



Fast Hydrogenation Reaction Examples Using the H-Cube® flow reactor

The hydrogenation of a series of functional groups has been performed using H-Cube®, a novel continuous-flow microfluidic hydrogenation reactor. These experiments demonstrate that the H-Cube® can perform a diverse range of heterogeneous hydrogenation reactions with high yields and conversion rates, and with reaction times of minutes. For example, 162 mg of 5-nitroindole was reduced in less than 10 minutes in quantitative yield.

INTRODUCTION

Heterogeneous catalytic hydrogenation is one of the most important techniques for the reduction of functional groups, but is severely limited by harsh experimental conditions and the potential hazard of handling pyrophoric catalysts (1), (2). Hydrogenation at elevated temperatures and pressures is accomplished in autoclave reactors, normally requiring specially trained staff and dedicated laboratory facilities. The use of the batch process means the size of the reaction is dependent upon the capacity of the device, which cannot be decreased or increased past certain limits, without changing the reactor. To address these limitations, ThalesNano has developed the H-Cube®, which generates hydrogen internally through the electrolysis of water, and through a novel CarCart® system, negates pyrophoric catalyst filtration. To demonstrate the capabilities of H-Cube® at reducing a wide range of functional groups, the six specific groups shown above, were reduced and the conversion and yield summarised. The efficiency of the mixing between the catalyst, substrate, and hydrogen in the H-Cube® is also highlighted and compared with that of a conventional batch reactor.

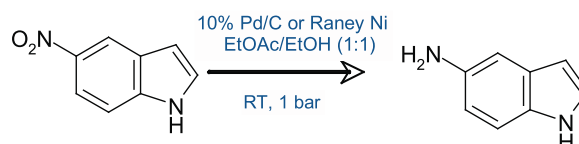


STANDARD EXPERIMENTAL PROTOCOL

The reaction solvent was initially allowed to flow through the CatCart® for 1 minute. Hydrogen production was then activated, and the mixture of solvent and hydrogen was allowed to flow through the solvent for 10 minutes to prepare the catalyst. The catalysts used were 10% Pd/C, 10% Pt/C or Raney/Nickel. The flow rate of the system was initially set to 1 mL/min, the hydrogen pressure to 1 bar, and the reaction allowed to commence.

When higher conversion rates were required, the temperature parameter was increased while the reaction was in progress. After passing through the instrument, the total amount of reaction mixture was collected, and the column was washed through with the solvent mixture to remove any substrate still adsorbed to the catalyst. The two solutions were combined and analyzed by thin layer chromatography to assess purity. The used CatCart® was removed and placed in a deactivating solution of sodium hydrogen sulfite (1 M).

1. Nitro reduction

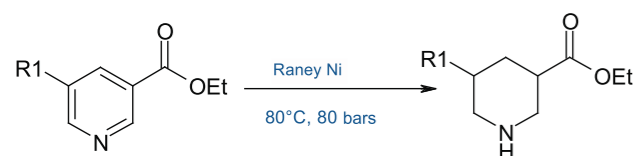


NITRO REDUCTION

Reduction of nitro compounds is an important route to the formation of amines, which are often used as a drug building block. The formation of amines usually take place under mild conditions, for example, room temperature and low pressure (3).

Experimental procedure

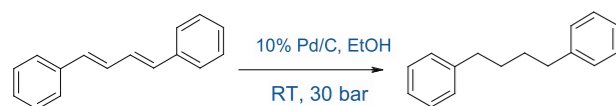
Using 10% Pd/C as catalyst, 20 mL of 5-nitroindole (1 mmol; 162 mg) in a 1:1 mixture of ethyl acetate was pumped through the H-Cube®. The pressure of the system was set to 1 bar, and the temperature to room temperature. After 20 minutes, all the reaction mixture had passed through the H-Cube®. The CatCart® was then washed with ethanol for approximately 10 minutes. The fraction was analyzed using TLC, which showed complete conversion to the product, and the solvent was reduced to dryness, affording the product in 98% yield. The reaction was repeated at 2 mL/min producing the same conversion and yield within 10 minutes.

2. Heterocycle saturation**HETEROCYCLE SATURATION**

Nicotinic acid esters are important intermediates for the preparation of commercial herbicides, anti-allergy agents, and for the treatment of gastric and duodenal ulcer diseases (4).

Experimental procedure

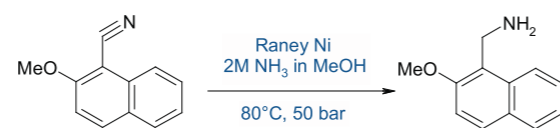
Using 10% Pd/C, 40% EtOH in water as solvent, 90°C and a pressure of 80 bars, a number of nicotinic acid ester analogs were reduced at a flow rate of 1 mL/min and a concentration of 0.05 M. ¹H-NMR analysis showed average product purity of >95%.

3. Double-bond saturation**DOUBLE-BOND SATURATION**

Carbon-carbon double bonds are readily hydrogenated unless highly-substituted and sterically hindered. Most easily hydrogenated alkenes can be reduced at atmospheric pressure and temperature, although use of elevated temperatures and/or pressures can increase reactivity substantially (5).

Experimental procedure

The reduction of 1 mmol (103 mg) of *trans, trans*-1,4-diphenyl-1,3-butadiene on the H-Cube® took only 10 minutes using 10% Pd/C at room temperature and 1 bar affording a 96% yield.

