



Scale-up of a Reductive Amination Reaction Using H-Cube Midi™ Reactor

INTRODUCTION

Reductive amination is widely used as a form of amination between an aldehyde or ketone and a primary amine or ammonia. The reaction can be done either in two steps, via indirect reductive amination and performing the reduction after isolation of the imine compound, or simultaneously by choosing a way of reduction which prefers the reduction of the protonated imine over the reduction of starting material. Catalytic hydrogenation matches these criteria, e.g. Raney Nickel can be used at low pressure as well as platinum oxide, and avoids the difficult purification processes when utilizing borohydrides. In this application note we will be focusing on how reductive amination was scaled up in the synthesis of a pharmaceutically important enzyme inhibitor.

At Genzyme, Cooper et al. attempted to synthesize a glucosylceramide synthesis inhibitor (Figure 1) on a large scale. After reviewing the literature, they decided to dedicate their work towards developing a novel, conventional economically viable method. The synthesis route involved a reductive amination step (Figure 2), carried out by using the H-Cube Midi™ reactor, the step before formation of the methanesulfonic acid salt final product.

Their work started with the synthesis of the aldehyde material. After several trials of different synthetic routes, including a 5 step synthesis route, they were able to optimize the process within 3 steps. The key step involved the endocyclic C-O bond cleavage, resulting in a yield of 85% and producing approximately 170 g 5-(Adamant-1-yl-methoxy)-1-pentanal that could then be used for the reductive amination reaction.



The H-Cube Midi™ reactor was chosen for the purpose because their batch equipment was not suitable and the H-Cube Midi™'s electrolytic hydrogen generation meant it was compatible with their lab without the need for hydrogen facilities.

When performed in batch, getting the product in solid form while the starting materials remained in liquid phase is the preferred way of synthesis. In flow, precipitation is avoided as it can block the system. Therefore, they first had to find a solvent system which is capable of dissolving all the materials present during the reaction process. Furthermore, as the product of reductive amination had to be converted to a methanesulfonic acid salt, the solvent could not have been the obvious choice of acetic acid because the formed acetate salt was difficult to free base and isolate for the next reaction.

Genzyme finally settled on the solvent mixture of 2:2:1 MeOH/THF/H₂O (Figure 3), which could keep the compounds in the solvent phase up to a concentration of 600 mmol/L at room temperature.

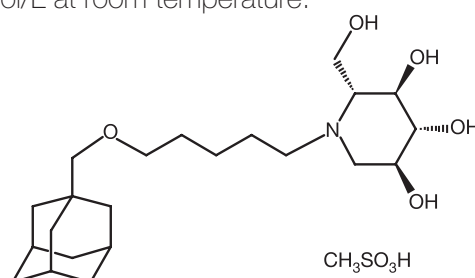


Figure 1: MZ-21: A potent GCS inhibitor



During the optimization process several catalysts (Figure 4) and conditions were tested in order to get the highest throughput in a single pass. Due to the difficulties associated with removal of the residues of the amine compound (deoxynojirimycin), although conversion was higher than 98% using equimolar amounts, an excess of 1.6 equ. aldehyde was needed. This helped avoid a highly problematic workup procedure.

EXPERIMENTAL PROCEDURE

The aldehyde compound was dissolved in THF/MeOH and was merged with the aqueous solution of deoxynojirimycin and filtered before pumping into the H-Cube Midi™ reactor. The following reaction parameters were set: temperature: 145 °C, pressure: 95 bar, flow rate: 15 mL/min, catalyst: Pd(OH)₂/C. After evaporation, the product was reacted with methanesulfonic acid to form 130.9 g of the final product with a 99.4% purity after filtration and drying. This H-Cube Midi™ step is capable of producing 1 kg of compound per day on one MidiCart™. No catalyst deactivation was observed. ICP studies showed less than 1 ppm residual Pd content.

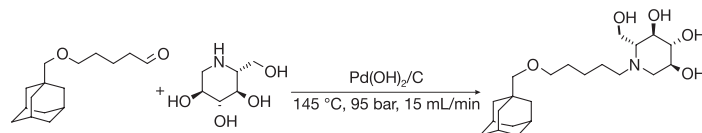


Figure 2: Reductive amination in flow

CONCLUSION

A novel route was developed to synthesize a biologically active compound. By applying flow hydrogenation they were able to produce the desired compound in the required scale with less than 1 ppm residual Pd content. Considering the used concentration and flow rate, the described process was capable of producing 1 kg of the reductive aminated product per day.

REFERENCES

Cooper, C.G.F.; Lee, E.R.; Silva, R.A.; Bourque, A.J.; Clark, S.; Katti, S.; Nivorozhkin, V.; Process Development of a Potent Glucosylceramide Synthase Inhibitor; *Org. Process Res. Dev.*; **2011**; In press



Figure 3: Solvent choice: 2:2:1 MeOH/THF/H₂O

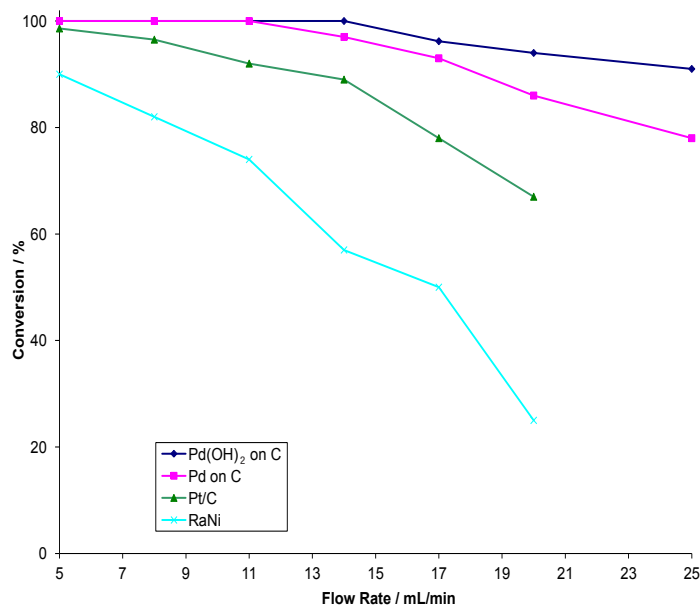


Figure 4: Optimization of flow rate and catalyst

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