



Deprotection Reactions Using the H-Cube® Continuous Flow Reactor

INTRODUCTION

Protecting groups play a central role in modern organic synthesis. The benzyl groups and benzyl carbamate or Cbz groups are some of the most commonly used protecting groups and play a central role in the protection of alcohols, carboxylic acids, and amines. The benzyl and benzyl carbamate groups are removed using catalytic hydrogenation using elevated temperature. The H-Cube® is able to remove benzyl groups from amines, acids, or alcohols very efficiently in one pass through a 10% Pd/C CatCart®. This application note gives examples of deprotection reactions performed on the H-Cube® from the recent articles.

O-BENZYL DEPROTECTION

Parameter Optimization

To find the optimal parameters of catalytic hydrogenolysis, the *O*-debenzylation of *O*-benzyl protected *N*-Boc-tyrosine (Figure 1.) was investigated by Knudsen et al¹. A series of experiments over 10% Pd/C catalyst in EtOH:EtOAc (1:1) solvent were performed to probe the effects of flow rate, temperature and concentration using an automated hydrogenation platform. Results showed a faster catalyst deactivation rate with increasing concentration and flow rate, but at higher temperature they found dramatically increased conversion rates. At room temperature the conversion rate was half of that observed at 60°C.

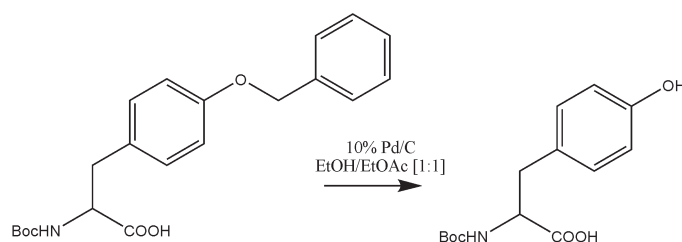


Figure 1: Debenzylation of *O*-benzyl protected *N*-Boc-tyrosine

100% conversion was reached, when the concentration of reactant solution was 0.1 M, the applied temperature was 60°C, and the flow rate was 1 mL/min.

Catalyst Reactivation

As the catalyst can be poisoned and deactivated over a long reaction time, catalyst reactivation is a key factor in heterogeneous catalysis. To increase the catalyst lifetime the following reactions were performed. Equal amount of reactant was introduced to the system in two different ways: continuously and through repeated injections of small amounts. With the injection method, there was a short period of time between each injection where the solvent regenerated the catalyst by washing off any adsorbed material. This short washing period generated higher conversion rates compared to continuous pumping the material through the catalyst.

N-CBZ DEPROTECTION

Reaction Optimization and Library Synthesis

An *N*-deprotection reaction was also optimized by Knudsen and co-workers¹ with the reaction shown in Figure 2. After finding the optimized reaction conditions, such as elevated temperature of 80°C, pressure of 1 bar, and solvent concentration of 0.05 M using 10% Pd/C as catalyst, a small library of *N*-protected compounds, including dipeptide and amino acid derivatives, was successfully hydrogenated. As seen in the previous reaction series, the temperature also had a significant effect on the conversion rate. The observed yield of isolated products were high in each case and are displayed in Table 1.

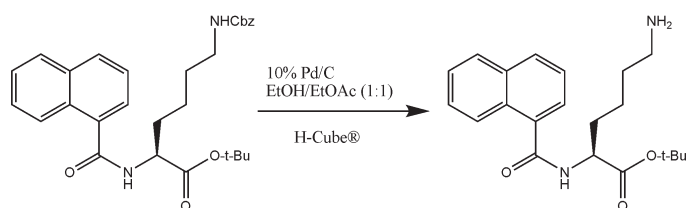


Figure 2: Deprotection of ϵ -[*N*-Cbz] lysine *tert*-butyl ester

Substrate	Conversion [%]	Yield [%]
Cbz-Pro-OMe	99	99
Cbz-Piperazine	99	80
Cbz-Asp(OMe)-OMe	99	77
Cbz-(OBn)Tyr-OMe	97	83
Cbz-Ser-OMe	98	82
Boc-(<i>N</i> -Cbz)-Lys-O(Naph)	95	86
Cbz-Thr-Tyr(O- <i>t</i> -Bu)-O- <i>t</i> -Bu	99	96
Cbz-Pro-tetrazole	99	99

Table 1: Deprotection of eight *N*-Cbz protected compounds

When Cbz-(OBn)Tyr-OMe (Table 1, line 4.) was introduced to the automated H-Cube® system, selective Cbz deprotection was observed and the desired product was isolated in 83% yield.

