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Aminoborohydrides. 9. Selective Reductions of Aldehydes, Ketones, Esters, and Epoxides in the Presence of a Nitrile Using Lithium *N,N*-Dialkylaminoborohydrides

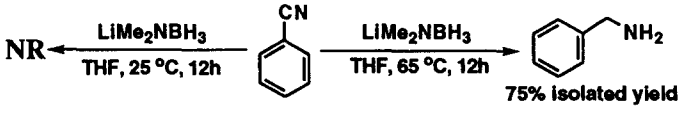
Christopher J. Collins, Gary B. Fisher, Adeena Reem, Christian T. Goralski,# and Bakthan Singaram*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, Santa Cruz, California 95064 and #Pharmaceutical Process Research, The Dow Chemical Company, Midland, MI. 48674

Summary: *A series of competitive reductions of several functional groups was carried out in the presence of aromatic and aliphatic nitriles using Lithium N,N-dimethylaminoborohydride ($LiMe_2NBH_3$) or Lithium Pyrrolidinoborohydride ($LiPyrrBH_3$) as the reducing agents. Both $LiMe_2NBH_3$ and $LiPyrrBH_3$ cleanly and quantitatively reduced aldehydes, ketones, esters, and epoxides in the presence of the nitriles to give the corresponding reduction products in yields ranging from 85 to 98%. In no case was the nitrile reduced: no products arising from the reduction of nitriles were detected by GC analysis. Two difunctional nitriles were also reduced to give complete reduction of the more active functional group with no reduction of the nitrile .*

The synthesis of primary amines is an important transformation in both synthetic[1,2] and medicinal[3-5] chemistry. Recently, we completed a study of the reductions of azides using lithium aminoborohydrides (LiR_2NBH_3),[6d,f] a new class of powerful, selective, non-pyrophoric reducing agents that can reproduce, in air, virtually all of the transformations for which lithium aluminum hydride ($LiAlH_4$) is now employed.[6] Both aliphatic and aromatic azides were reduced to the corresponding primary amines is nearly quantitative yields using a 1.5:1 ratio of LiR_2NBH_3 : azide. These results suggested that LiR_2NBH_3's might be a simple and effective route for the reduction of nitriles to the corresponding primary amines. Numerous methodologies for the synthesis of primary amines from nitriles exist in the literature.[7a,b] Since nitriles can be synthesized by essentially the same routes as azides, the reduction of nitriles is a useful adjunct to the reduction of azides for the creation of a homologous series of primary amines. We felt that the LiR_2NBH_3 reduction of nitriles would be a useful addition to existing methods for carrying out this transformation.

Benzonitrile was the initial substrate investigated in the LiR_2NBH_3 reduction of nitriles. The reduction was carried out with lithium *N,N*-dimethylaminoborohydride ($LiMe_2NBH_3$). Although benzonitrile was recovered quantitatively when the reduction was performed at room temperature, a 75% isolated yield of benzylamine was obtained when the reduction was performed in refluxing THF (eq. 1).



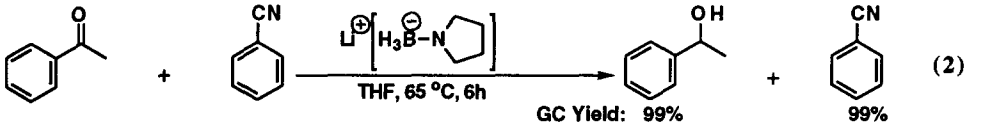
(1)

Encouraged by these results, the reductions of 1-octyl cyanide, cinnamonitrile, 3,7-dimethyl-2,6-octadiene-nitrile, and citronitrile were attempted. However, all of these nitriles were recovered essentially quantitatively under the conditions that had led to the successful reduction of benzonitrile. These results suggested the use of

LiR_2NBH_3's to carry out the selective reduction of more reactive functional groups in the presence of a nitrile. Consequently, we investigated the competitive reductions of aldehydes, ketones, esters, and epoxides, respectively, in the presence of various nitriles. The results of our study are presented herein.

