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N,N-Diethylaniline·Borane, an Efficient Reducing Agent for Reduction of Representative Functional Groups

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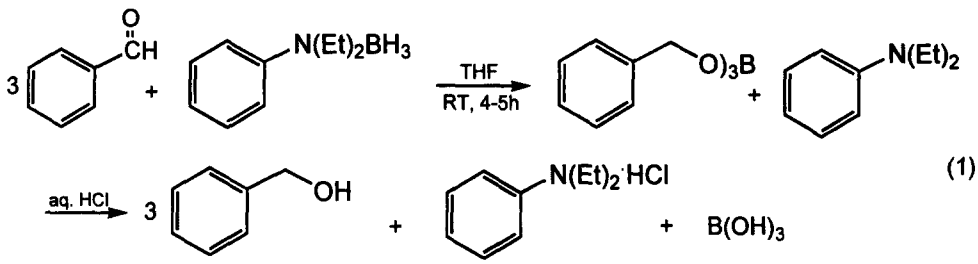
Abstract: *N,N-Diethylaniline·borane (DEANB), a thermally stable, commercially available, amine·borane reagent, reduces a variety of functional groups, such as aldehydes, ketones, carboxylic acids, tertiary amides, and lactams in excellent yields. It also reduces Schiff bases to the corresponding amines in very good yields. Besides these reducing properties, it readily hydroborates 1-octene to provide the trialkylborane which in turn on alkaline peroxide oxidation furnished the 1-octanol in excellent yield and usual regioselectivity.* © 1997 Elsevier Science Ltd. All rights reserved.

Amine borane complexes have been known for decades.[1] They possess a broad range of stability and reactivity; some are even stable in aqueous solution over extended periods of time. The solubility properties and mild reducing abilities of dimethylamine·borane and morpholine·borane lead to their use in the electronics industry as reducing agents in the manufacture of circuit boards[2] and electroless plating applications.[3] The utilization of amine borane complexes in organic synthesis, however has been relatively inactive since the late 1970's primarily because of their lack of reactivity towards organic functional groups.[4] In order to exploit the reducing characteristics of amine boranes such as pyridine·borane, acidic or harsh conditions are required.[5]

One set of amine borane complexes derived from *N,N*-dialkylanilines is significantly more reactive than most amine boranes. *N,N*-Diethylaniline is an inexpensive amine used in large quantities in the dye industry and can be easily converted to *N,N*-diethylaniline·borane (DEANB) for commercial applications. Periasamy and others have shown that this reagent is useful for hydroborations,[6] asymmetric reductions[7] and the preparation of boron triiodide.[8] To further expand its use as a hydride source, we have demonstrated that DEANB is a mild reducing agent for a number of functional groups. In this communication, we report preliminary results for the reduction of representative functional groups such as aldehydes, ketones, carboxylic acids, esters, tertiary amides, lactams and Schiff bases with commercially available[9] *N,N*-diethylaniline·borane in tetrahydrofuran.

Benzaldehyde (3 equiv.) reduction employing one equivalent of amine·borane reagent at room temperature was selected to compare the reactivity of pyridine·borane, ethyldiisopropylamine·borane, and *N,N*-diethylaniline·borane. This study revealed that the rate of reduction of benzaldehyde with *N,N*-diethylaniline·borane is faster than reduction with pyridine·borane or ethyldiisopropylamine·borane. Benzaldehyde reduction with pyridine·borane is very slow, only 30 % reduction in 18 h at room temperature as indicated by ^{11}B NMR spectroscopy. Ethyldiisopropylamine·borane reduced benzaldehyde in 16-18 hrs at room temperature in tetrahydrofuran, whereas with *N,N*-diethylaniline·borane the reduction was complete in 4-5 hrs, (Eqn. 1).



(1)

In addition all three hydrides of the *N,N*-diethylaniline·borane are available for the reduction of benzaldehyde. We then turned our attention to testing the efficacy and the generality of *N,N*-diethylaniline·borane for the reduction of variety of functional groups of variable structural requirements. The results are summarized in Table 1.

Table 1: Reduction of Representative Functional Groups with *N,N*-Diethylaniline·Borane (DEANB) in Tetrahydrofuran[a]

Entry	Reducible Compound	Product Obtained[d]	Ratio (BH_3:Cmpd)	Reaction Conditions (hr)	% Yield[e]
1	Benzaldehyde	Benzyl alcohol	1.1:3	RT (4-5)	85
2	2-Fluoro-4-bromo-benzaldehyde	2-Fluoro-4-bromo-benzyl alcohol	1.1:3	RT (4-5)	89
3	Acetophenone	*sec*-Phenethyl alcohol	1.1:3	Reflux (6-8)	90.5 (60)[f]
4	Cyclohexyl methyl ketone	1-Cyclohexylethanol	1.1:3	Reflux (25)	95[g] (88.5)[f]
5	Ethyl-4-bromobenzoate	4-Bromobenzyl alcohol	1:2	Reflux (45)	50.8[h]
6	Isopentyl acetate	Isoamyl alcohol	1:1	Reflux (16)	80[i]
7	Benzoic acid[b]	Benzyl alcohol	1:1	Reflux (2)	90
8	Decanoic acid[b]	Decyl alcohol	1:1	Reflux (2-3)	88.5
9	*N,N*-Dimethylbenzamide[c]	*N,N*-Dimethylbenzyl-amine	2.66:1	Reflux (7-8)	93.5[j]
10	δ-Valerolactam[b]	Piperidine	2.2:1	Reflux (7-8)	85.3[j]
11	$PhCH{=}N(CH_2)_3CH_3$	*N*-Butylbenzylamine	1.25:1	Reflux (8-9)	92[j]

