

Catalytic Transfer Hydrogenolysis of *N*-Benzyl Protecting Groups

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The catalytic transfer hydrogenolysis of a number of *N*-benzyl compounds has been examined. Of the three hydrogen donors studied, ammonium formate and hydrazine hydrate were more effective than sodium hypophosphite. In general, debenzilation of secondary and tertiary benzylamines could be readily accomplished by refluxing the substrate with an excess of the hydrogen donor in alcoholic solvents for a few hours using catalytic amounts of 10% palladium on carbon. The two *N*-benzyl heteroaromatic amines studied were stable to the above conditions.

The use of catalytic transfer hydrogenation and hydrogenolysis (CTH) has increased dramatically in the last ten years, and a large number of functional groups have been reduced^{2,3} using a variety of hydrogen donors such as cyclohexene,⁴ ammonium formate, hydrazine, formic acid, and sodium hypophosphite.⁶ However, despite the importance of the benzyl group in the protection of amines,⁷ the deprotection of *N*-benzyl amines using CTH has been largely overlooked. To the best of our knowledge the *N*-debenzilation of only three substrates by CTH has been reported to date. These are Boc-His(*N*^ε-Bzl),⁸ Z-Lys(*N*^ε-bzl),⁵ and an *N*-(α -methylbenzyl) pyrrolidine,⁹ using either palladium black^{5,8} or 10% palladium on carbon^{8,9} in large amounts (substrate: catalyst ratio (wt/wt) of 2:1⁸ or 1:1^{5,9}).

We have carried out a systematic study using 10% palladium on carbon as catalyst and either ammonium formate, hydrazine or sodium hypophosphite as hydrogen donor in an attempt to establish the scope and generality of *N*-debenzilation using CTH.

Table. Catalytic Transfer Hydrogenolysis of *N*-Benzyl Derivatives

Entry No.	Substrate	Hydrogen Donor						Product ^d	m.p. (°C) or b.p. (°C)/torr	
		Ammonium Formate in Methanol ^a		Hydrazine Hydrate in Ethanol ^b		Sodium Hypophosphite in Methanol ^c			Found	Reported ¹²
		yield ^e (%)	Pd/C used ^f (mg/mmol)	yield ^e (%)	Pd/C used ^f (mg/mmol)	yield ^e (%)	Pd/C used ^f (mg/mmol)			
1	<i>N</i> -Benzyl, <i>N</i> -ethyl-aniline	91	18	82	8	64	21	<i>N</i> -Ethylaniline	204	205
2	2-Benzylaminonorbornane	62	16	84	16	No Reaction		2-Aminonorbornane	150/150	49/12
3	<i>N</i> -Benzyldehydroabietylamine ¹⁰	84	30	86	16	No Reaction		Dehydroabietylamine	140–142 ¹³	141–143 ¹³
4	<i>N</i> -Benzyl, <i>N</i> -methylaminoethanol	– ^g	14	42	16 ^h	– ⁱ	16	<i>N</i> -Methylaminoethanol	170	159
5	Ethyl <i>N</i> -Benzylglycinate	49 ^j	15	– ^k	–	No Reaction		Ethyl Glycinate		
6	<i>N</i> -Benzylpiperazine	– ^l	14	– ^m	16	– ⁱ	18	Piperazine		
7	2-Benzylamino-pyridine	No Reaction		No Reaction		No Reaction				
8	<i>N</i> ⁶ -Benzyladenine	No Reaction		No Reaction		No Reaction				

^a All reactions were carried out on a 5–70 mmol scale in refluxing 25% aqueous methanol using a 4-fold molar excess ammonium formate.

^b All reactions were carried out on a 25–50 mmol scale in refluxing ethanol using a 8-fold molar excess of hydrazine hydrate.

^c All reactions were carried out on a 5–25 mmol scale in refluxing 25% aqueous methanol, using a 3-fold molar excess of sodium hypophosphite.

^d The isolated products showed spectroscopic characteristics identical to the corresponding authentic amines.

^e Isolated yield.

^f The catalyst used was 10% Pd/C, 56% wet with water. The figures given here refer to the equivalent dry weight of catalyst used.

^g After 1 h the TLC analysis (eluent: ethyl acetate/methanol/c. ammonium hydroxide, 5:1:1) indicated that complete debenzylation had occurred, however isolation of the product from an excess of ammonium formate was not possible.¹¹

^h Half of the catalyst and hydrazine hydrate was added initially and the mixture refluxed for 2 h. The catalyst was removed by filtration, the remainder of the catalyst and hydrazine hydrate was added and refluxing was continued for a further 3 h.

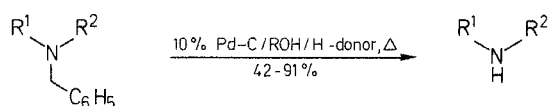
ⁱ TLC analysis (eluent: ethyl acetate/methanol/c. ammonium hydroxide, 5:1:1) indicated that complete debenzylation had occurred, however isolation of the product was not possible.

