DIFFICULT HYDROGENATIONS - SATURATION OF FUNCTIONALIZED PYRIDINES

INTRODUCTION

The saturation of aromatic ring systems is one of the hardest reactions in hydrogenation. Reactions are typically performed at high temperature and pressure (above 80 bar, 80 °C). Typical laboratory batch reactors are not capable of reaching these conditions and so, either the reaction does not work or the reactions take days. The H-Cube® Advance flow hydrogenation reactor is capable of performing reactions at 150 °C and 100 bar safely. The H-Cube® Advance's improved mixing efficiency coupled with high temperature and pressure abilities means difficult reactions can be performed in minutes. Here are a few examples.

BACKGROUND

Piperidine derivates often appear as building blocks of natural products and other pharmaceutically important compounds. Desoxypipradrol (2-diphenylmethylpiperidine), is a piperidine containing psychoactive drug, which acts as a long-lasting stimulant by functioning as a norepinephrine-dopamine reuptake inhibitor (NDRI). Synthesis of these compounds frequently involve ring closing reactions, but when the starting material is a pyridine a metal catalysed hydrogenation is the widely accepted synthetic route. In order to be able to saturate the aromatic ring high temperature, elevated hydrogen pressure and long reaction times are required. Prof. Kappe's group at University of Graz has published results on the hydrogenation of different substituted pyridines using the H-Cube® Advance, different catalysts (Pt, Pd, Rh containing solid supported), and reaction conditions [1.]. Mono- and disubstituted pyridines were used to investigate the effect of reaction parameters and the nature of the catalyst on the stereoselectivity. Comparison reactions using microwave reactors were also performed.

RESULTS OF OPTIMIZATION REACTIONS

It was found that in the case of 7 different starting materials, applying 30-80 bar of pressure, 60-80 °C of temperature, and a 0.5 mL/min flow rate resulted in full conversion. It is notable that when pyridine-2-acetic ester underwent hydrogenation (Figure 1.), 80-90 bar pressure and 80 °C temperature were required to achieve full conversion. A decrease in pressure to 50 bar resulted in a significant drop in conversion even at elevated temperature (100 °C). It was reported when using asymmetrical pyridine derivates both in microwave (4 bar hydrogen pressure, PtO2 catalyst) and in the H-Cube® Advance reactor (30 bar, Pt/C catalyst) a 1:1 mixture of cis and trans substituted piperidines are generated, but when the pressure was increased to 80 bar (only possible in H-Cube® Advance) the diastereomeric ratio changed to 1.7:1 in flavour of the cis derivate.

PARTIAL HYDROGENATION OF PYRIDINE RING

As it was shown beforehand, for full dearomatization not just an active catalyst is necessary, but the use of elevated pressure and temperature as well. Experiments with ethyl nicotinate (Figure 2.) showed that by changing the solvent and applying only 30 bar produces partially hydrogenated material with 95% selectivity.

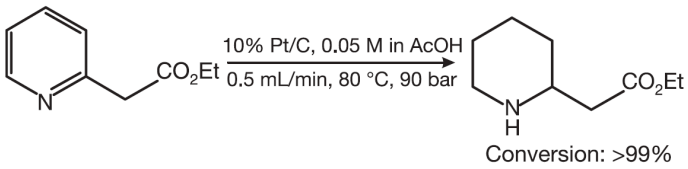

Figure 1. Hydrogenation of pyridine-2-acetic ester

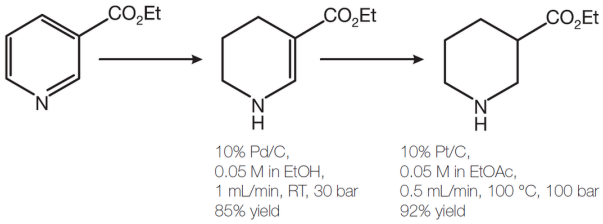

Figure 2. Partial and full hydrogenation of ethyl nicotinate

RING SATURATION COUPLED WITH DEHALOGENATION

It is well known that halogen substituted aromatic systems can be easily dehalogenated during hydrogenation reactions causing a mixture of products instead of the selectively hydrogenated one. However, when the goal is to remove the halogen function as well, then applying hydrogenation gives another advantage by eliminating a further synthetic step. This advantage was used by Whelligan et al. [2.] in the synthesis of mitotic kinase Nek2 inhibitors. Acetic acid, used to activate the pyridine ring, coupled with 10% Pt/C catalyst at 70 °C and ambient pressure were enough to give the cis isomer of the dehalogenated product in a 56% yield after workup (Figure 3.).

SCALE-UP OF PYRIDINE HYDROGENATION

One of the biggest advantages of flow chemistry is the fast and safe scale-up of hazardous reactions. In many cases, even the optimization process is not necessary when moving to a larger scale flow reactor such as the Phoenix large scale flow reactor. Prof. Ley's group at the University of Cambridge also dedicated some of their work to the modification of pyridines and monitored their results using inline FTIR. In one of their examples, the Phoenix Flow Reactor was used for the hydrogenation of methyl-nicotinate. Similarly to the Kappe group, they also used a non-acidic solution coupled with high pressure and temperature (80 bar and 90 °C respectively) to get the desired product in 90% yield (Figure 4.).

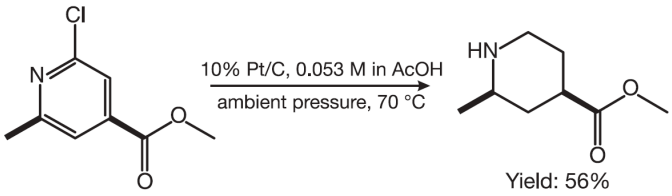

Figure 3. Ring saturation coupled with dechlorination

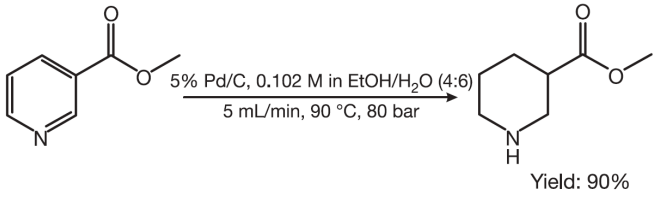

Figure 4. Scale-up of pyridine hydrogenation

REFERENCES

1.) Irfan, M.; Petricci, E.; Glasnov, T. N.; Taddei, M.; Kappe, O.C.; Continuous Flow Hydrogenation of Functionalized Pyridines; Eur. J. Org. Chem.; 2009; 9; 1327-1334
2.) Whelligan, D. K.; Solanki, S.; Taylor, D.; Thomson, D. W.; Cheung, K. J.; Boxall, K.; Mas-Droux, C.; Barillari, C.; Burns, S.; Grummitt, C. G.; Collins, I.; van Montfort, E. L. M.; Aherne, G. W.; Bayliss, R.; Hoelder, S.; Aminopyrazine Inhibitors Binding to an Unusual Inactive Conformation of the Mitotic Kinase Nek2: SAR and Structural Characterization; J. Med. Chem.; 2010; 53; 7682-7698
3.) Carter, C. F.; Lange, H.; Ley, S.V.; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L.; ReactIR Flow Cell: A New Analytical Tool for Continuous Flow Chemical Processing; Org. Process Res. Dev.; 2010; 14; 393-404

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