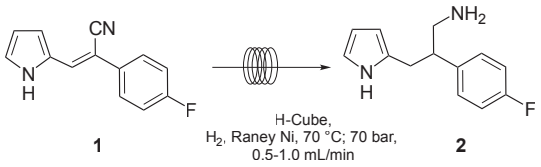
H-CUBE PRO

Medicinal chemistry application of chemoselective hydrogenation of multiple functional groups

Introduction

Flow hydrogenation can be applied in many different reaction pathways complementing traditional batch chemistry efforts, however articles describing chemoselective hydrogenations in a single flow process are scarce.[1,2]

In a medicinal chemistry project McCluskey and co-workers employed a series of chemoselective sequential hydrogenation reactions in order to access highly decorated norcantharidin analogues.[3,4] This application note analyses the excellent work which showed how the judicious choice of reaction conditions (H_2 pressure, temperature, flow rate and the catalyst) can allow the simultaneous reduction of an olefin and a nitrile (**1** to **2** in Scheme 1, and **3** to **4** in Scheme 2), the selective reduction of an olefin adjacent to a nitrile (**3** to **5**), the saturation of a furan ring and an olefin without hydrogenatingthe nitrile (**3** to **6**) or even the simultaneous reduction of all three aforementioned (olefin, nitrile, furan) moieties (**3** to **7**).



Scheme 1. The simultaneous reduction of an olefin and a nitrile

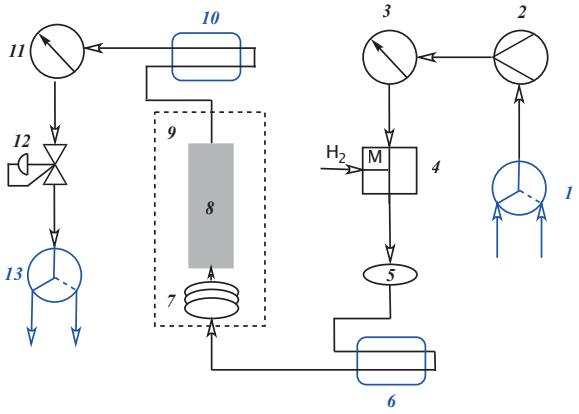


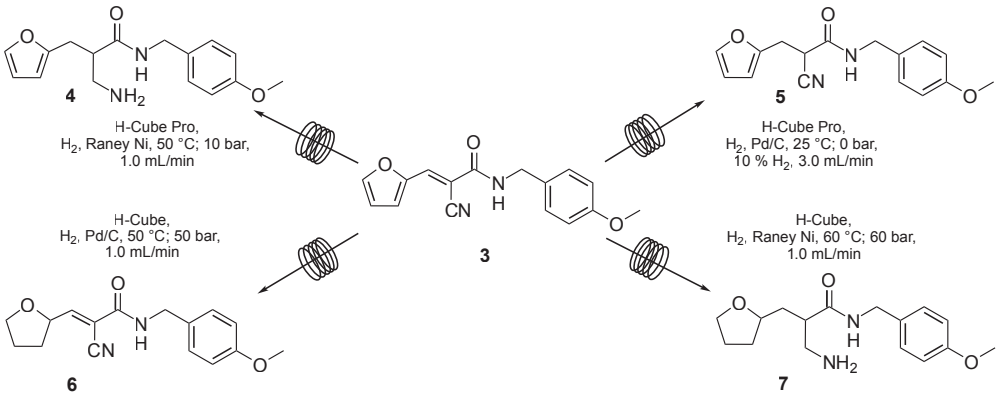
Figure 1. Schematic representaion of the H-Cube Pro™.

1. Inlet switching valve 2. HPLC pump 3. Inlet pressure sensor; 4. Gas – liquid mixer; 5. Bubble detector; 5. Preheater coil; 6. Loop attachment module before CatCart®; 7. Preheater coil; 8. Catalyst bed; 9. Peltier heating unit; 10. Loop attachment module after CatCart®; 11. System pressure sensor; 12. Back pressure regulator, 13. Outlet switching valve

Instrumentation

In his studies, McCluskey used both the H-Cube Pro™ and H-Cube™ instruments. In these reactors (Figure 1), the pump delivers the liquid through the pressure sensor to the gas-liquid mixer, where the *in situ* generated H_2 gas is released into the reaction line. The gas-liquid mixture flows through the temperature controlled catalyst bed after passing the bubble detector. Finally, the mixture flows through the system pressure sensor and the back-pressure regulator before collection in a flask or vial.

Scheme 2.
Hydrogenation of compound 3.



Experimental

HOW TO SETUP A HYDROGENATION IN THE H-CUBE PRO™?

First, ensure that the water reservoir contains sufficient amount of deionized water (14 MOhm/cm conductivity), the water level appears on the display. Then, place the appropriate CatCart® into the holder, then tighten the CatCart® cap (fingertight). Set the following parameters on the touch screen: flow rate, temperature, H_2 pressure. Push the start button on the screen and read the status window:

1. Priming – the system starts to wash the reaction line at 2 mL/min flowrate
2. Building up temperature and system pressure
3. Building up H_2 gas pressure (gradient pressure is needed compared to the system pressure)
4. Release H_2 gas into the gas-liquid mixer
5. Stable message appears, the reaction mixture can be introduced into the system by using the inlet switching valve.