Part of New Synthesis Pathway

A practical and safe synthesis of (*S*)-pyrrolidine-2-yl-1*H*-tetrazole was developed by Franckevicius and co-workers² to prepare a catalyst which can be used in Mannich and aldol reactions leading to high yields. The synthetic steps eliminate the generation of hazardous materials such as, ammonium azide and the use of non-volatile solvent.

In the first synthetic step a protected pyrrolidine derivative was synthesized, which was subsequently transformed to the tetrazole derivative of the Cbz protected pyrrolidine with sodium azide. Overall yield was 92%.

In the last step, Cbz deprotection (Figure 3.) was achieved by the H-Cube® using a volatile solution mixture of EtOAc:EtOH:AcOH = 1:1:1. The method dramatically reduces the reaction time. In batch when 9:1 acetic acid:water solvent mixture was used, the reaction time and time consuming work-up extended the total reaction time to 3 days. While in flow mode 3 g of desired compound was synthesized in 3.5 hours. The reaction seen in Figure 4. was performed using full hydrogen mode at a flow rate of 1 mL/min, temperature of 80°C and a starting material concentration of 0.05 M. 10% Pd/C was used as catalyst. Working-up the reaction was carried out by simple evaporation of the solvent.

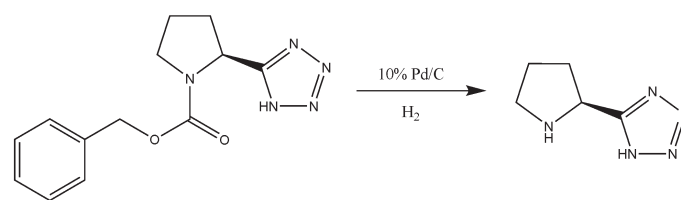


Figure 3: Deprotection step of (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole synthesis

Yield of the deprotection was 98% and resulted in an overall yield of 90% for the total synthesis.

O-DEBENZYLATION

Part of New Reaction Pathway

A debenzylation step was performed by Desai and Kappe to produce dihydropyrimidines (DHPM) C5 carboxylic acids³. The synthesis of the acids can be readily achieved by hydrogenolysis of the corresponding benzyl esters. The previously reported batch reaction resulted in high yields and used an external hydrogen gas source, while when the H-Cube® was used with 10% Pd/C catalyst there was no need for a gas cylinder. The reaction scheme and the isolated yield values obtained are seen in Figure 4. and Table 2. Under these circumstances in continuous flow („CF”) mode 80 - 95% isolated yields of the DHPMs acids were obtained.

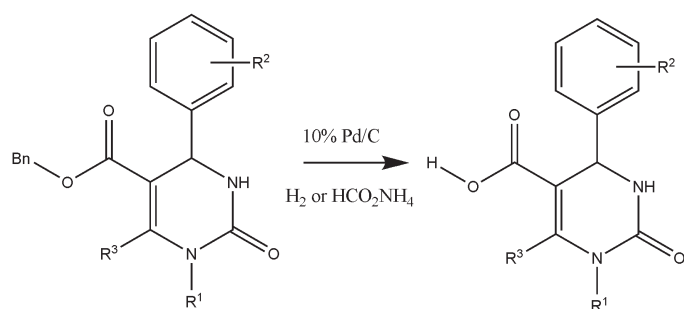


Figure 4: Hydrogenation of DHPM C5 Benzyl Esters

Yields were also obtained from the deprotection reaction of DHPM esters under other conditions. Namely, room temperature catalytic transfer hydrogenation („rt”) in ammonium formate, and microwave-assisted transfer hydrogenation („MW”) in ammonium formate⁴. When room temperature hydrogenation was applied, reactions took 8-10 h reaction time and only 56 - 66% yields were obtained. The microwave assisted method did not result in significant enhancement of the yields. The obtained values were between 53 - 62%, but the reaction times were reduced to minutes.

R ¹	R ²	R ³	Conditions	Yield [%]
H	H	Me	rt	66
			MW	62
			CF	95
H	H	Ph	rt	65
			MW	60
			CF	80
Me	H	Me	rt	57
			MW	55
			CF	85
H	4-Me	Me	rt	56
			MW	53
			CF	85

Table 2: Isolated yield values of hydrogenation of DHPM C5 benzyl esters

Compared to the batch and microwave techniques, H-Cube® gave yields between 80 – 95%. The major advantage as they emphasized that these excellent yields were obtained after a simple evaporation thus this easy work-up makes this method an attractive solution for automated library generation.

MULTIDEBENZYLATION AND DOUBLE BOND REDUCTION

A debenzylation in conjunction with a double bond reduction reaction plays an important role in the synthesis of polyhydroxylated oxamacrolides, as reported by Matos and Murphy⁵ in a multistep synthesis.

