Pd/C Slurry Transfer Hydrogenation in Continuous Flow

Ryan Skilton[a], Duncan Guthrie[a], Roger Moses[b]
[a]Vapourtec Ltd, 16 Park Farm Business Centre, Fornham St. Genevieve, Suffolk, IP28 6TS,
[b]Chemical Consultancy Ltd, Launceston, Cornwall

Abstract

Recently at Vapourtec:

- Over 6 g/h of an API intermediate
- Pumping slurries of 5 and 10% palladium on charcoal under pressure continuously
- Heterogeneously catalysed transfer hydrogenation without catalyst scale limitations enabling straightforward scale-up
- 81% isolated yield
- Use of the V-3 pump to control back pressure
- Versatile ability to optimise catalyst conditions

Background

The antibiotic Linezolid is a commonly used pharmaceutical used to target disease causing Gram-positive bacteria such as VRE and MRSA,[1] and is considered as a possible replacement for vancomycin.[2] During a common route in the drug synthesis, 4-(2-fluoro-4-nitrophenyl)morpholine, **1** is hydrogenated to 3-fluoro-4-(4-morpholinyl)aniline, **2**, Figure 1.[3]

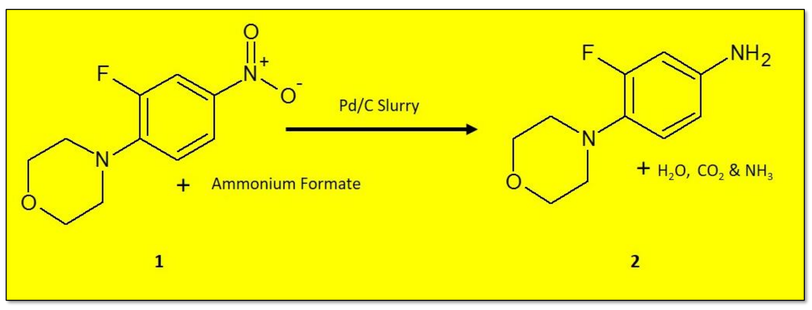


Figure 1:The synthesis of Linezolid intermediate **2** via catalytic hydrogenation of nitrophenyl morpholine **1**.

As part of a continuing research program, Vapourtec has shown, using the Vapourtec easy-MedChem, with patented V-3 peristaltic pumps, it is possible to pump suspensions with particles of up to **80 µm** in size (depending on concentration). Palladium (5 and 10%) on activated charcoal, is a very fine powder which suspends well in methanol. Using the Vapourtec V-3 pumps it was possible to pump concentrations as high as **150 mg/ml**. This allows a variable concentration of Pd/C relative to the substrate, but significantly removes the scale limitations associated with column beds by continuously delivering Pd/C through the reactor.

Setup

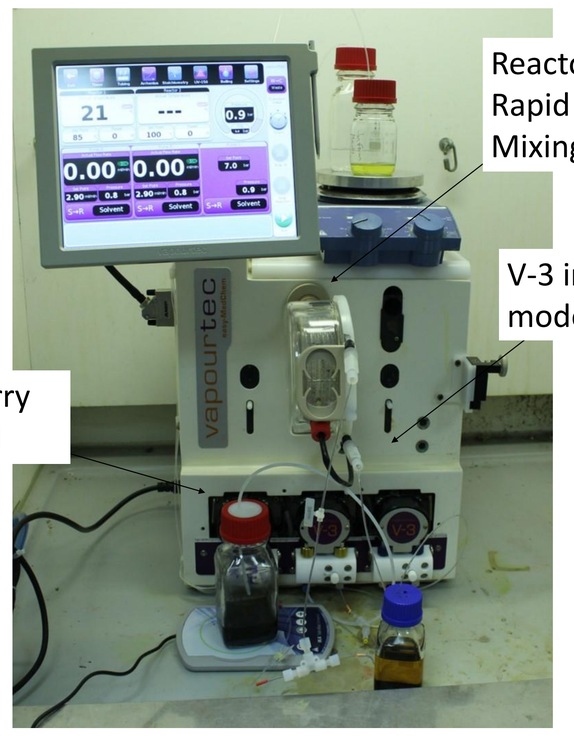


Figure 2: Vapourtec easy-MedChem E-series reactor configured for palladium on charcoal slurry hydrogenation. Pump C is being used as a BPR to allow the slurry to be used above the boiling point of the solvent.

Why a Slurry?

- Handling solids in continuous flow has traditionally presented a problem because of their difficulty to pump, and likelihood of blocking constrictions in the flow path such as compressed tubing or back-pressure regulators.
- Catalysts like palladium on carbon are usually isolated in a packed bed column or cartridge. This method is scale limited because of the back-pressure generated by pumping through the packed column, and becomes rate limiting as the catalyst deactivates, requiring laborious catalyst cleaning and reactivation steps, or rendering the catalyst unusable.
- Using the Vapourtec easy-MedChem, with patented V-3 peristaltic pumps, Pd/C can be pumped continuously and mixed with the reagent stream, so there is no longer a problem with catalyst deactivation.
- Using a slurry, Pd/C is delivered to the reaction without experiencing the significant back-pressure that would limit the scale of a fixed bed reactor.
- The Pd/C concentration can be increased by increasing the slurry flow rate relative to the reagent flow, allowing rapid screening of different catalyst concentrations.

