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Utilization of lithium triethylborohydride as a selective *N*-acyl deprotecting agent

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Abstract—Lithium triethylborohydride has been found to be a superior and selective reagent for the removal of tertiary *N*-acyl protecting groups. The reagent selectively removes tertiary amide acyl functionality without affecting secondary amide functionality even when they are present in the same molecule. Some tertiary carbamates may be also removed under the same conditions.
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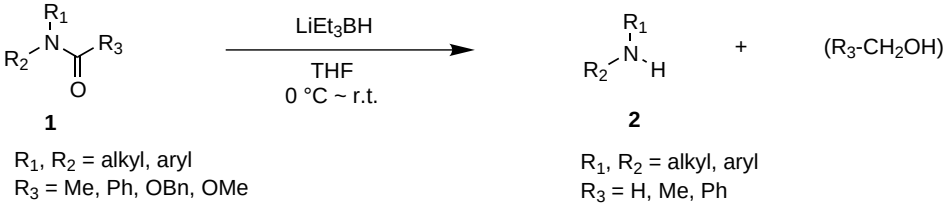
The use of simple acyl functionalities such as acetyl and benzoyl groups as readily removable protecting groups for amino functionality would greatly facilitate amine chemistry. We report here an efficient method for the selective removal of tertiary amide acyl functionalities, in particular, *N*-acetyl and *N*-benzoyl groups using a commercially available THF solution of lithium triethylborohydride (Super hydride).[1] The reagent may be used for the selective removal of tertiary amide acyl functionalities, without affecting a secondary amide functionality, to give secondary amine products while leaving the secondary amide functionality intact even when they are present in the same molecule. It was also found that the reagent may also be used for the removal of some tertiary carbamate acyl functionalities (Scheme 1).

In their extensive study utilizing lithium triethylborohydride, Brown and co-workers[1] found that, unlike most other hydride reagents, the reaction of the hydride with both aliphatic and aromatic *N*,*N*-dimethylamides produced the corresponding primary alcohols instead of the corresponding tertiary *N*,*N*-dimethylamine products. Several modified methods for producing primary alcohols from tertiary amides have since been reported.[2] However, no reports have concentrated on the fate of the amine moiety also liberated (Scheme 2).

Their observation prompted our interest in the liberated amines, and we decided to utilize the reagent as a convenient *N*-deacylation agent to make simple acyl functionalities, such as acetyl and benzoyl groups, and tolerable under various conditions, more practical *N*-protecting groups. We first examined the reaction of a series of tertiary amides using lithium triethylborohydride. The reaction proceeded well on addition of 3 equiv. of lithium triethylborohydride in THF to a 0.2 M THF solution of the amide substrates at 0°C to room temperature to yield the corresponding secondary amines in good to excellent yields within 1 h (Table 1). The reductive cleavage reaction readily occurred with both the *N*-acetyl and *N*-benzoyl functionalities to give the corresponding secondary amines. Although the compatibility of other functional groups was not examined extensively, acetal and TBS-O- functionalities in the substrates[3] **1d** and **1e** were compatible under the



1

R_1, R_2 = alkyl, aryl
R_3 = Me, Ph, OBn, OMe

2

R_1, R_2 = alkyl, aryl
R_3 = H, Me, Ph

Scheme 1.

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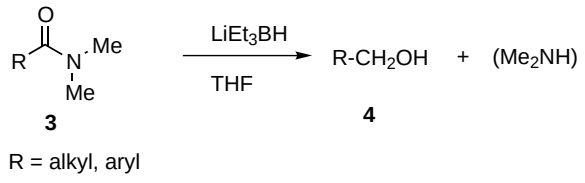
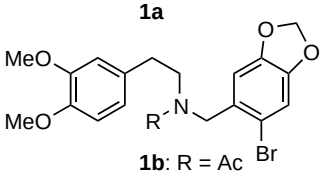
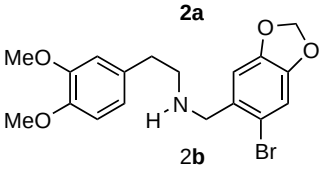
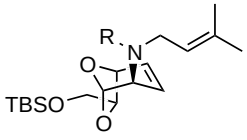
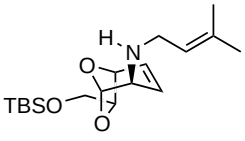
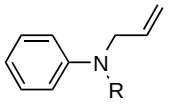
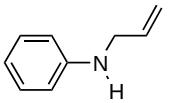