In the previous step, before the reduction, a mixture of macrolactones was produced, separated and then introduced into the H-Cube®. Deprotection of the four benzyl groups and the saturation of the double bond (Figure 5.) was carried out at 80 bar pressure, 60°C reaction temperature and a flow rate of 1 mL/min over 5% Pd/C catalyst in ethanol. In the first experiment lower yield was observed due to the low solubility of the product in ethanol. The structure of colorless oil was confirmed by X-ray crystal structure.

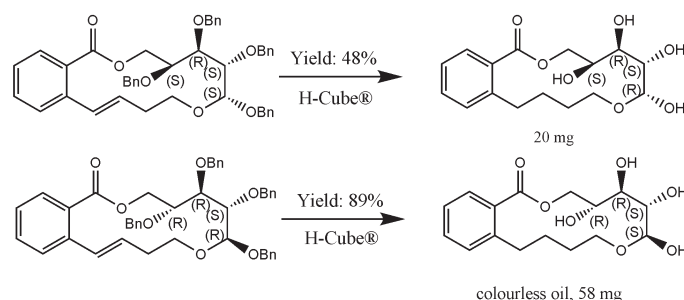


Figure 5: Synthesis of polyhydroxylated oxamacrolides

CONCLUSION

H-Cube® continuous flow reactor is proven to be an ideal tool for performing deprotection catalytic hydrogenation. The excellent yields in all cases and the easy handling of catalysts suggest this method to be a fast, efficient, and safe way to perform benzyl deprotection compared to batch and microwave methods.

REFERENCES

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The following CatCarts® are currently available:

Inert CatCart: Quartz	5% Pd/C
Inert CatCart: Titanium	5% Ru/Al ₂ O ₃
10% Pd/C	5% Pt/Al ₂ O ₃
Raney Nickel	5% Pd/CaCO ₃ , poisoned with lead (Lindlar Catalyst)
10% Pt/C	5% Ru/C
5% Rh/C	5% Re/C
20 % Pd(OH) ₂ /C	5% Pt/C, Sulfided
Raney cobalt	5% Rh/Al ₂ O ₃
Raney copper	PtO ₂
5% Pd/Al ₂ O ₃	NP Pd(0)EnCat™ 30*
CuO/Al ₂ O ₃	5% Pd/BaSO ₄
Rh(COD) ₂ BF ₄ /Al ₂ O ₃	Pricat Ni 55/5P
1% Rh/SiO ₂ /Polyethyleneimine	Nickel Sponge, 1% Mo
0,5% Ir/C	5% Pd (+1% Fe)/C
1% Pt/SiO ₂	(2,5% Pd + 2,5% Pt)/C
1% Pt/SiO ₂ /Polyethyleneimine	4,5% Ru - 0,5% Pd on carbon
5% Pt/C (doped with Bi)	1% Pd/Al ₂ O ₃
Nickel Sponge	10% Pd/Al ₂ O ₃
Re ₂ O ₇	1% Ir/C
1% Pt/C (doped with V)	Pd/C-Ethylenediamine
10% Pd/CaCO ₃	Ni/SiO ₂ -Al ₂ O ₃
5% Pd/CaCO ₃	5% Pd/SiO ₂
5% Pd/BaCO ₃	1% Pd/C
1% Pd - 0,3% Cu/Al ₂ O ₃	2% Pd/SrCO ₃
Pt EnCat™	1% Pt/Al ₂ O ₃
10% Rh 1% Pd/C	PdO
10% Re/C	Pd black
Ru black	PdEnCat™ 30*
5% Pt/CaCO ₃	PdEnCat™ TPP30*
Al ₂ O ₃ /HPA[Rh(NBD)(S,S)-BDPP]PF ₆	Pd(II) EnCat™ BINAP 30*
Al ₂ O ₃ /HPA[Rh(COD)(S,S)-BDPP]Cl	Tetrakis (TPP)-palladium
Al ₂ O ₃ /PTA[Rh(COD)(2R,4R)-BDPP]Cl	Pd(II) EnCat™ TOTP 30*
Al ₂ O ₃ /HPA[Rh(COD)(DIPAMP)]BF ₄	Ru(II) (TPP, monosulphonated) ₂ Cl ₂
Rh(COD)(dppf)/SiO ₂	Wilkinson's catalyst RhCl(TPP) ₃
Au/Fe ₂ O ₃	RuO ₂
1% Pt/SBA	IrO ₂
Au/C	FibreCat® 1001**
Au/TiO ₂	FibreCat® 1007**
Mercaptopropyl modified silica	FibreCat® 2003**
Phoshotungstic modified activated carbon	FibreCat® 2006**
Phoshotungstic modified alumina	1% Pt/C
Ethylenediamine modified silica	5% Ir/CaCO ₃
	5% Pt/C

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