Transfer Hydrogenation with a Pd/C Slurry

Residence time

The effect of residence time on conversion of **1** was explored using a Vapourtec standard 10 ml PFA reactor, with a ratio of 0.8:0.2 of **1** solution:Pd/C (18 mg/ml 5% Pd/C in methanol) at 100 °C. Analysis was performed using TLC at 254 nm, and later confirmed with ^{1}H NMR and Raman, summarised below:

Residence Time/ mins	Conversion/ %
10	~ 90
5	> 95
3	~ 95

It is clear that at 100 °C, the hydrogenation takes place rapidly, enabling low residence times within the reactor.

Temperature

Typically, batch hydrogenations that need to be carried out at above the normal boiling point of the solvent require the use of autoclaves. Using the Vapourtec easy-MedChem it is possible to use one of the V-3 pumps as a **peristaltic BPR**, which is as tolerant to solid dispersions as when operating in pump mode. As a result, it was possible to perform the reaction at temperatures higher than the boiling point of the solvent by increasing the system pressure, even with solids present in the flow stream.

Scale-up

In order to scale-up the reaction, a Vapourtec 20 ml large diameter PFA Reactor for Rapid Mixing was used, the enhanced mixing permitted a reduced temperature of 85 °C. Under these conditions and with a residence time of 3 mins at 7 bar, TLC showed no starting material remaining in the reactor output.

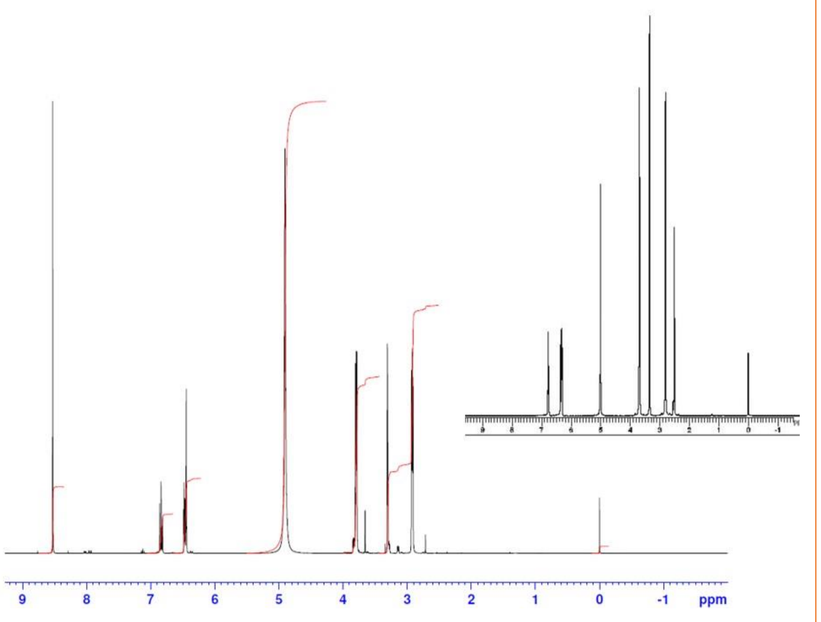
These conditions were run for 1 hour continuously and all output collected. The product was worked up and extracted into ethyl acetate, which was removed using a V-10 evaporator, fed continuously, giving an isolated yield of **80.5 %** and **6.27 g in 1 hour.**

Reactor for Rapid Mixing

The Reactor for Rapid Mixing is filled with static mixers that create a very dynamic mixing environment. These reactors are ideal for biphasic reactions where effective mixing is vital to achieve fast reaction times for process scale-up.

Analysis

Immediate analysis was performed using TLC at 254 nm, and later confirmed using ^{1}H and Raman spectroscopy.



^{1}H (MeOD, 400 MHz) spectrum of product obtained from the collected reactor output. No workup was performed beyond removing the Pd/C via filtration, and solvent removal using a V-10 evaporator. Inset is a literature ^{1}H (d6-DMSO, 500 MHz) spectrum of the product. The extra peaks that can be seen in the crude product are due to residual ammonium formate (δ 8.5 ppm), and 1,4-dioxane (δ 3.7 ppm).

Conclusions

Using the Vapourtec patented V-3 pumps it has been possible to perform a non-scale limited heterogeneously catalysed transfer hydrogenation of an API intermediate, with high yield in continuous flow. The ability to handle slurries of relatively high solid density makes it possible to rapidly adjust the relative catalyst concentration, and the pressure regulation mode has enabled access to up to 10 bar pressure even when handling solids in flow, permitting reaction temperatures above the boiling point of the system solvent. The Vapourtec 20 ml Reactor for Rapid Mixing has been used to scale up the hydrogenation and ensured that there was sufficient mixing in this unique biphasic mixture to give high conversion. The scale-up has been applied to the API synthesis and run continuously for 1 hour, resulting in a high isolated yield, and over 6 g per hour.

References

1. Marino PL, Sutin KM (2007), "Antimicrobial therapy", The ICU book, Hagerstown, MD: Lippincott Williams & Wilkins, p. 817
2. Pfizer (2010-07-16), "Zyvox (linezolid) Label Information" (PDF), Retrieved 04/01/2017
3. Wang, P. Pan, Q. Li, Y. Zheng, D. (2011), Method for preparing linezolid and intermediates thereof, US20110275805