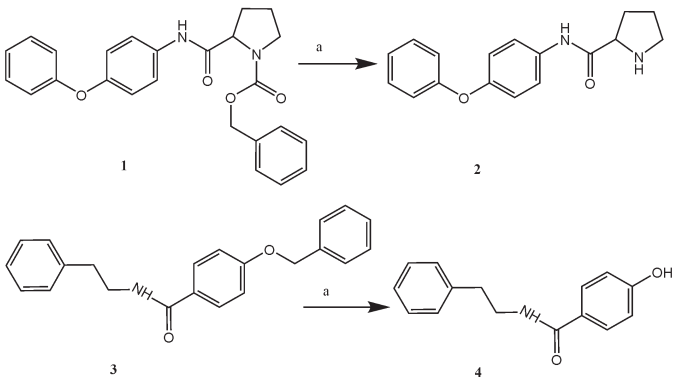
THALESNano

Automated Hydrogenation Using the H-Cube® Continuous Flow Reactor

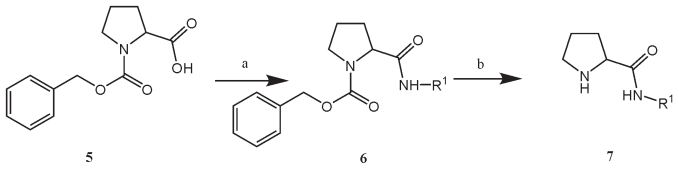
The pharmaceutical industry is continually searching to automate techniques for rapid optimization or library production. The automation of hydrogenation is one of those processes that is drawing high interest due to its frequency in drug synthesis.

OPTIMIZATION OF HYDROGENOLYSIS REACTIONS

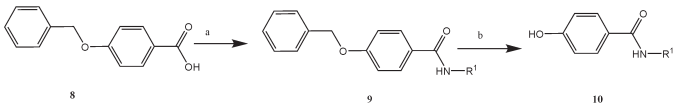
Automated H-Cube® was used for hydrogenolysis and deprotection reactions by Clapham et al[1]. Using this system hydrogenolysis (Scheme 1.) and deprotection (Schemes 2. and 3.) reactions were carried out.



Scheme 1. Hydrogenolysis Optimization Reactions



Scheme 2. Deprotection of Cbz Protected Library



Scheme 3. Deprotection of a Benzyl Ether Protected Library

STANDARD EXPERIMENTAL PROTOCOL

Before the reaction the catalysts were pretreated by flowing the reaction solvent and hydrogen for several minutes at set reaction conditions. Then the reaction mixture was allowed to continuously flow through the prepacked catalyst cartridge, CatCart®, where the actual reaction takes place and combined with the regulated hydrogen. After the waiting time, samples were taken for analytical measurement. Post treatment of the catalyst was carried out by flowing the solvent through the CatCart® to remove any absorbed substrate from the surface of the catalyst.

EXPERIMENTAL PROTOCOL OF HYDROGENOLYSIS REACTIONS

Both the 1 and 3 components were dissolved in 10 mL EtOAc:EtOH = 1:1. The optimal parameters were found to be Pd/C as catalyst, 10 mg/mL starting material in the solvent, flow rate of 1 mL/min and temperature of 60°C using the H-Cube® in full hydrogen mode.

DEPROTECTION

First the authors synthetised 39 different amides **(6)** from Cbz-Prolin coupled with aniline derivates in the presence of HATU and Et_3N in DMA. After isolation and purification by preparative HPLC, the amides were redissolved in EtOAc/EtOH for deprotection using the automated H-Cube®.

EXPERIMENTAL PROTOCOL OF DEPROTECTION REACTIONS

Flow rate of 1 mL/min, 3 mL of wash volume, temperature of 60°C were found as optimal parameters with 10 mg/mL of reagent solution in EtOH/EtOAc using Pd/C as catalyst in full hydrogen mode.

Performing reactions at these conditions LC-MS and ^{1}H-NMR measurements indicated complete conversions of 34 protected amides. Deprotection processes resulted in **7** as a single homogeneous compound. In case of benzyl ether deprotection all of the 36 deprotected amides gave the corresponding phenol derivates.

RESULTS OF DEPROTECTION

Crude and isolated yields of the required Cbz deprotected products were analyzed and presented in Figure 1. with an average crude yield of 93%. The crude product was finally purified by HPLC resulting average purified yield of 67%. Debenzylation reactions were also performed successfully with an average crude yield of 88% and a preparative HPLC purification average purified yield of 58%.

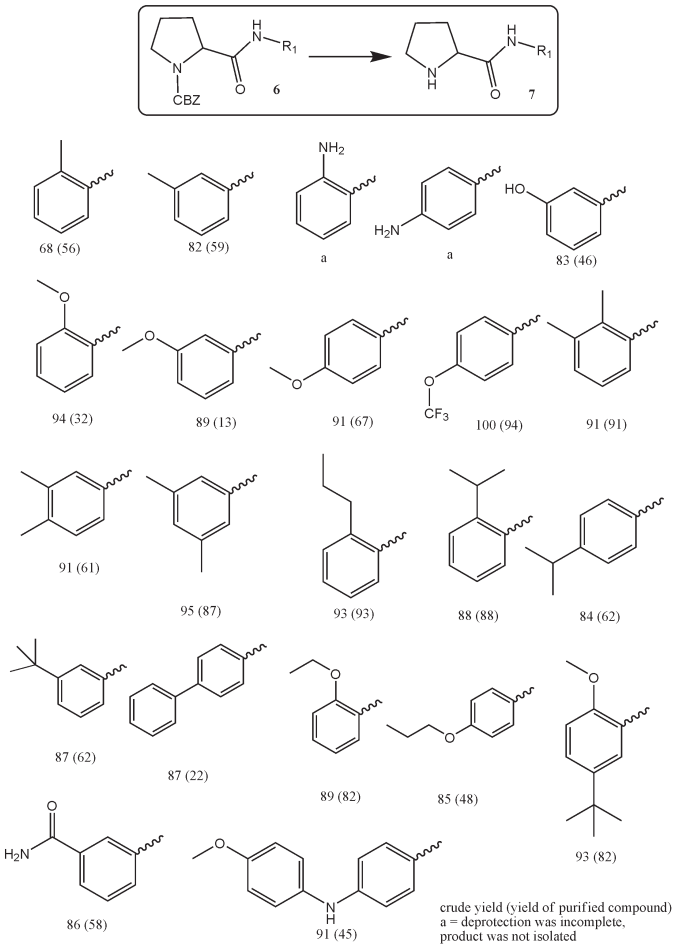


Figure 1. Deprotection of Cbz Protected Library

CONCLUSION

These experiments demonstrate how well the H-Cube® can be integrated with an autosampler in a high throughput manner for compound library synthesis.

REFERENCES

[1] Clapham, B., Wilson, N.S., Michmerhuizen, M.J., Blanchard, D.P., Dingle, D.M., Nemcek, T.A., Pan, J.Y., Sauer, D.R., *J. Comb. Chem.*, **2008**, 10, 88-93

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