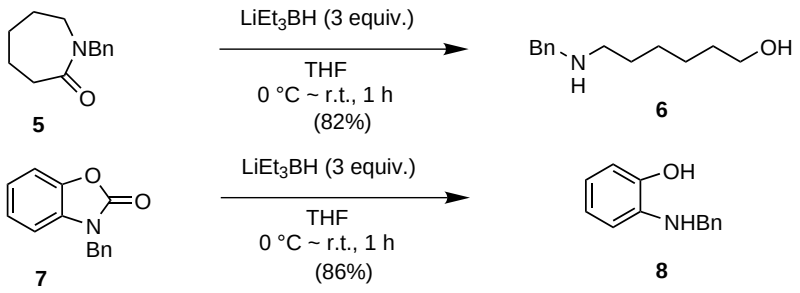
Scheme 2.

reaction conditions (Table 1: entries 4 and 5). A typical example of the reductive cleavage reaction of the tertiary amide is as follows: To a stirred solution of the benzamide **1g** (393 mg, 1.66 mmol) in THF (8.3 ml) was added lithium triethylborohydride (1 M in THF, 5 ml, 5 mmol) at 0°C and the stirring was continued for 1 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl followed by 1N NaOH and extracted with Et_2O. The extract was washed with brine, dried (K_2CO_3), evaporated under reduced pressure and chromatographed (SiO_2, elution with hexane/AcOEt 10:1) to give the secondary amine **2d** (218 mg, 99%) (Table 1: entry 7). The reductive cleavage of a cyclic tertiary amide **5** and a cyclic carbamate **7** also occurred readily to afford the corresponding *seco*-amines **6** and **8**, respectively, in good yields though extensive examination has not been carried out (Scheme 3).

It was also found that the reaction could be applicable to cleavage of the tertiary carbamates to give the corresponding secondary amines under the same conditions though the reaction was somewhat slower than the tertiary amide counterparts. However, the reaction proceeded at a much faster rate when the hydride/THF solution was added to a carbamate in a higher concentration (1 M in THF) as shown in the typical example below (Table 2). The cleavage reaction seemed to be very sensitive to the steric environment as the substrates

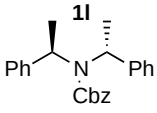
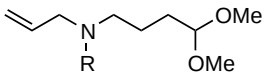
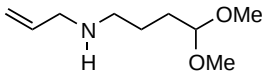
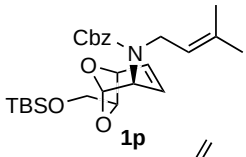
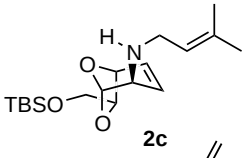
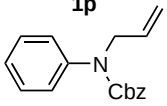
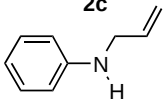
Table 1. Reductive removal of *N*-acyl groups with triethylborohydride

Entry	Substrate **1** (amide)	Product **2** (amine)	Yield (%)
1	$(C_8H_{17})_2N$–Ac **1a**	$(C_8H_{17})_2N$–H **2a**	76
2	 **1b**: R = Ac	 **2b**	90
3	**1c**: R = Bz	**2b**	96
4	 **1d**: R = Ac	 **2c**	81
5	**1e**: R = Bz	**2c**	98
6	 **1f**: R = Ac	 **2d**	93
7	**1g**: R = Bz	**2d**	99



Scheme 3.