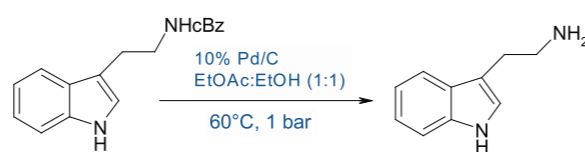
4. Nitrile reduction**NITRILE REDUCTION**

The reduction of nitriles is of industrial importance, and has been applied to the commercial production of various amines, for example, various aliphatic amines from fatty acid nitriles (6).

Experimental procedure

The reaction was carried out using dry solvents and flame-dried glassware. All starting materials, solvents and products were kept under an argon atmosphere. Using Raney Nickel as catalyst, a dry solution of 2.0 M of ammonia in methanol under argon was flushed through the system at 1 mL/min for 5 minutes at 80°C and 50 bars, with a constant flow of hydrogen.

The flow was stopped, and a solution of 2-methoxy-1-naphthonitrile (92 mg, 1 mmole) in 10 mL of 2.0 M of ammonia in methanol under argon was then pumped through the system at a flow rate of 1 mL/min.

5. Protecting-group hydrogenolysis**PROTECTING-GROUP HYDROGENOLYSIS**

The use of benzyl and carbobenzyloxy functionalities as protecting groups is an important facet of chemoselectivity. The C-N, or C-O bonds can undergo facile cleavage in the presence of a metal catalyst and hydrogen (7).

Experimental procedure

Carbobenzyloxy-protected tryptamine was subjected to hydrogenolysis using H-Cube®. The hydrogenolysis of the *N*-carbobenzyloxy-tryptamine proceeded smoothly at 60°C and 1 bar affording a quantitative yield.

REDUCTIVE ALKYLATION

The direct reductive amination (DRA) of aldehyde and ketones is an important reaction in organic chemistry with a great potential for application in industry.

Reductive amination carried out using heterogeneous catalysts has one main advantage over the use of other reducing agents, for example, boranes, which is the avoidance of any waste production (8).

Experimental procedure

The imine was formed in situ by mixing the aldehyde and amine in dry methanol (10 mL) using 4Å molecular sieves under argon. The imine was then passed through the system at room temperature and 1 bar pressure, a flow rate of 1 mL/min, and Raney Ni as catalyst, for 10 minutes. NMR analysis at the end of the experiment showed 97% product conversion.

H-CUBE® AND BATCH REACTORS: A COMPARISON

The residence time of the substrate in a 30x4 mm CatCart® is 30 seconds. A 2 mL sample of dissolved substrate will therefore take 2 minutes and 30 seconds to pass through the catalyst at a flow-rate of 1 mL/min.

To show a comparison in the efficiency of a reaction performed in the H-Cube® with that of one performed in a conventional batch reactor, the following experiment was performed.

BATCH REACTOR TEST

135 mg of 10% Pd/C (the amount of catalyst present in a 30x4 mm CatCart®) was added to a 2 mL solution of 5-nitroindole (0.05 M) and placed in a reaction bomb. The reaction mixture was flushed with nitrogen 3 times, and then flushed with hydrogen at a pressure of 1 bar and at room temperature.

The reaction was stirred vigorously for 2 minutes and 30 seconds, and the hydrogen was then evacuated from the reactor. The reaction mixture was filtered, reduced to dryness, and an ¹H-NMR taken to obtain a % conversion.

H-CUBE® TEST

A CatCart® was washed with only ethanol, and a 2 mL solution of 5-nitroindole was flowed through the catalyst at 1 mL/min at room temperature and 1 bar. The total reaction time was 2 minutes and 30 seconds. The resulting solution was reduced to dryness, and an NMR sample taken.

Both reactions were performed twice.

RESULTS AND DISCUSSION

The results of the batch reactor and H-Cube® experiments are as follows:

5-nitroindole Reduction	Conventional Batch Reactor	H-Cube® Reactor
Reaction 1: RT and 30 bars; reaction time: 150 seconds	20% Conversion	100% Conversion
Reaction 2: RT and 30 bars; reaction time: 150 seconds	11% Conversion	100% Conversion

Table 1

From the results we can see that the efficiency of the H-Cube® is substantially greater than that of the batch reactor. In a typical batch reactor, a stirred suspension of substrate and catalyst is reacted under an atmosphere of hydrogen. The mass-transfer between the gas-liquid and liquid-solid phases in a batch reactor is therefore, very low since there is a low interfacial area between the three phases. In the H-Cube®, the dissolved substrate and hydrogen flow through the microchannels formed by the compressed catalyst. The interfacial area between the three phases is higher, resulting in a more efficient gas-liquid-solid reaction as demonstrated by the better product conversion.

The efficiency of the H-Cube® is further demonstrated from the results of the 6 reductions, as summarised in Table 2, overleaf.

Reaction type (Reaction time: 10 mins)	Product conversion	Yield
Nitro reduction	99%	98%
Heterocycle saturation	>95%	74%
Double bond reduction	96%	92%
Nitrile reduction	98%	88%
Protecting group hydrogenolysis	98%	>90%
Reductive alkylation	97%	80%

Table 2



CONCLUSION

These experiments demonstrate that the H-Cube[®] can perform heterogeneous hydrogenation reactions with high yields and conversion rates.

The H-Cube[®] was capable of reducing quantities of up to 2 mmols within minutes, and all reactions were consistently reproduced. The reactions can be easily monitored, allowing a rapid optimization of the reaction conditions. No filtration was required with just the solvent reduced to dryness to yield the product in a pure form.

Current investigations centre around the use of novel immobilised palladium catalysts for the asymmetric reductions of ketones.

Work is also underway towards the integration of the H-Cube[®] with an automated liquid handler for the multiple reductions of small scale compounds as part of a final step library synthesis.

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