[a]All reactions were carried out in tetrahydrofuran at 1.0 M concentration with respect to DEANB unless otherwise mentioned. [b] DEANB was added to the 1.0 M solution of substrate in tetrahydrofuran at room temperature and after hydrogen evolution ceased (0.25 h) the reaction mixture was refluxed. [c]DEANB was added to the refluxing 1.0 M solution of benzamide in tetrahydrofuran. [d]All compounds gave satisfactory spectral analysis. [e]Percent yield of the isolated products based on the amount of reducible compound used. [f]Reaction was carried out in presence of one equivalent of boron trifluoride etherate at room temperature. [g]Yield was determined by GC. [h]Based on recovery of the ester, the yield is 95.3 %. [i]Percent yield of isoamyl alcohol. [j]After the reduction, the reaction mixture was hydrolyzed with 6N HCl (reflux for ~ 1hr) and then cooled to room temperature and made strongly alkaline with KOH. Percent yield were determined by GC analysis using a suitable internal standard.

Aldehydes are readily reduced with this reagent at room temperature in a short period of time and excellent yields of the corresponding alcohols were realized (see Table 1). The haloaldehyde in entry 2 was

reduced to the corresponding alcohol without touching the halogen. Reduction of acetophenone is slow at room temperature (27 h with only 56 % completion as shown by ^{11}B NMR spectropscopy), however, in refluxing THF the reaction is complete in 6-8 hrs and a 90 % yield of the corresponding alcohol was isolated. Reduction of cyclohexyl methyl ketone in refluxing THF was quite slow. This rate difference in the reduction of benzaldehyde and acetophenone suggests that this reagent will selectively reduce aldehydes in the presence of ketones or other less easily reduced functional groups.[10]

In order to evaluate the effect of a Lewis acid, the reduction of acetophenone was carried out in presence of $BF_3{\cdot}OEt_2$[4b] at room temperature, only to realize a lower yield of the *sec*-phenethyl alcohol (60 %) in ~20 hrs. In contrast, reduction of cyclohexyl methyl ketone in presence of one equiv. of $BF_3{\cdot}OEt_2$ was complete in 20 hours at room temperature and corresponding alcohol was isolated in 88.5 % yield (entry 4).

Aliphatic and aromatic carboxylic acids are readily reduced by DEANB to the corresponding alcohols in very good yields in a relatively short period of time. A one to one ratio of reagents was used since one hydride is lost to acid hydroysis and two hydrides are required for the carbonyl reduction. As expected, reduction of esters is sluggish, requiring many hours at reflux. Ethyl-4-bromobenzoate was not completely reduced even after 45 hours of reflux. Reduction of isopentyl acetate was somewhat faster, see entry 6.

DEANB worked well for the reduction of *N,N*-dimethyl benzamide and δ-valerolactam giving the corresponding amines in very good yields. Greater than two equivalents were needed because of formation of the amine borane complex of the reduction product. The complete reduction of Schiff base was achieved with this reagent without using acidic medium. Thus, all the functional groups except esters were reduced in a relatively short period of time and in excellent yields under the selected conditions.

Even though Brown has thoroughly studied the hydroboration kinetics of amine borane complexes,[4c-e] we examined the hydroboration of 1-octene and cyclohexene with this reagent in tetrahydrofuran. As expected, hydroboration of three equivalents of 1-octene with one equivalent of DEANB was completed in 2 hrs at room temperature to give trioctylborane. Upon alkaline peroxide oxidation the trioctylborane provided 1-octanol in excellent yield (94 %). The expected regioselectivity (94:6) with the boron atom at the terminal position was observed during the hydroboration. Hydroboration of cyclohexene in refluxing THF (4 hrs) provided tricyclohexylborane which in turn yielded cyclohexanol (88 %). Reaction of a 2:1 ratio of cyclohexene and DEANB gave a 90 % yield of dicyclohexylborane.[11]

N,N-Diethylaniline·borane has certain advantages over the currently available borane reagents, such as borane·tetrahydrofuran and borane·dimethyl sulfide. Pure DEANB is 1) quite concentrated at 5.6 M, 2) thermally stable, 3) easily handled, and 4) not disagreeably odorous. Its slightly lower reactivity compared to these other commercially available borane reagents can be advantageously used for enantioselective reduction in the presence of oxazaborolidine catalysts, see the following article.

In conclusion, we have demonstrated the successful utilization of commercially available *N,N*-diethylaniline·borane for achieving the reduction of representative functional groups in excellent yields. It readily

reduces aldehydes, ketones, carboxylic acids, tertiary amides, lactams and Schiff bases in very good yields. This reagent enjoys certain advantages over the other commercially available borane reagents.

The following procedure for the reduction of acetophenone is representative: A dry 100 mL round-bottomed flask equipped with a magnetic stirring bar, septum inlet and reflux condenser was charged with a one molar solution of DEANB (20 mmols, 3.26 g) in tetrahydrofuran. Acetophenone (54 mmols, 6.49 g) was added to the amine borane at room temperature, then, the reaction mixture was refluxed for 6-8 hrs. The reaction was monitored by ^{11}B NMR spectroscopy. The reaction mixture was then cooled to room temperature, diluted with an equal volume of diethyl ether and carefully hydrolyzed with aq. HCl (3N, 10 mL, 0.5h). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined diethyl ether extracts were washed with 3N HCl (2 x 10 mL), water, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave *sec*-phenethyl alcohol in 90.5 % yield. The crude sec-phenethyl alcohol was purified by distillation. Spectral data were identical with an authentic sample.

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