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Selective Reduction of Oximes to N-Monosubstituted Hydroxylamines with Lithium Borohydride

Byung Tae Cho* and See Yearl Seong

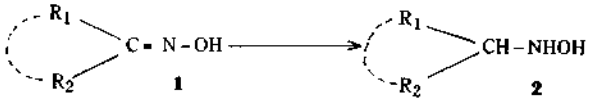
Department of Chemistry, Hallym University, Chunchon, 200-010. *Received July 1, 1988*

Selective reduction of aldoximes and ketoximes with lithium borohydride in tetrahydrofuran was investigated. Thus, aldoximes and cyclic ketoximes such as hexanaldoxime, heptanaldoxime, cyclopentanone oxime and cyclohexanone oxime were reduced smoothly to the corresponding N-monosubstituted hydroxylamines at room temperature in 65-93% yield. The reduction of alicyclic ketoxime was very slow, requiring somewhat high reaction temperature (65 °C) for the complete reduction to give the hydroxylamines. The reduction of aromatic oximes such as benzaldoxime and acetophenone oxime was very sluggish, giving a mixture of the corresponding hydroxylamines and amines at 65 °C.

Introduction

Lithium borohydride is a mild reducing agent which reduces only aldehyde, ketone and acyl chloride.[1] Recently, much efforts have devoted to selective reduction of organic functional groups with this hydride,[2] since it is soluble in organic solvent(diethyl ether or tetrahydrofuran) and simply prepared from the reaction of sodium borohydride and lithium chloride.[3]

There are many reports for the reduction of oximes with several kind of metal hydrides.[4-16] Of these reagents, only mild reducing agents such as borane,[4-5] pyridine-borane[8-9] and sodium cyanoborohydride[10-12] could accomplish the reduction of oximes **1** to give the corresponding N-monosubstituted hydroxylamines **3**. However, the reduction with borane required the restricted reaction condition to obtain



the desired hydroxylamines without over reduction. In the case of pyridine-borane, the reaction should be performed with excess reagent under strong acidic condition. On the other hand, cyanoborohydride could smoothly reduce oximes to the hydroxylamines, but the reduction of aldoximds is extremely pH-dependent.[17] To overcome these difficulties, therefore, we decided to investigate the reduction of oximes with lithium borohydride in tetrahydrofuran.

Results and Discussion

Procedure for Approximate Rate and Stoichiometry

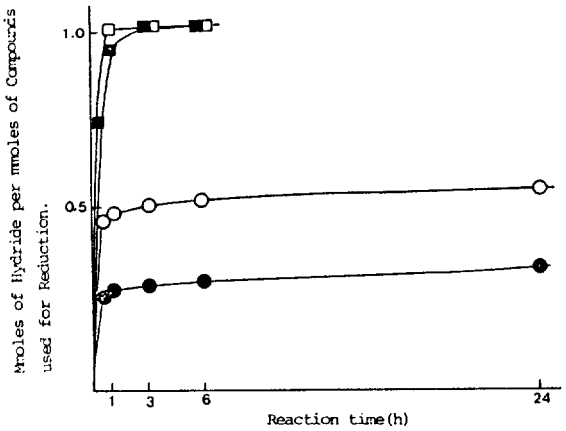


Figure 1. Reduction of cyclohexanone oxime with lithium borohydride in THF at R. T. (H^-/Cpd) = 1.0(●), 2.0(○), 4.0(■), 8.0(□).

Study. Cyclohexanone oxime was chosen as a representative oxime. It was treated with 2, 1, 0.5 and 0.25 molar equivalents of lithiym borohydride (i, e, 8, 4, 2 and 1 equivalents as hydride) in tetrahydrofuran. The reaction mixture was maintained at room temperature (ca. 25 °C). Hydrogen evolution following addition of the oxime to the reagent was measured. A blank reaction was run under identical conditions but without addition of the compound. At appropriate intervals of time, the aliquots were removed from the reaction mixture and analyzed for the remaining hydride by hydrolysis.[18] From the difference in yields of hydrogen in the two cases, the number of mmoles of hydride used by the compound for reduction was calculated.

Approximate Rate and Stoichiometry. Using 1 and 2 molar equivalents of lithium borohydride, the oxime took up 1 hydride rapidly (<3 h), with a second equivalent of hydride being taken up only quite slowly (1.03 hydride uptake for 24 h), liberating 1 equivalent of hydrogen. The result suggested that the reaction underwent to reduction of oxime to hydroxylamine stage selectively. In fact, N-cyclohexylhydroxylamine was isolated in the yield of 93% from this reaction. When the oxime was treated with 0.25 and 0.5 molar equivalents of lithium borohydride, the reaction proceeded in the same manner, but give incomplete hydride uptake. The results shown in Figure 1 indicated that at least 1 molar equivalent of lithium borohydride was required for the selective reduction.

