PHOENIX H-GENIE

SCALING-UP A CONTINUOUS FLOW HYDROGENATION REACTION IN A LAB ENVIRONMENT

Introduction

The importance of hydrogenations in the pharmaceutical, agrochemical, and fine chemical industries cannot be underestimated. Approximately 25% of the synthesis of marketed drugs as well as clinical drug candidates have at least one hydrogenation step in their synthetic sequence.[1] Nevertheless, the use of hydrogen gas in synthetic chemistry laboratories is oftentimes not preferred or even avoided due to regulatory, safety, and technical challenges.

Regulatory	Safety	Technical
Dedicated laboratory might be needed	Explosion and fire risk: Explosive mixture of H_2 and O_2, pyrophoric catalyst	Pressure limitations

Figure 1. Challenges associated with catalytic hydrogenation

The H-Genie® smart hydrogen generator combined with the Phoenix Flow Reactor™ from ThalesNano is an all-in-one flow chemistry setup for catalyst testing, synthesis, optimization, and scale-up that is useable in any fume hood in any lab. This combination offers you a wide temperature and pressure range in addition to high pressure hydrogen generated safely without cylinders for your reactions, granting you the capability of synthesizing from milligrams to kilograms of product on the same system without the need to spend on expensive infrastructure or equipment.

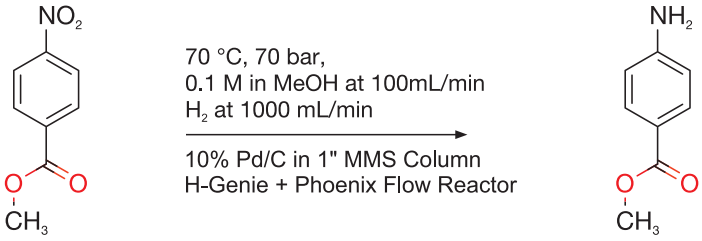

Figure 2. Nitro reduction of methyl-4-aminobenzoate

In a previous application note,[2] the nitro reduction of methyl-4-nitrobenzoate was already performed on a H-Cube® Midi. Having the H-Genie® and Phoenix Flow Reactor™ in hands, it was decided to scale-up this reaction to reach an input of 0.6 mol/hour of starting material (**Figure 2**).

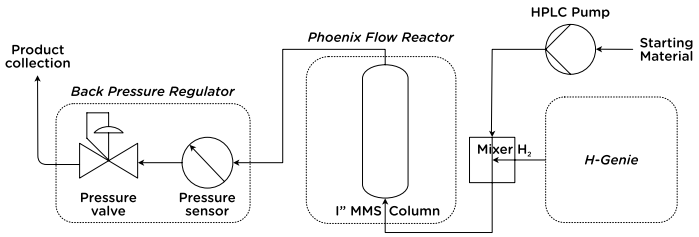

Figure 3. Schematic representation of Phoenix - H-Genie® system

Instrumentation

The H-Genie® was connected to the Phoenix Flow Reactor™ via a gas-liquid mixer (ThalesNano assembled mixer). A high flowrate HPLC pump (1-100 mL/min, Teledyne SSI) was used to create the flow and a backpressure module (ThalesNano's Pressure Module™) to build the pressure in the system. The pump delivers the liquid through the gas-liquid mixer, where the generated hydrogen gas from the H-Genie® is mixed with the liquid. The gas-liquid mixture flows through the temperature-controlled catalyst bed packed inside the metal-metal sealed (MMS) column, placed in the Phoenix Flow Reactor™. Finally, the mixture flows through the pressure sensor and the back-pressure regulator before being collected in a flask or vial (**Figure 3**).

How to perform a hydrogenation reaction with the Phoenix Flow Reactor™ - H-Genie® system?

Materials preparation

10% Pd/C with particle size distribution (d10: 7 µm, d50: 35 µm, d90: 150 µm) was purchased from Johnson Matthey, glass beads unwashed (212-300 µm) and methanol from Sigma Aldrich. The catalyst was loaded into the 1" MMS column (L: 230 mm, ID: 21.2 mm, internal volume: 81 mL) in the following order and quantities: 4 g of glass beads, 35 g: 3.5 g of 10% Pd/C: glass beads, ~25 g glass beads. The solution of 0.1 M of methyl-4-nitrobenzoate was prepared by dissolving 724.6 g in 40 L of MeOH.

Preparation of the setup

The 1" MMS column (with the catalyst previously packed inside) was placed into its appropriate holder in the Phoenix Flow Reactor™. When the flow line was fully completed and every part was connected and tightened (gas liquid mixer, pump head, check valve from the H-Genie®, cartridge, pressure sensor, etc.), a leak test was performed by pumping a solvent through and setting a high pressure. The water reservoir of the H-Genie® was filled with sufficient amount of MilliQ grade water and H_2 flow rate was set at 1000 mL/min and 100 bar. When H_2 was introduced to the system, the flow rate on the HPLC pump was set at 100 mL/min using MeOH and the pressure on the Pressure Module™ to 70 bar. When it was stable, the temperature on the Phoenix Flow Reactor™ was set to 70°C.

Reaction

After all parameters were stable for 5 minutes, the injection started by switching the inlet tubes from the MeOH flask into the stock solution of methyl-4-nitrobenzoate. Fractions were collected in order to monitor the reaction by TLC (cyclohexane: ethyl acetate 3:2) and LCMS.

End of the reaction

To finish the reaction, the inlet tubing was switched into the solvent in order to wash the system for 10-15 minutes, the different modules were stopped (allowing cooling of the Phoenix Flow Reactor™, pressure release on the Pressure Module™, ending H_2 flow from the H-Genie®), and finally stopping liquid flow from the HPLC Pump.

