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# Aminoborohydrides. 5. Reduction of Alkylcyclohexanones to the Corresponding Alcohols with Unique Steric Selectivity

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***Summary:*** *Lithium aminoborohydrides (LAB), obtained by the reaction of n-butyllithium with amineboranes, are powerful reducing agents for a wide range of functional groups including the carbonyl group of alkylcyclohexanones. Reduction of 2-methylcyclohexanone with LAB reagents shows superior formation of the axial alcohol as compared to sodium borohydride ($NaBH_4$). Reduction of 3- and 4-methylcyclohexanones shows formation of the equatorial alcohol in proportions similar to that obtained with $NaBH_4$. Reduction of 4-tert-butylcyclohexanone leads predominantly to the corresponding cyclohexanol containing an equatorial alcohol group. Unlike $NaBH_4$, LAB reagents are soluble in ether solvents allowing for homogeneous reductions.*

Synthesis of isomerically pure alkyl substituted cyclohexanols remains an interesting target because of their value in organic synthesis. This has led to the development of many stereoselective syntheses including Mitsunobu type inversion of substituted cyclohexanols.[1] These inversion reactions are tedious and often involve the use of large amounts of triphenylphosphine. More recent alternatives involve the reduction-epimerization of alkylcyclohexanones with heterogeneous metal reagents.[2,3] Unfortunately, these reagents display insufficient stereoselectivity in the formation of the substituted cyclohexanols and use metals such as nickel or chromium which represent an environmental concern. A direct reduction of the alkylcyclohexanones to the alcohol would be a preferable alternative. Such reductions of alkylcyclohexanones to the thermodynamically less stable axial alcohol have been achieved by hydride reagents.[4a,4b] Conversion of the axial alcohol to the equatorial alcohol may then be performed by inversion methods.[1] However, an efficient reduction of alkylcyclohexanones to the corresponding cyclohexanols containing an equatorial alcohol group has not been achieved. Herein, we describe the reduction of various alkylcyclohexanones with lithium aminoborohydrides (LAB) which give predominantly the corresponding substituted cyclohexanols containing an equatorial alcohol group.

Recently, we demonstrated that LAB reagents are powerful reducing agents, comparable in power to lithium aluminum hydride ($LiAlH_4$).[5a] LAB reagents, unlike $LiAlH_4$, are non-pyrophoric and thermally stable. LAB reagents are quantitatively prepared by the deprotonation of an amine-borane complex with *n*-butyllithium, as illustrated with pyrrolidine in (eq. 1).


(1)

Our initial study showed that a wide variety of substituted LAB reagents can be readily synthesized.[5] The potential for controlling steric selectivity by choosing the appropiate amine in different LAB reagents interested us. We have found that the steric requirements of different amine substitutions can dramatically alter the course of the reaction in the reduction of tertiary amides. For example, in the reduction of *N,N*-diisopropylbenzamide, lithium pyrrolidinoborohydride yields the corresponding alcohol while reduction with lithium diisopropylaminoborohydride yields the tertiary amine.[5b]

In order to study the difference in steric selectivity associated with different aminoborohydrides we reduced several alkylcyclohexanones (**1-4**) to the corresponding alcohols.

**1**

**2**

**3**

**4**

Our results show that LAB reagents offer excellent selectivity in the reduction of 4-*tert*-butylcyclohexanone under mild conditions to afford predominantly the corresponding alcohol containing the equatorial hydroxyl group.

Typically, the reduction of alkylcyclohexanones with complex borohydrides is performed at low temperatures to enhance stereoselectivity.[4] Initial studies with $LiBH_3NMe_2$, however, showed little difference in the *cis:trans* selectivity between reactions performed at -78 °C and those performed at 0 °C (**Table 1**).

**Table 1:** Percentages of equatorial alcohols from the reaction of $LiBH_3NMe_2$ with alkylcyclohexanones.[a,b]

| | Substituted Cyclohexanone | | | |
|---|---|---|---|---|
| T, °C | 1 | 2[c] | 3[c] | 4 |
| 0 | 64 | 92 | 89 | 95 |
| -78 | 59 | 93 | 92 | 98 |

[a] Reactions performed in THF with 12mmol aminoborohydride and 10 mmol ketone.
[b] Analysis by capillary GC. [c] Analysis performed on the acetylated alcohol.

Consequently, we chose to study the reduction of alkylcyclohexanones with a variety of lithium aminoborohydrides (**5-12**) at the more convenient temperature of 0 °C.[6]

$LiBH_3NMe_2$

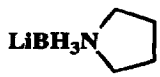
**5**

$LiBH_3N$-(*n*-Pr)$_2$

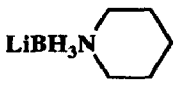
**6**

$LiBH_3N$-(*i*-Pr)$_2$

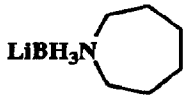
**7**



**8**



**9**



**10**

**11**

**12**

The *cis:trans* ratios of the resulting 2-methyl and 4-*tert*-butylcyclohexanols were determined by capillary GC analysis directly. However, analysis of the resulting 3-methyl and 4-methylcyclohexanols could not be performed directly since the diastereomers of these alcohols did not separate well on a Methylsilicone capillary column. Conversion of the alcohols to the less polar acetates facilitated their separation.[7] The results are presented in **Table 2.**

