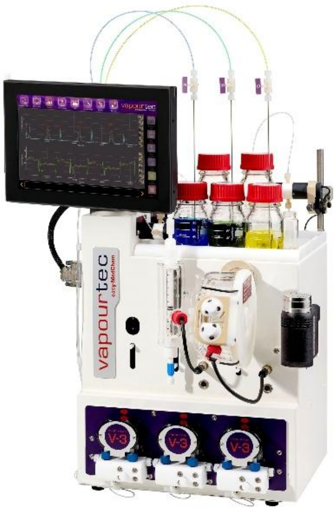

Application Note 51:

Palladium on Charcoal Slurries in Continuous Flow for Transfer Hydrogenation

Produced by Vapourtec

Abstract

This application note describes:

- Over 6 g/h of an API intermediate
- Pumping slurries of 5 and 10% palladium on charcoal under pressure continuously
- Heterogeneously catalyzed 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 optimize catalyst conditions

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

Background

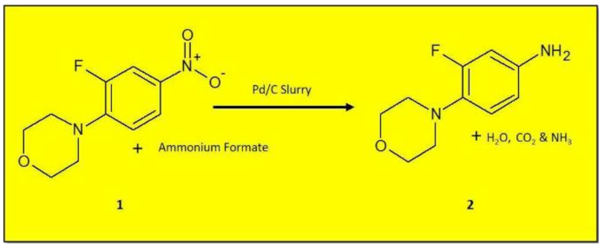

Figure 1: The synthesis of Linezolid intermediate 2 via catalytic hydrogenation of nitrophenyl morpholine 1

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.[3]

Although heterogeneous reactions using palladium on charcoal (among other catalysts) are common in batch chemistry, handling solids in continuous flow has 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.

As such, catalysts like palladium on carbon are usually isolated in a packed bed column or cartridge, which is at the desired reaction temperature, and reagents are pumped through the column for the reaction. 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.

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 (depending on concentration). Palladium (5 and 10%) on activated charcoal, Pd/C, 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

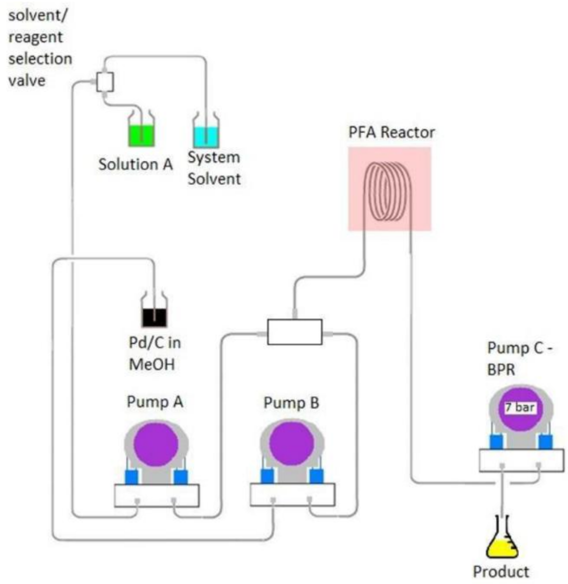

Figure 2: Reactor configuration for continuous pumping of Pd/C slurry heterogeneous transfer hydrogenation

All reactions were performed using a Vapourtec easy-MedChem E-series, equipped with slurry pump manifolds, and with either a Vapourtec 10 ml PFA reactor, or a 20 ml large diameter PFA Reactor for Rapid Mixing. Reagent bottle A contained a 0.12 M solution of 1 (Produced at Vapourtec, see Application Note 3 for details: https://www.vapourtec.com/flow-chemistry-resource-centre/application-note-3/) in a 1:1 v/v mixture of methanol and 1,4-dioxane, as well as 5 molar equivalents of ammonium formate. The solution was warmed to approximately 40 °C on a hot plate throughout to assist with ammonium formate solubility. Reagent bottle B contained a continuously stirred suspension of palladium on carbon (Aldrich 5% palladium on activated charcoal, cat. No. 75992 or Aldrich 10% palladium on activated charcoal, cat. No. 75990) in methanol. A 2 mm bore tube was used on pump B to allow easy aspiration into the pump. A system solvent of 1:1 v/v methanol and 1,4- dioxane was also pre-heated to approximately 40 °C to ensure no cold crystallization occurs when the solvent begins pumping. Reagent streams mixed in a standard tee-mixer. Reactor output was passed to the third V-3 pump (pump C) which was in the back-pressure regulation mode. Product was collected manually following depressurization. Figure 3 shows the actual system in reaction configuration.

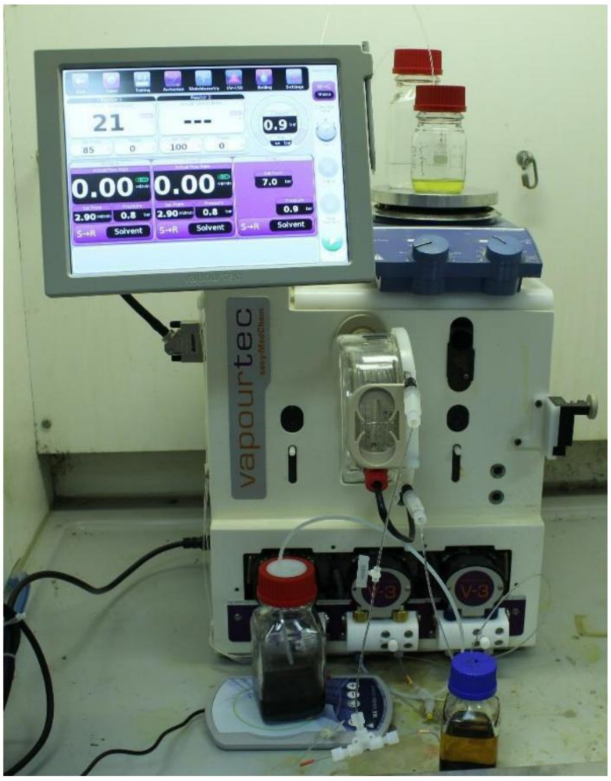

Figure 3 Vapourtec easy-MedChem E-series reactor configured for palladium on charcoal slurry hydrogenation

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 1H NMR and Raman, summarized in Table 1:

Table 1: Effect of residence time on conversion of 1

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. Significantly unlike more common needle-type BPRs, the peristaltic pump BPR 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.