Results and discussion

The same reaction was previously performed on a H-Cube® Midi using a 5% Pd/C catalyst during 12 h to give a yield of 89% for an NMR purity of 98%[3]. The repeat of this reaction, using the same conditions except for the catalyst (10% Pd/C), along with monitoring of the conditions was the first step of this scale-up study using the Phoenix Flow Reactor™ - H-Genie® platform.

The initial 10 hours long control run performed on the MidiCart™ showed a conversion not less than 98.5%at the end of the run (**Figure 4**).

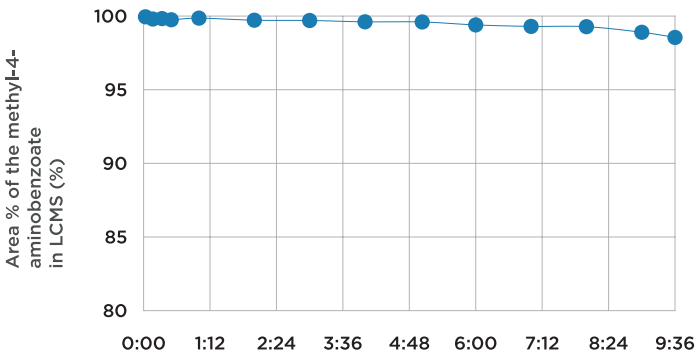

Figure 4. Conversion to methyl-4-aminobenzoate with the MidiCart™ (% LCMS)

The reaction was then scaled up with a factor 10 (catalyst volume, liquid and hydrogen flow rates) to demonstrate the scalability of the different modules of the set-up. This 7-hours long scaling-up run performed on the 1" MMS column showed a stable conversion (> 99%) for the first hours before dropping (**Figure 5**). A decrease in liquid flow rate (from 100 to 80 mL/min), meaning an increase in both the residence time and hydrogen equivalency, could partially overcome this decrease in catalytical activity by maintaining the conversion above 90% for the remaining runtime. An average productivity of 83 g/h with an overall isolated yield of pure methyl-4-aminobenzoate (LCMS purity > 98%) could have been achieved. Besides, even with a drop in yield over time, possibly due to a decrease in catalyst activity, we could succeed this process with a catalyst loading of 5.6%, which is similar to batch processes.

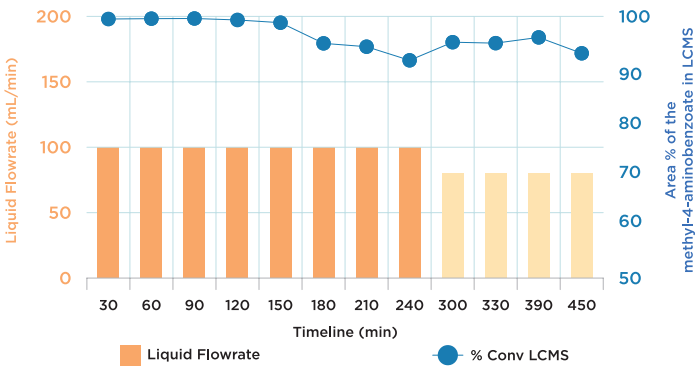

Figure 5. Conversion to methyl-4-aminobenzoate with the 1" MMS column

Conclusion

This reaction, used as a model for high-demanding (3 to 4.5 equivalents of H_2) and challenging reactions, demonstrate the high capability of hydrogen production of the H-Genie® combined with thelarge volume reactor compatible a the Phoenix Flow Reactor™.

Although deactivation of the catalyst led to a decrease in conversion, the capabilities of the Phoenix Flow Reactor™ - H-Genie® system to handle throughput as high as 100 mL/min liquid flowrate, 1000 mL/min of H_2 with an 81 mL reactor have been used with this system with this very first reaction.

The conversion drop associated with this kind of reduction has been widely studied without showing any efficient way of preventing the deactivation of the catalyst.[4]

Further screening, especially regarding the temperature should then be investigating to optimize even more the conversion.

	Pump / H_2 flow rate (mL/min)	Time of use (h)	Yield (g / %)		Purity (%)	Substrate / Catalyst ratio	Productivity (g/h)
MidiCart™	10 / 100	10	87	>99	99[a]	3.4%	8.7
1" MMS Column	100-80 / 1000	7	513	95[b]	>98[c]	5.6%	80

[a] Determined by ^{1}H NMR. [b] Yield of product after recrystallisation. [c] Weighted average was calculated based on ^{1}H NMR spectra of fractions collected during the run.

Acknowledgement

ThalesNano would like to thank the authors for their contribution.

References

[1]Cossar PJ, Hizartzidis L, Simone MI, McCluskey A, Gordon CP. The expanding utility of continuous flow hydrogenation, Organic and Biomolecular Chemistry 2015, 13, 7119–7130.

[2]ThalesNano Application Note, Scaling-up Hydrogenation Reactions – Using the H-Cube Midi™ Continuous-flow Reactor.

[3]Fine Chemicals through Heterogeneous Catalysis, Wiley 2008, H. van Bekkum, R. A. Sheldon

[4]K.K. Yeong et al., Catalysis Today 2003, 81, 641–651

For more information, please visit
www.thalesnano.com
Linkedin: /company/thalesnano-inc-
Twitter: /thales_nano
Instagram: /thalesnano_inc/
Facebook: /ThalesNano/

ThalesNano Inc.
Záhony utca 7. | H-1031 Budapest | Hungary
Phone: +36 1 880 8500
Fax: +36 1 880 8500
Email: sales@thalesnano.com
www.thalesnano.com

US Office
50 S. Penn St. Suite B-2
Hatboro PA. 19040
USA
Phone: 215-534-3365
E-mail: USAsales@thalesnano.com