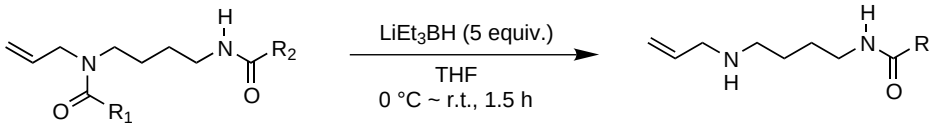
Table 2. Reductive removal of *N*-alkoxyacyl groups with triethylborohydride

Entry	Substrate (carbamate) **1**	Product (amine) **2**	Yield (%)
1	$(C_8H_{17})_2N–CO_2Me$ **1h**	$(C_8H_{17})_2NH$ **2a**	66
2	$(C_8H_{17})_2N–Cbz$ **1i**	$(C_8H_{17})_2NH$ **2a**	72
3	$Bn_2N–CO_2Me$ **1j**	Bn_2NH **2e**	43
4	$Bn_2N–Cbz$ **1k**	Bn_2NH **2e**	57
5	$Bn_2N–Boc$ **1l**	N.R.	–
6	 **1m**	N.R.	–
7	 **1n:** R = CO_2Me	 **2f**	92
8	**1o:** R = Cbz	**2f**	96
9	 **1p**	 **2c**	91
10	 **1q**	 **2d**	86

having bulky alkoxy or *N*-substituents were found to be inert under the conditions used (Table 2: entries 5 and 6). A typical example of reductive cleavage of a tertiary carbamate substrate is as follows: To a stirred solution of the carbamate **1o** (460 mg, 1.50 mmol) in THF (1.5 ml) was added lithium triethylborohydride (1 M in THF, 4.5 ml, 4.5 mmol) at 0°C, and the stirring was continued for 1 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl followed by 1N NaOH and methyl chlorocarbonate (0.23 ml, 3.0 mmol) (to isolate as the secondary amine as more readily isolable carbamate). After 1 h, the mixture was extracted with Et_2O and the extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure and chromatographed (SiO_2, elution with hexane/AcOEt 4:1) to give the methyl carbamate of the secondary amine **2f** (332 mg, 96%) (Table 2: entry 8).

In contrast, both the secondary amides and the secondary carbamates were virtually inert under the same reduction conditions and the substrates were recovered unchanged. Even under forcing conditions, the cleavage reaction did not proceed completely, giving only low yields of the primary amine products. The striking difference noted between the tertiary and the secondary *N*-acyl compounds toward lithium triethylborohydride prompted us to investigate the selective removal of a tertiary amide or tertiary carbamate functionality in the presence of a secondary amide functionality in the same molecule. Although there are limited examples, the cleavage occurred selectively at the tertiary amide center in the presence of 5 equiv. of the hydride to give the secondary amines without affecting the secondary amide functionality. As shown, the reaction occurred in a straightforward manner with four combinations of amides **9a–d** bearing either *N*-acetyl or *N*-benzoyl functionality and two bearing tertiary carbamates **9e–f** (Scheme 4).

In conclusion, it has been found that lithium triethylborohydride can selectively remove tertiary amide acyl functionalities regardless of the presence of aliphatic and aromatic amides to afford the corresponding secondary amines, whereas the reaction does not occur with secondary amides under the same conditions. Its efficacy and selectivity will make simple acyl functionalities convenient protecting groups for secondary amines.



9a: R_1= R_2= Me
9b: R_1= Me, R_2= Ph
9c: R_1= Ph, R_2= Me
9d: R_1= R_2 = Ph
9e: R_1= OMe, R_2= Ph
9f: R_1= OBn, R_2= Ph

10a: R= Me (97% from **9a**; 96% from **9c**)
10b: R= Ph (95% from **9b**; 95% from **9d**; 97% from **9e**; 88% from **9f**)

Scheme 4.

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