THALESNano

Scaling-up Hydrogenation Reactions – Using the H-Cube Midi™ Continuous-flow Reactor

The difficulties involved in scaling up reactions from laboratory to process scale are well known, especially when dangerous materials are involved. This paper will demonstrate the capability of the H-Cube Midi™ to successfully scale-up hydrogenation reactions.

Reaction pathways are usually designed in laboratories on a small scale using stirred, glass vessels. When scale-up is attempted using a larger vessel, unexpected reactions may occur or problems including catalyst and inhibition effects. Also, the time taken for the reaction to go to completion is often significantly increased.

The advent of flow technology has offered a methodology that can overcome these restrictions and allow rapid preparation of compounds with minimum workup. Reactions are carried out on a small scale but the amount of product can be increased by allowing a larger volume to flow through the system. This has a number of advantages. The thermo-chemistry of the reaction doesn't change, so the reaction result will be constant. The heat production is highly controllable meaning many hazardous reagents that were prohibited previously may now be used in a safe controlled manner. Furthermore, reagents or compounds only undergo short reaction times and are then eluted into a collection vial, so further reaction with starting materials or thermal decomposition is unlikely.

INTRODUCTION

The H-Cube Midi™ represents the first step in ThalesNano, Inc.'s development of process scale flow hydrogenation. Utilizing current H-Cube® technology, the H-Cube Midi™ seeks to increase the capacity of the present H-Cube® without compromising efficiency and safety. The H-Cube Midi™ will allow users of the H-Cube® to scale up reactions and achieve the same results.

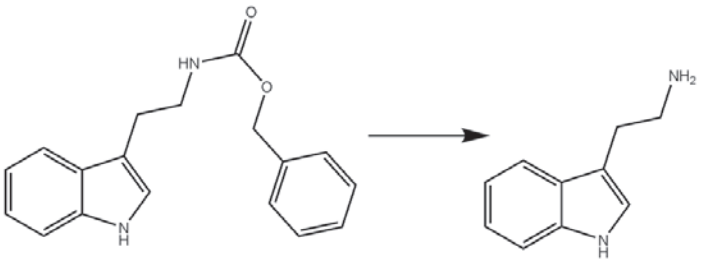
STANDARD EXPERIMENTAL PROTOCOL

After switching on the H-Cube Midi™ and filling the water reservoir with de-ionized water, the desired MidiCart® is fixed into its holder. The required flow rate can be selected via the main window of the touch screen and pushing the Information field enables the reaction details to be set (concentration of the reagent, molar ratio of hydrogen in the reaction and excess of hydrogen required). The system software will then automatically calculate and set the volume of hydrogen to be produced (max. 125 mL/min).

Automatic or manual mode can be selected for the control of the inlet and outlet valves and the desired pressure can be set. Once the flow of solvent has started you can also set the desired temperature. The hydrogenation process can then start once the system has stabilized and the inlet valve is switched to the substrate solution. The outlet valve is then switched to collect the product and the system can be run until the required quantity is eluted. The difficulties involved in scaling up reactions

EXPERIMENTAL PROTOCOL-DEPROTECTION

14,7 g of CBz-Tryptamine was dissolved in ethanol to give 1 L of solution. Using the touch-screen, the flow rate was set to 10 mL/min and the reaction parameters were entered: concentration of starting material (0,05 M), molar ratio of hydrogen in the reaction (1.0) and excess of hydrogen required (40%). The software calculated and set the appropriate level of hydrogen production (16 mL/min, 10%). The CBz-Tryptamine solution was then pumped through a 10% Pd/C (3.1 g) filled MidiCart™ at a temperature of 60°C and a pressure of 50 bars. The collected product solution was analyzed by HPLC-MS and ^{1}H-NMR.

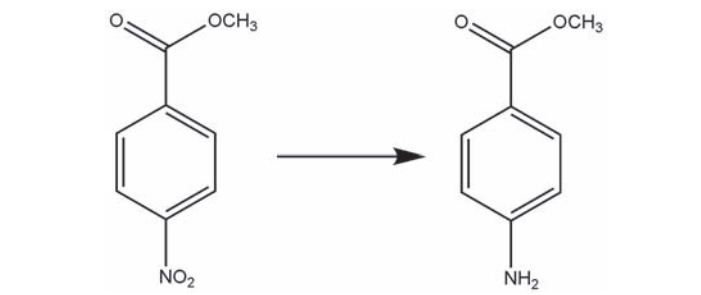


RESULT

After 1 hour 40 minutes, 7.6 g of de-protected Tryptamine had been produced with a yield of 95% and NMR purity of 95%.

EXPERIMENTAL PROTOCOL – NITRO REDUCTION

130.4 g of Methyl-4-nitrobenzoate was dissolved in methanol to give 7.2 L of solution (0.1 M). The software calculated and set the hydrogen production at 100 mL/min (80%) based on a flow rate of 10 mL/min, a concentration of 0.1 M, a molar ratio of 3.0 and a hydrogen excess of 40%. The reaction was carried out using 5% Pd/C (2.17 g) filled MidiCart™ at a pressure of 70 bar and a temperature of 70°C. Every 30 minutes, samples were taken for HPLC-MS analysis.

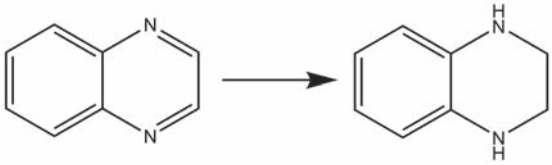


RESULT

After 12 hours, 96.8 g of Methyl-4-aminobenzoate had been produced (yield 89%, NMR purity 98%).

EXPERIMENTAL PROTOCOL - RING SATURATION

91 g of Quinoxaline was dissolved in EtOH:EtOAc (1:1) to give 7 L of solution. The software calculated and set the hydrogen production at 67 mL/min (50%) based on a flow rate of 10 mL/min, a concentration of 0.1 M, a molar ratio of 2.0 and a hydrogen excess of 40%. The starting material was passed through a 20% $Pd(OH)_2/C$ (2,64 g) filled MidiCart™ at 100°C and 70 bar. Every 30 minutes, samples were taken for HPLC-MS analysis.



RESULTS

After 11.5 hours, 78.64 g of the desired compound had been produced with a yield of 85% and NMR purity of 90%.

CONCLUSION

These reactions demonstrate the successful application of scale-up hydrogenation performed using the H-Cube Midi™. The wide range of possible conditions (up to 25 mL/min flow rate, 150°C temperature and 100 bar pressure) and the increased amount of catalyst and hydrogen available make the H-Cube Midi™ an invaluable laboratory synthesis system .

If you require any further information on the H-Cube Midi™, please contact:

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