The reaction temperature of 100 °C permitted conversions of > 95%, at residence times of 3 mins. An experiment was performed at 50 °C and residence time of 10 mins, however a conversion of only 50% (by TLC) was obtained. This indicates that the nature of the reaction in the flow environment benefits from the accelerated reaction kinetics achieved at the higher reaction temperature. The use of the V-3 pump in BPR mode has allowed access to higher conversions than would be achievable without being able to maintain elevated pressures while handling solid suspensions.

Catalyst

The effect on the reaction of catalyst concentration was determined by making up different concentration suspensions of Pd/C that were pumped at the same flow rate, maintaining the same residence time overall. The effect of these concentrations of 5% Pd/C in methanol on conversion of 1 is shown in Table 2 at 100 °C, 3 mins residence time:

Table 2: Effect of changing catalyst concentration on conversion of 1 at 100 °C and 3 mins residence time

Concentration/ mgml^{-1}	Conversion/ %
18	95
12	37
6	52
4	66

Unsurprisingly, the higher concentration of catalyst has resulted in the highest conversion, but interestingly there appears to be a reduction in conversion at 12 mgml^{-1} which then increases as the concentration is decreased. Further optimization of different catalyst loadings may reveal different results, but it was clear that 18 mgml^{-1} provided the most favorable conversion for scale-up.

Solutions of 18 and 4 mgml^{-1} of 10% Pd/C in methanol were also examined at 100 °C and a residence time of 3 mins, Table 3:

Table 3: Comparison of conversions obtained using 10% and 5% Pd/C

Concentration/ mgml^{-1}	Conversion (10% Pd/C)/ %	Conversion (5% Pd/C)/ %
4	30	66
18	50	95

It is clear that under these reaction conditions, 10% Pd/C in methanol results in a lower conversion than the equivalent loading using 5% Pd/C.

Scale up

In order to scale-up the reaction, a Vapourtec 20 ml large diameter PFA Reactor for Rapid Mixing was used, initially at 100 °C as the previous reactions. It was observed however that even at the lower temperature, gas was being evolved very rapidly. This was considered likely to be a kinetic effect of increased mixing within the reactor, resulting in the decomposition of ammonium formate at the palladium surface more rapidly than occurs in the standard reactor. To reduce this effect, the reaction temperature was lowered to 85 °C. Following the observation that a higher catalyst concentration resulted in higher conversion, the catalyst solution was increased to 30 mgml^{-1} of 5% Pd/C in methanol. 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 palladium was filtered from the product solution under vacuum, and the resulting filtrate acidified with concentrated HCl to pH 1. Any organic impurities were extracted with ethyl acetate, and the aqueous solution was basified with NaOH to pH 12. The product was 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.

Conclusion

Using the Vapourtec patented V-3 pumps it has been possible to perform a non-scale limited heterogeneously catalyzed 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.

Analysis

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

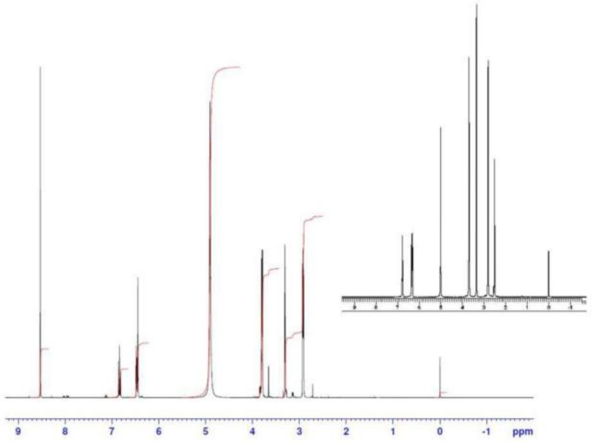

Figure 4: ^{1}H (MeOD, 400 MHz) spectrum of product obtained from the collected reactor output. No workup was performed beyond removing the Pd/C via filtration, and solvent removal using a V-10 evaporator. Inset is a literature ^{1}H (d6-DMSO, 500 MHz) spectrum of the product. The extra peaks that can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

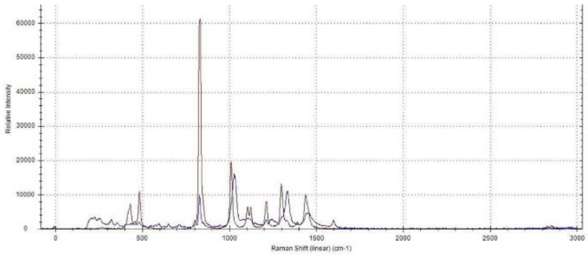

Figure 5: Raman spectrum of 1 (blue) and product 2 (red) collected directly from the reactor output and without workup, other than removal of Pd/C by filtration. It is clear that the peak in the starting material at 1600 cm^{-1} is not present in the product, indicating that there is no, or very little presence of starting material in the collected sample.

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