Selective Reduction of Oximes to N-Monosubstituted Hydroxylamines. With 1 molar equivalent of lithium hydride, selective reduction for a series of oximes such as hexanaldoxime, heptanaldoxime, cyclopentanone oxime, 2-butanone oxime, 4-heptanone oxime, benzylacetone oxime, benzaldoxime, acetophenone oxime, α-tetralone oxime and benzophenone oxime was examined. The reduction was performed at room temperature at 65 °C in tetrahydrofuran. To isolate reaction products, the reaction mixtures were hydrolyzed with 2 normal methanolic hydrogen chloride, basified to pH 13 with 10% potassium hydroxide solution and then extracted by chloroform. As shown in Table, aldoxime **1 a-b** and cyclic ketoxime **1a-b** were reduced smoothly to the corresponding N-monosubstituted hydroxylamines **2a-d** at room temperature in 65-93% yields, whereas the reduction of alicyclic ketoximes **1e-g** was very slow, requiring the tetrahydrofuran reflux condition(65 °C) for the complete reduction to give the hydroxylamines **2e-g**. However, the reduction of aromatic oximes such as benzaldoxime and acetophenone oxime did not go to completion even after 48 h at room temperature. Under tetrahydrofuran reflux condition, the reaction did not undergo clearly to the corresponding hydroxylamine, giving a mixture of hydroxylamines and amines(overreduction products). α-Tetralone oxime and benzophenone oxime were not reduced even after 72 h at 65 °C. In

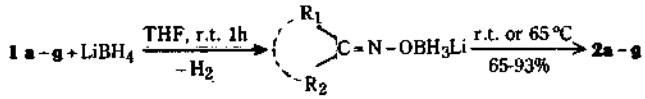


Table 1. Reaction of oximes with Lithium Borohydride in THF[a,b]

1	R_1	R_2	Reaction Time(h)	Yield(2) (%)	mp (°C)	mp(°C) reported	IR(KBr) ν(cm^{-1})	^{1}H-NMR($CDCl_3$/TMS) δ(ppm)
a	n-C_6H_{13}	H	3	65	63-64	62[5]	3270	0.85(t, 3H, CH_2CH_3), 1.4(m, 8H, 4×CH_2)
				60[c]	62-65		3150	2.67(t, 2H, CH_2CH_2N), 5.8(br s, 2H, NHOH)
b	n-C_7H_{15}	H	3	70	73-74	73.5[5]	3280	0.88(t, 3H, CH_2CH_3), 1.4(m, 10H, 5×CH_2)
							3150	2.7 (t, 3H, CH_2N), 5.9(br s, 2H, NHOH)
c	—$(CH_2)_4$—		6	90	92-94	95-96[10]	3270	1.3-1.9(br s, 8H, 4×CH_2), 3.43(m, 1H, CHNHOH)
							3150	6.2 (br s, 2H, NHOH)
d	—$(CH_2)_5$—		3	93	138-140	140[5]	3250	1.1-2.1(br s, 10H, 5×CH_2), 3.23(m, 1H, CHNHOH)
				83[c]	139		3120	6.1 (br s, 2H, NHOH)
e	C_2H_5	CH_3	12[d]	86	62-64	64-65[10]	3230	0.8-1.1(m, 6H, 2×CH_3), 1.3(m, 2H, CH_3CH_2)
							3110	2.75(m, 1H, CHNHOH), 6.2(s, 2H, NHOH)
f	n-C_3H_7	n-C_3H_7	18[d]	78	48-50	48-50[8]	3250	0.92(m, 6H, 2×CH_3), 1.5(m, 8H, 4×CH_2)
							3120	2.82(m, 1H, CHNHOH), 5.6(br s, 2H, NHOH)
g	n-$C_6H_5C_2H_4$	CH_3	20[d]	79	72-73	74-75[8]	3270	1.2 (d, 3H, $CHCH_3$), 1.5-1.7(m, 2H, CH_2CH)
							3150	2.7 (t, 2H, $phCH_2$), 2.92(m, 1H, CHNHOH)
								6.5 (br s, 2H, NHOH), 7.2 (s, 5H, $C_6H_5CH_2$)

[a]The reaction was carried out in tetrahydrofuran at room temperature, unless otherwise noted. The reaction mixtures were 1.0 molar solution both for **2a-g** and for **1**. [b]The products were isolated by hydrolysis with 2 normal methanolic hydrogen chloride. [c]The products were isolated by hydrolysis with 6 normal hydrochloric acid. [d]The reaction was carried out at 65 °C.

conclusion, this procedure provides a convenient method for the preparation of the corresponding N-monosubstituted hydroxylamine from readily available aliphatic oximes.

