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Lithium borohydride: a reagent of choice for the selective reductive amination of cyclohexanones

Shawn Cabral,[a,*] Bernard Hulin[a] and Makoto Kawai[b]

[a]*Department of Cardiovascular and Metabolic Diseases, Groton, United States*
[b]*Department of Medicinal Chemistry-2 G3, Nagoya, United States*

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Abstract—Traditional reductive amination of substituted cyclohexanones are either selective toward the formation of cis-products or show low selectivity. Herein we report a selective procedure for the reductive amination of substituted cyclohexanones with primary amines using lithium borohydride that is selective toward formation of trans-products.

Carbon–nitrogen bond forming reactions are critical to the synthesis of natural products and biologically active compounds. Of these reactions, the reductive amination of ketones to amines of known configurations is particularly useful. As our drug discovery program was confronted with the necessity to generate trans-4-substituted cyclohexylamine intermediate **2**, we decided to explore the possibility of selectively producing these isomers from the corresponding ketones. In the analogous reduction of substituted cyclohexanones to cyclohexanols, bulky hydride reagents provide axial alcohols and, in the absence of steric factors, small reagents such as sodium borohydride or lithium aluminum hydride give the more stable equatorial isomers.[1] In the reductive amination of substituted cyclohexanones, the axial attack of the imino group to give the equatorial amine has not been as successful.[2] Sodium borohydride is selective toward the formation of equatorial isomers but competes with reduction of the ketone to the alcohol,[3] a problem that can be avoided by the prior formation and isolation of the imine.[4] However, the reported selectivity from reduction of these imines has been moderate.[2] The use of other reagents such as sodium cyanoborohydride results in moderate equatorial selectivity[2] or may give the reverse selectivity toward the axial amines in a similar manner as bulkier hydride reagants such as sodium triacetoxyborohydride.[5] The reduction of substituted cyclohexanone oximes with sodium metal in ethanol is selective toward the equatorial isomers but it is not practical on large scale.[1] Herein, we report a convenient and selective procedure for the reductive amination of substituted cyclohexanones to the equatorial amines, suitable for development scale.

Sodium borohydride afforded the best conditions for a scaleable reaction. In order to avoid the cumbersome removal of water and the isolation of the intermediate imine, we increased the number of equivalents of benzylamine relative to ketone **1** as a means of shifting the equilibrium toward the formation of the imine. Thus, the reductive amination of the substituted cyclohexanone **1** using 3 equiv of benzylamine and sodium borohydride in methanol produced the desired secondary amine **2** with no detectable reduction of **1** to alcohol **3**. Lesser equivalents of benzylamine resulted in the formation of the alcohol by-product in varying amounts, which made purification difficult. In addition, performing the reduction with sodium borohydride at −30°C resulted in a better trans-selectivity than previously reported[1] (Scheme 1). The poor solubility of sodium borohydride in methanol at low temperatures prompted us to try lithium borohydride. Lithium borohydride solution in THF was added to the mixture of substituted cyclohexanone and the primary amine in methanol at −78 °C and the reaction mixture was allowed to slowly warm to room temperature.[6] The results show superior ratios of equatorial to axial amine products to those obtained using other reagents.[7]

The results from reductive amination of several substituted cyclohexanones with a variety of primary amines are summarized in Table 1. Lithium borohydride

* Corresponding author. Tel.: +1 860 715 1383; e-mail: shawn.cabral@pfizer.com

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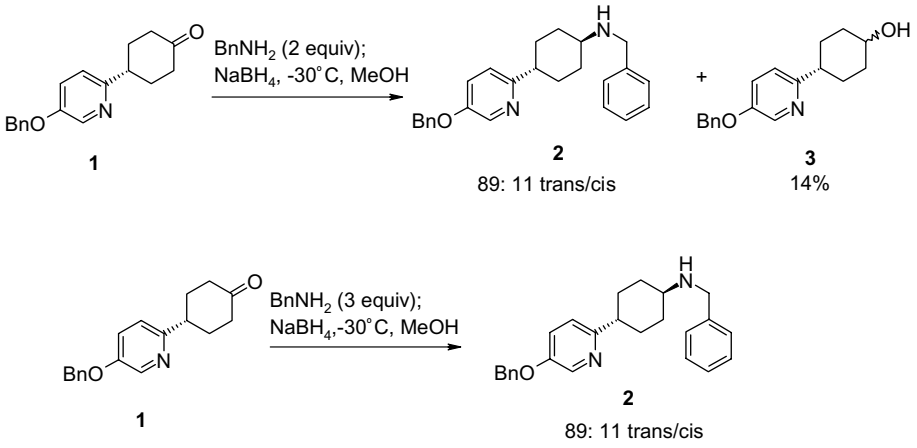
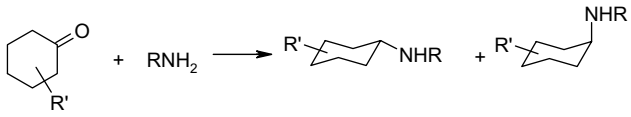
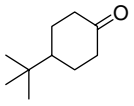
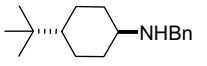
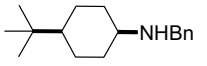
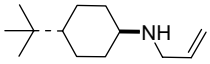
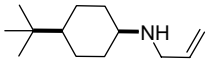
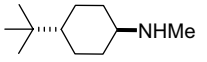
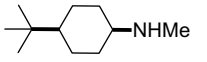
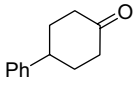
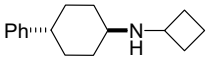
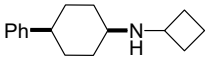
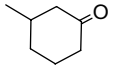
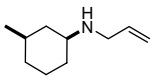
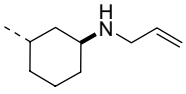
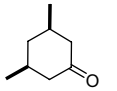
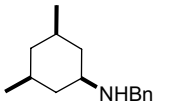
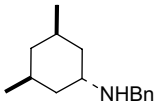


