It is clear that even at a residence time of 2 mins, high conversion of the product can be obtained.

Residence Time/min	Conversion/%
3	97.6
2	91.5
1:42	85.7
1	63.6

The conditions identified using the Vapourtec 20 ml Reactor for Rapid Mixing that gave the highest throughput were transferred to the Vapourtec 60 ml Reactor for Rapid Mixing. It was found that an equivalent conversion of 91.5% of 4NBA was achieved. This is a demonstration that a small-scale optimization can be performed using a smaller scale reactor, before the optimized conditions are applied to the larger-scale reactor, to minimize the use of starting material.

Temperature

The effect of temperature on conversion was studied so that, if higher temperature resulted in greater conversion, throughput could be further increased.

A 2:1 excess of NaOCl was chosen to permit an increase in the flow rate of 4NBA as much as possible while retaining the same residence time, and resulted in a conversion of 58.0% at 25 °C. The effect of temperature on conversion at this stoichiometry was determined, Figure 2. An initial increase in conversion from 25 °C to 35 °C is observed, after which the conversion is unchanged at approx. 85% until 50 °C, after which the conversion begins to fall. From this, 50 °C was selected as an optimal temperature for the final scale-up, and it was presumed that at this temperature the NaOCl concentration had become the limiting factor.

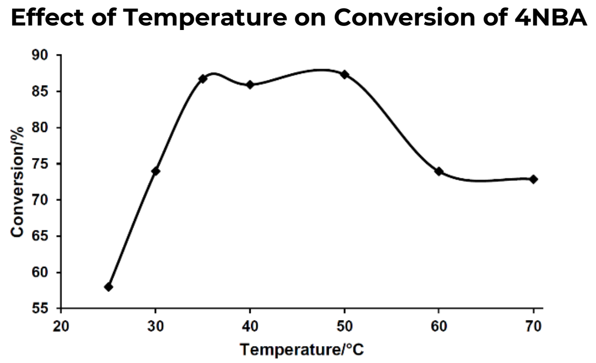

Figure 3: Effect of temperarture on conversion of 4NBA in a Vapourtec 20 ml reactor for rapid mixing at a residence time of 2 mins and 2:1 excess of NaOCl. It can be seen that conversion increases between 25 and 35 °C, above which the NaOCl concentration becomes rate limiting until above 50 °C where conversion falls, likely as a result of equilibria effects

Throughput Maximization

To increase the reactor output at the optimal conditions, the NaOCl concentration was increased by increasing the flow rate of pump B, while retaining the flow of 4NBA. An excess of 2.3:1 gave a conversion of greater than 90%, despite the reduced residence time of 1 min 54 s. Total throughput was increased through gradual rise of total flow, while retaining the optimal stoichiometric ratio and reactor temperature. A throughput of 374 $mmolh^{-1}$ (67.8 gh^{-1}) was achieved at a residence time of 58 s, which still achieved a conversion of approx. 95%, and only the desired product was formed. For comparison, a standard Vapourtec 10 ml reactor, without static mixers, was used at 50 °C, a residence time of 58 s and 2.3:1 excess of NaOCl, achieving approx. 65% conversion. These conditions were again transferred to the Vapourtec 60 ml reactor for rapid mixing and Vapourtec High Flow pump module to determine the effect on throughput of scaling up. Interestingly, the efficiency of mixing is affected by flow velocity, so the greater total flow rate needed to achieve the 58 s residence time likely improves mixing further. It was found that at 50 °C and a ratio of 2.3:1 NaOCl:4NBA greater than 99% conversion was achieved using the Vapourtec 60 ml reactor for rapid mixing, resulting in a total throughput of 1123 $mmolh^{-1}$ (203 gh^{-1}), which equates to over 4.5 kg in a 24 hr period. Table 3 shows a comparison of throughput at the different scales investigated.

Table 3: A comparison of conversion and gh^{-1} throughput on different scale reactors at fixed residence time and temperature

Reactor	Residence Time (s)	Conversion (%)	Throughput (gh^{-1})
10 ml Standard	58	64.6	22.4
20 ml Mixed	58	94.5	67.8
60 ml Mixed	58	99.9	203.3

Conclusion

The Vapourtec large diameter Reactors for Rapid Mixing have been developed with internal static mixers to ensure efficient mixing during reaction scale-up. This application note has compared the Reactors for Rapid Mixing against a standard non-mixed reactor for a biphasic synthesis of a methyl ester using a Stevens oxidation, to demonstrate the effect of the enhanced mixing on maximum achievable throughput. It is clear that the Reactors for Rapid Mixing greatly enhance the reaction kinetics by ensuring highly effective reactant mixing, even with a biphasic mixture, permitting a much higher throughput than can be achieved in a standard tubular reactor alone, enabling Vapourtec reactors to achieve small scale production with just the footprint of an R-Series.

References

1. A.B. Leduc, T. *Jamison, Organic Process Research & Development*, **2012**, (16.5), 1082–1089