*The synthesis of 3-amino-2-(furan-2-ylmethyl)-N-(4-methoxybenzyl)-propanamide (**4**)*.[3] Compound **3** (0.1 g, 0.35 mmol) in MeOH (7 mL) was hydrogenated using the H-Cube Pro™ with a RaNi catalyst (30×4 mm CatCart®) at 1 mL/min flowrate, 50°C and 10 bar H_2 pressure (100% H_2). The solvent was removed in vacuo to afford **4** as a clear oil in quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (dd, 1H), 7.12 (d, 2H), 6.82 (dd, 2H), 6.26 (dd, 1H), 6.09–5.96 (m, 1H), 4.38 (dd, 1H), 4.29 (dd, 1H), 3.78 (s, 3H), 3.02 (dd, 1H), 2.92 (dd, 1H), 2.88–2.80 (m, 1H), 2.76 (d, 1H), 2.56 (dd, 1H), 1.46 (s, 2H). Please consult ref. 4 for details on full characterization.

*2-Cyano-3-(furan-2-yl)-N-(4-methoxybenzyl) propanamide (**5**)*.[3] Compound **3** (0.1 g, 0.35 mmol) in MeOH (7 mL) was hydrogenated using the H-Cube Pro™ with 10% Pd/C catalyst (30×4 mm CatCart®) at 3 mL/min flow rate, 25°C and 0 bar (formal value) 10% H_2 pressure. The solvent was removed in vacuo to afford **5** as a white solid in quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, 1H), 7.15 (d, 2H), 6.88–6.83 (m, 2H), 6.34 (br s, NH), 6.31 (dd, 1H), 6.22 (d, 1H), 4.47–4.32 (m, 2H), 3.80 (s, 3H), 3.70 (dd, 1H), 3.32 (m, 2H). Please consult ref. 4 for details on full characterization.

For details on the synthesis and characterization of compounds **1**–**7** please consult references 3 and 4.

RISK ASSESSMENT AND HAZARDS

The H-Cube family of flow reactors enhances laboratory safety with pyrophoric catalysts contained in sealed cartridges and hydrogen generated *in situ* from water.[5] Therefore the need for hydrogen cylinders is eliminated. The reaction line is made up of stainless steel (0.5 mm internal diameter, SS 316L). The catalyst cartridge reduces human exposure to the catalyst significantly, which in turn reduces the risks involved with the handling of pyrophoric catalysts. The hydrogenation process takes place solely inside the cartridge. The reaction zone is less than 0.3 mL (void volume of 30×4 mm CatCart®). The extremely low volume complies with NFPA 45, Annex C part C.5.3 paragraphs (5 and 6). (NFPA – National Fire Protection Association – 45: Standard on Fire Protection for Laboratories Using Chemicals).

TECHNICAL NOTE

The H-Cube Pro™ is an improved version of the original H-Cube®. The key advantages of the H-Cube Pro™ are its bigger H_2 production capacity up to 60 mL/min and the precise control of the H_2 amount in the reaction line. See the main differences from a chemist's aspect in the table below:

Properties	H-Cube®	H-Cube Pro™
H_2 amount	"no H_2", "controlled" and "full H_2" modes are available	can be set between 0–100% independently from the gas pressure
	up to 30 mL/min H_2 (NTP)*	up to 60 mL/min H_2 (NTP)*
Pressure setting increments	10 bar	1 bar
Temperature range (°C)	rt – 100	10–150
Software	graphical user interface to control the instrument	graphical user interface; Simplex for optimization; timer function for automation

NTP = NORMAL TEMPERATURE AND PRESSURE

Summary and Conclusion

There are several functional groups that can be reduced by molecular hydrogen under heterogeneous catalytic condition. McClusky and co-workers were among the first ones who showed that flow chemistry offers new opportunities for medicinal chemists to achieve chemoselective hydrogenations with dihydrogen in "single-flow" processes by making use of the precise parameter control (using a narrow parameter "window") and rapid parameter optimization. The H-Cube Pro™ even allows for the selective reduction of an internal olefin adjacent to a nitrile (reduction of **3** to **5**). Using standard batch synthesis chemoselective hydrogenations under heterogeneous conditions are much more difficult or even impossible to achieve.[2]

REFERENCES

(1) Ürge, L.; Alcazar, J.; Huck, L.; Dormán, G., *Ann. Rep. Med. Chem.* **2017**, *50,* 87–147. (2) Osako, T.; Torii, K.; Hirata, S.; Uozumi, Y. *ACS Catal.* **2017**, *7*, 7371–7377. (3) Tarleton, M.; McCluskey, A. *Tetrahedron Lett*. **2011**, *52*, 1583–1586. (4) Hizartzidis, L.; Tarleton, M.; Gordon, C. P.; McCluskey, A. *RSC Advances*, **2014**, *4*, 9709–9722. (5) Dormán G.; Kocsis L.; Jones R.; Darvas F. *J. Chem. Health Safety* **2013**, *20*, 3–8.

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