The general procedure for the competitive reductions utilized a 1:1:1 molar ratio of nitrile:competing substrate: mesitylene as internal standard with 1.1-1.2 equivalents of LiR_2NBH_3 per mmol of nitrile. The reductions were carried out at 25 °C or 65 °C in anhydrous THF. Aliquots of the reaction mixture were removed hourly, quenched with 3M HCl (~5 eq. HCl/1 eq. of substrate), extracted with Et_2O, and analyzed by GC (50 m methyl silicate capillary column). In all cases, GC analysis indicated that the reductions were >99% complete after 6 hours.

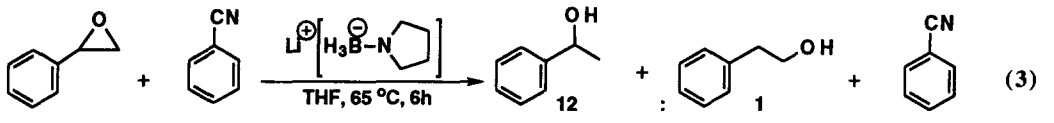
The initial competitive reductions were carried out with acetophenone and benzonitrile or ethyl benzoate and benzonitrile, respectively, using mesitylene as an internal standard. Since benzonitrile was found to be partially reduced under the reaction conditions used, benzonitrile was a particularly sensitive probe of the selectivity of these competitive reductions. For the competitive reduction of acetophenone and benzonitrile, GC analysis indicated the quantitative formation of *sec*-phenethyl alcohol while benzonitrile was recovered quantitatively after 6 hours with no trace of residual acetophenone or of benzylamine (eq. 2, **Table 1**).



(2)

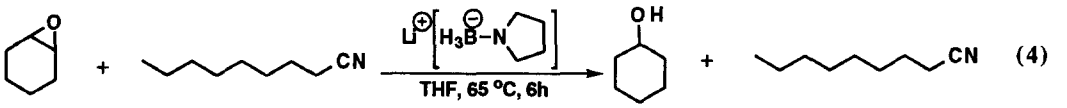
Similarly, analysis of the competitive reduction of ethyl benzoate with benzonitrile gave a 99% yield of benzyl alcohol and a quantitative recovery of benzonitrile. No ethyl benzoate or benzylamine was detected.

We then investigated the competitive reductions of nitriles and epoxides. When benzonitrile and styrene oxide were reacted with $LiPyrrBH_3$, a quantitative yield of *sec*-phenethyl alcohol and 2-phenyl-1-ethanol, in a 12:1 ratio,[6c] and benzonitrile was obtained (eq. 3, **Table 1**).



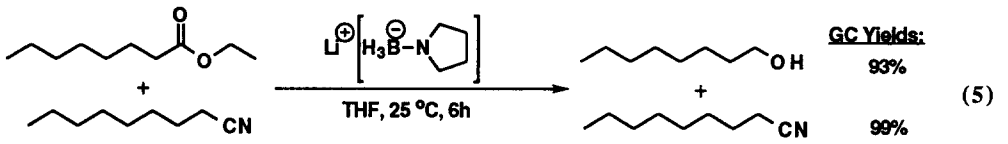
(3)

In contrast, the reduction of cyclohexene oxide in the presence of benzonitrile gave partial reduction of the benzonitrile and a quantitative yield of cyclohexene oxide, even in refluxing THF, thus delineating some of the limits of the selectivity of LiR_2NBH_3's in competitive reductions. However, since our initial results indicated that 1-octyl cyanide was not reduced by LiR_2NBH_3's under any conditions, the reduction of cyclohexene oxide in the presence of 1-octyl cyanide was carried out in refluxing THF. Under these conditions, cyclohexanol and 1-octyl cyanide were obtained in quantitative yields with no detectable amount of cyclohexene oxide or 1-octylamine present (eq. 4, **Table 1**).



(4)

Competitive reductions of esters with 1-octyl cyanide were carried out in THF at 25 °C using mesitylene as an internal standard. Thus, the reduction of ethyl octanoate in the presence of 1-octyl cyanide gave 1-octanol in 93% yield and a quantitative recovery of 1-octyl cyanide (eq. 5, **Table 1**).



(5)

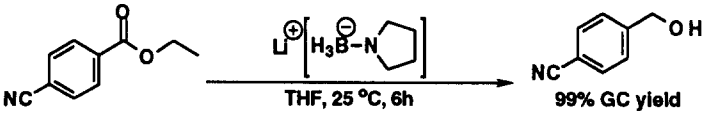
Similarly, the reduction of ethyl benzoate in the presence of 1-octyl cyanide gave an 84% yield of benzyl alcohol with no trace of nonylamine detected by GC analysis.