Experimental

General. All m.p.s are uncorrected. I. R. spectra were obtained with a Shimadzu IR-440 spectrophotometer and H n.m.r. spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as an internal standard. All glassware was dried at 140 °C overnight, assembled hot, and cooled to room temperature in a stream of nitrogen. All reactions involving air-sensitive materials were carried out under a static pressure of nitrogen. The liquids were transferred with dry syringes or double-ended needles.[18]

Materials. Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under a nitrogen atmosphere in an ampule. Lithium borohydride was prepared by the known method.[3] Cyclopentanone oxime (Ic), cyclohexanone oxime (Id), 2-butanone oxime (Ie), benzaldoxime and acetophenone oxime were purchased from commercial sources. The other oximes were prepared from the corresponding carbonyl compounds with hydroxylamine hydrochloride in ethanol pyridine or sodium carbonate solution.

Approximate Rates and Stoichiometry Study. The reduction of cyclohexanone oxime is representative. An oven dried, 10 m*l* flask with a side arm, fitted with a rubber cap, a magnetic stirring bar, and a reflux condenser connected to a gas burette was cooled down to room temperature under a stream of nitrogen. Into the flask, lithium borohydride (4 mmol) in THF (2 m*l*) was introduced, and the solution of cyclohexanone oxime (4 mmol) in THF (2 m*l*) was added slowly at room temperature (ca. 25 °C). A blank reaction was performed under identical condition, but without addition of compound. When the reaction mixture was maintained at room temperature, it was observed 100 m*l* of hydrogen evolution and this corresponds to 0.97 mmol of compound. After 3 h, the reaction mixture was hydrolyzed with 2 normal sulfuric acid. 211 m*l* of hydrogen evolution was measured, corresponding to 2.04 mmol per mmol of compound. The difference, 1.98 mmol (4.02-2.04 = 1.98), represents the number of hydride used per mmol of the compound (oxime). Therefore, the number of mmol of hydride used for reduction per mmol of compound is 1.01 (1.98-0.97 = 1.01). Hydride uptake for reduction at different intervals of time was calculated by the exactly same manner, giving 0.74 mmol at 0.5 h, 0.95 mmol at 1.0 h. and 1.03 mmol at 24 h. Using 2, 0.5 and 0.25 molar equivalents of lithium borohydride, rates and stoichiometry for reduction was determined by the same manner as described above. The results are summarized in Figure 1.

Selective Reduction of Oximes to N-monosubstituted hydroxylamines. The reduction of cyclohexanone oxime is representative. Into the reaction flask, lithium borohydride (10 mmol) in THF (5 m*l*) was introduced. To this, the solution of cyclohexanone oxime (10 mmol) in THF (5 m*l*) was added slowly at room temperature. Hydrogen (10 mmol) was evolved immediately (<1 h). The reaction mixture was maintained at room temperature. After 3 h, THF was removed in vacuo, and then hydrolyzed with 2 normal methanolic hydrogen chloride (15 m*l*) at 10-15 °C for 3 h. After methanol was removed under reduced pressure, the residue was dissolved in water (5 m*l*), basified to pH>13 with 10% potassium hydroxide solution, saturated with sodium chloride, and extracted with chloroform (3 × 2 m*l*). The combined extracts were dried over anhydrous magnesium sulfate, and evaporated in vacuo to give solid. One recrystallization from n-pentane afforded N-cyclohexyl hydroxylamine (1.07g, 93% yield), m.p. 138-140 °C (lit[5]. 140 °C). IR (KBr) ν_{max} = 3250 cm^{-1} (NHOH), ^{1}H-NMR (60 MHz, $CDCl_3$/TMS): δ= 1.1-2.1 (brs, 10H, 5 CH_2), 3.23(m, 1H, CHNHOH), 6.1(brs, 2H, NHOH).

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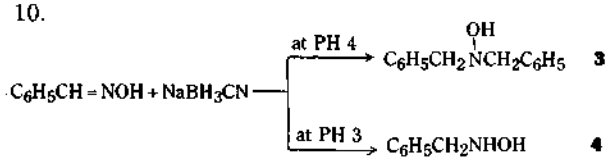
17. Reduction of benzaldoxime with sodium cyanoborohydride at pH 4 gave dialkylhydroxylamines **3**. However, at pH 3, the aldoxime was reduced to give the monoalkylhydroxylamines **4** as the major products: see ref. 10.



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