**Table 2.** Percentages of equatorial alcohols obtained with various LAB reagents.[a,c]

| LAB | Substituted Cyclohexanone 1 | 2[b] | 3[b] | 4 |
|---|---|---|---|---|
| 5 | 64 (73)[d] (75)[e] | 92 (88)[d] (84)[e] | 89 (89)[d] | 95 (87)[d] (89)[e] |
| 6 | 60 | 90 | 86 | 99 |
| 7 | 59 | 87 | 86 | 91 |
| 8 | 59 | 90 | 85 | 93 |
| 9 | 54 | 90 | 86 | 92 |
| 10 | 53 | 88 | 88 | 92 |
| 11 | 53 | 85 | 82 | 89 |
| 12 | 60 | 91 | 86 | 92 |

[a] Reactions performed at 0 °C, 10 mmol of ketone, 12 mmol of LAB reagent in THF. [b] Analysis of 3- and 4-methylcyclohexanol isomers was performed on the acetates. [c] Analysis on a 60 m, Methylsilicone column. [d] Percentage of alcohol obtained by sodium borohydride reduction. [e] Percentage of equatorial alcohol obtained with $LiAlH_4$.

The results summarized in **Table 2** indicate that LAB reagents give predominantly axial attack in the reduction of the relatively unhindered ketones, such as 3-methylcyclohexanone (**2**), 4-methylcyclohexanone (**3**) and 4-*tert*-butylcyclohexanone (**4**). For all of the ketones used in our study axial attack is preferred by small reducing agents, such as $LiAlH_4$.[8] However, reduction of these ketones with $LiAlH_4$ routinely gives a mixture of *cis*- and *trans*-alcohols.[8] On the other hand, the reduction of 4-*tert*-butylcyclohexanone (**4**) using $LiBH_3N$-(*n*-Pr)$_2$ (**6**) gives 99% of *trans*-4-*tert*-butylcyclohexanol, a substantial improvement over conventional methods which still require separation.

LAB reagents, like $LiAlH_4$, are soluble in ether solvents and are extremely reactive. However, LAB reagents, unlike $LiAlH_4$, are easy to handle, much like sodium borohydride ($NaBH_4$). Unfortunately, $NaBH_4$

is highly insoluble in the majority of ether solvents and thus must be handled as a slurry, which is at times inconvenient. When working in ether solvents, LAB reagents offer an excellent alternative to the insoluble $NaBH_4$ since they show similar selectivity in the reduction of alkylcyclohexanones. As shown in **Table 2**, $NaBH_4$ reduces 3-methylcyclohexanone and 4-methylcyclohexanone to the equatorial alcohol with 88% and 89% selectivity, respectively, values closely mimicked by LAB reagents.[9]

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## References and Notes

(1) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Mitsunobu, O. *Synthesis* **1981**, 1.
(2) Fort, Y.; Feghouli, A.; Vanderesse, R.; Caubere, P. *J. Org. Chem.* **1990**, *55*, 5911.
(3) Eliel, E. L.; Schroeter, S. H. *J. Am. Chem. Soc.* **1965**, *87*, 5031.
(4) (a) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *98*, 3383. (b) Yoon, N. M.; Kim, K. E. *J. Org. Chem.* **1987**, *52*, 5564.
(5) (a) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533. (b) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 1091.
(6) $LiBH_3NR_2$ (12 mmol) was added to a 100-mL flask, dissolved in THF (10 mL), and cooled to 0 °C. A 1.0M THF solution of the ketone was then added over 5-10 minutes and the reaction mixture allowed to stir for 1h. The solution was then quenched by addition of 3M HCl (16 mL, 48 mmol) and the solution stirred for 1h [*Caution: Hydrogen evolution*]. The reaction solution was then extracted with ether (3 X 20 mL) and the combined ether extracts were washed with 3M NaOH (1 X 20 mL). The organic phase was washed with water (1 X 10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure (25 °C, 20 Torr) leaving the crude alcohol which was used for the analysis.
(7) Either 3- or 4-methylcyclohexanol (1 mmol) was added to a 20-mL vial. Ether (10 mL) and pyridine (0.8 g, 10 mmol) were added. Acetyl chloride (0.4 g, 5 mmol) was then added very slowly. Upon addition of the acetyl chloride a white precipitate immediately formed. The vial was then allowed to stir (25 °C, 18h). The reaction mixture was then quenched by addition to 3M HCl (4 mL) and extracted with ether (2 X 4 mL). The ether solution thus obtained was then washed with 3M NaOH (1 X 2 mL) and then with water (1 X 4 mL). The ether solution was then diluted to give a final volume of 30 mL. GC analysis was conducted using 1μL samples of this solution.
(8) (a) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. (b) Catelini, G.; Monti, L.; Ugazio, M. *J. Org. Chem.* **1980**, *45*, 919. (c) Rei, M. H. *J. Org. Chem.* **1979**, *44*, 2760.
(9) (a) Wigfield, D. C.; Phelps, D. J. *J. Org. Chem.* **1976**, *41*, 2396. (b) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (c) Wigfield, D. C.; Phelps, D. J. *Can. J. Chem.* **1972**, *50*, 388.

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