Table 1. Results of Selective Reductions of Various Functional Groups in the Presence of a Nitrile

Nitrile[a,b]	Competing[a,b] Substrate	LiR_2NBH_3[c,d]	% Recovery of Nitrile[f]	% Redn., Competing Substrate[e,f]	Reduction Product[e,f]
Benzonitrile	Acetophenone	$LiPyrrBH_3$	99[g]	99[g]	1-Phenyl-1-ethanol
Benzonitrile	Ethyl benzoate	$LiPyrrBH_3$	99[g]	99[g]	Benzyl alcohol
Benzonitrile	Styrene oxide	$LiPyrrBH_3$	99[h]	99[h,i]	1-Phenyl-1-ethanol[i] 2-Phenyl-1-ethanol[i]
1-Octyl cyanide	Cyclopentene oxide	$LiPyrrBH_3$	99[h]	99[h]	Cyclopentanol
1-Octyl cyanide	Cyclohexene oxide	$LiPyrrBH_3$	99[h]	99[h]	Cyclohexanol
1-Octyl cyanide	Ethyl octanoate	$LiMe_2NBH_3$	99[g]	93[g]	1-Octanol
1-Octyl cyanide	Ethyl benzoate	$LiMe_2NBH_3$	99[g]	84[g]	Benzyl alcohol

[a]Purchased from the Aldrich Chemical Co. and used without further purification. [b]A 1:1 molar ratio of nitrile:competing substrate was used in all reductions. [c]1M THF solutions of LiR_2NBH_3's were generated *in situ*.[4] as follows: (1) R_2NH + Me_2S:BH_3, 0 °C, 1h; (2) 2.5M *n*-BuLi, 1 eq., 0 °C -> 25 °C, 1h. [d]All reductions analyzed by GC were carried out on a 1 mmol scale; isolation-scale reductions were carried out on a 10 mmol scale according to literature precedent.[4] [e]Reductions were carried out in THF at 25 °C for 2-6h. [f]Determined by GC analysis (50m methyl silicate column) of the ethereal extract of the reaction mixture after quenching with 5 eq. 3M HCl. [g]Mesitylene used as an internal standard. [h]Isolation-scale reaction product identified by GC and 250 MHz ^1H- and ^{13}C-NMR. [i]The GC ratio of 1-phenyl-1-ethanol : 2-phenyl-1-ethanol was 12:1.

Finally, the competitive reduction of difunctional nitriles containing a second reducible functional group was investigated using 4-cyanobenzaldehyde and methyl 4-cyanobenzoate as substrates. In both cases, the nitrile functional group was not reduced while the aldehyde and ester functionality were quantitatively reduced to the corresponding alcohol (eq. 6).



(6)

The results of this study of the competitive reductions of various functional groups in the presence of aromatic and aliphatic nitriles using LiR_2NBH_3's further demonstrates the selectivity of LiR_2NBH_3's. LiR_2NBH_3's cleanly and quantitatively reduced aldehydes, ketones, esters, and epoxides in the presence of a nitrile in yields ranging from 85 to 98% with no detectable reduction of the nitrile. In difunctional nitriles, only the more reactive functional group was reduced, suggesting that LiR_2NBH_3's may be useful reagents for the synthesis or modification of natural products bearing both a nitrile group and a more reactive functional group. Although other reagents are capable of effecting the selective reduction of nitriles in the presence of other functional groups, LiR_2NBH_3's appear to offer the greatest selectivity. Thus, while $LiBH_4$ reduces aldehydes, ketones, esters and epoxides in the presence of nitriles, reductions of esters and epoxides require either extended refluxing or the use of catalysts such as triethyl borane or B-methoxy-9-BBN.[8a] Sodium borohydride[8c] and 9-BBN[8b] selectively reduce aldehydes and ketones, but not esters, in the presence of nitriles. Finally, $LiEt_3BH$[8d] and $LiAlH_4$[8e] are not selective in their reducing properties and reduce both the nitrile and the competing functional group in competitive reductions like those described in this paper.

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