^j The reaction was carried out in 25% aqueous acetic acid at room temperature.

^k Reaction was not attempted because of reactivity of esters with hydrazine.

^l After 1 h TLC analysis (eluent: ethyl acetate/methanol/c. ammonium hydroxide, 5:1:1) indicated that complete debenzylation had occurred and ¹H-NMR analysis of the crude oil confirmed this. It was not possible to isolate the product from an excess of ammonium formate.¹¹

^m GC analysis of the reaction mixture after 2 h indicated that ca. 15% debenzylation had occurred. The isolation of this small amount of product was not attempted.



R = CH₃, C₂H₅

H-donor = NH₄OOCCH₃, N₂H₄ · H₂O, NaH₂PO₂

The results we have obtained using commercially available substrates¹⁰ are shown in the Table. The conditions reported here were not optimised although it is known³ that the ease of reaction is very dependent on the hydrogen donor and solvent used. In the cases where hydrogenolysis was observed, the reactions were essentially quantitative as judged by TLC or GC (except entry 6). The low isolated yields obtained in some instances reflect the difficulty in isolation of the volatile and/or highly water soluble products.

It can be seen from the results in the Table that the removal of *N*-benzyl groups from secondary or tertiary benzyl amines can be accomplished using CTH. However the fact that 2-benzylaminopyridine and benzyladenine were stable to the reaction conditions used here shows that the method does have limitations. Worthy of note is that the palladium on carbon was used in catalytic amounts, unlike previous examples.^{5,8,9} Ammonium formate and hydrazine were found to be more effective hydrogen donors than sodium hypophosphite, but whether this is a general feature for *N*-debenzylation remains to be seen.

From the above work it is clear that *N*-debenzylation of benzyl amines may now be added to the host of other functional group reductions which have been successfully carried out using CTH.^{2,3}

Catalytic Transfer Hydrogenolysis; Typical Procedures:

a) Dehydroabietylamine:

A suspension of *N*-benzyldehydroabietylamine¹⁰ (3.50 g, 9.3 mmol) in methanol (35 ml) is stirred and treated with 10% palladium on carbon (0.63 g, 56% wet with water) followed by a solution of ammonium formate (2.35 g, 37 mmol) in water (8 ml). The resulting mixture is refluxed until TLC (eluent: ethyl acetate) indicated that the reaction is complete (2 h). The reaction mixture is filtered and evaporated. The residue is partitioned between dichloromethane (3 × 50 ml) and water (50 ml) at pH = 12. Evaporation of the dichloromethane extracts *in vacuo* gives dehydroabietylamine as a colourless oil; yield: 2.24 g (84%).

b) 2-Aminonorbornane:

2-Benzylaminonorbornane (10.05 g, 50 mmol) is dissolved in ethanol (75 ml) and stirred. 10% Palladium on carbon (1.80 g, 56% wet with water) is added, followed by hydrazine hydrate (20 g, 400 mmol). The mixture is refluxed until TLC (eluent: ethyl acetate/methanol/c. ammonium hydroxide, 20:2:1) indicated that the reaction is complete (2 h), cooled, filtered through celite and water (100 ml) is added to the filtrate. The filtrate is basified and the product extracted into dichloromethane (2 × 50 ml) and dried. The dichloromethane is removed *in vacuo*, and the residual oil is purified by careful distillation to give 2-aminonorbornane; yield: 4.64 g (84%); b.p. 150°C/150 torr (bath temp.)

c) *N*-Ethylaniline:

A solution of *N*-benzyl-*N*-ethylaniline (5.30 g, 25 mmol) in methanol (25 ml) is stirred and treated with 10% palladium on carbon (1.2 g,

56% wet with water) followed by a solution of sodium hypophosphite (6.75 g, 75 mmol) in water (10 ml). After the initial exothermic reaction subsided the mixture is refluxed until TLC (eluent: pet. ether 60–80°C/ethyl acetate, 4:1) indicated that the reaction is complete (6 h). The reaction mixture is filtered and the filtrate is evaporated *in vacuo*. The residue is partitioned between water (50 ml) and dichloromethane (3 × 30 ml). Evaporation of the dried dichloromethane extracts *in vacuo* gave *N*-ethylaniline; yield: 1.90 g (64%).

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- (10) *N*-Benzyldehydroabietylamine was prepared from dehydroabietylamine (Fluka) by direct alkylation with an excess of benzyl bromide or reductive alkylation with benzaldehyde. The hydrobromide salt (m.p. 261–263°C) gave the following analysis:

$C_{27}H_{38}BrN$	calc.	C 71.03	H 8.39	N 3.06
(456.6)	found	71.07	8.62	2.93
- (11) One of the Referees has pointed out that the excess ammonium formate could be decomposed by prolonged heating of the reaction mixture once the reaction is complete, and we thank him for this comment.
- (12) Aldrich Catalogue/Handbook, Aldrich Chemical Company.
- (13) M.p. of acetate salt, reported in Fieser, L.F., Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, John Wiley & Sons, New York, 1967, p. 183.