Scheme 1.

Table 1. Reductive amination selectivity using various borohydrides



Ketone	Amine	Products		Product ratio[a] (yield, %)			
		Equatorial amine	Axial amine	$LiBH_4$, −78 °C	$NaBH_4$, −30 °C	$NaBH_3CN$, 0 °C	$NaBH(OAc)_3$, 0 °C
	$BnNH_2$			92:8 (90)	83:17 (84)	73:17 (82)	31:69 (98)
	Allylamine			92:8 (65)	83:17 (85)	76:24 (95)	23:77 (99)
	$MeNH_2$			91:9 (76)	87:13 (77)	78:22 (75)	24:76 (85)
	Cyclobutyl-amine			93:7 (84)	75:25 (95)	69:31 (83)	25:75 (96)
	Allylamine			84:16 (73)	87:13 (36)	80:20 (68)	33:67 (42)
	$BnNH_2$			78:22 (81)	67:33 (91)	63:37 (86)	15:85 (82)

[a] Ratios determined by H NMR and GC–MS.

consistently gave better trans-selectivity than sodium cyanoborohydride.[8] It was also slightly more selective than sodium borohydride, the one exception being 3-methyl-cyclohexanone, where sodium and lithium borohydride reagents gave equivalent results. The lower selectivity with sodium cyanoborohydride and the cis-selectivity from sodium triacetoxyborohydride are consistent with the size of the hydride reagent being a controlling factor for the direction of hydride delivery.

The reductive amination procedure of substituted cyclohexanones with primary amines described herein for the synthesis of substituted cyclohexylamines provides better trans-selectivity than other methods previously reported. The use of excess amine shifts the ketone-imine equilibrium toward the imine, so that the presence of a dehydrating agent is not necessary. The borohydride preferentially adds from the axial direction particularly at low temperature. Lithium borohydride has the advantage over sodium borohydride in that

the reaction can be performed at −78 °C due to its better solubility in THF.

References and notes

1. Wu, Y.-D.; Houk, K. *J. Am. Chem. Soc.* **1987**, *109*, 908, and references therein.
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4. Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 3447–3450.
5. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
6. *Representative procedure for trans-N-benzyl-4-tert-butylcyclohexanamine*: Benzylamine (322 mg, 3.0 mmol) was added to a solution of 4-*tert*-butylcyclohexanone (154 mg, 1.0 mmol) in methanol (2 mL). The mixture was stirred at room temperature for 1 h, cooled to −78 °C, and treated with a 2 M solution of lithium borohydride in tetrahydrofuran (0.55 mL, 1.1 equiv). After stirring at −78 °C for 1 h, the mixture was slowly warmed to room temperature and stirred for 16 h. It was then partitioned between ethyl acetate (10 mL) and saturated sodium bicarbonate (2 mL). The aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic phases were washed with brine (5 mL), dried over magnesium sulfate, filtered, concentrated, and the residue was dried under high vacuum. The product was isolated as a colorless solid. (222 mg, 90%) ^{1}H NMR ($CDCl_3$) 7.37–7.22 (m, 5H), 3.83 (s, 2H), 2.45 (m, 1H), 2.05 (d, 2H), 1.75 (d, 2H), 1.15 (m, 2H), 1.00 (m, 3H), 0.82 (s, 9H).
7. The reducing agent in these reactions is probably borohydride itself rather than mono-, di-, or trimethoxyborohydride, since borohydride reacts slowly with methanol at low temperatures: Schlesinger, H. I.; Brown, H. C.; Hoekstra, H. R.; Rapp, L. *J. Am. Chem. Soc.* **1953**, *75*, 199–204, Switching the solvent to ethanol had no effect on the isomer ratio.
8. In most cases the ratio of trans-isomer was improved further upon formation of the hydrochloride salt.