

Simple Reduction of Various Ketones with Sodium Tetrahydroborate and Alumina in Hexane†

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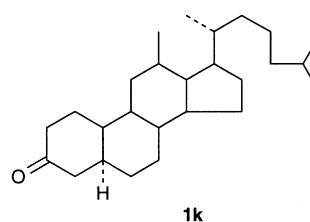
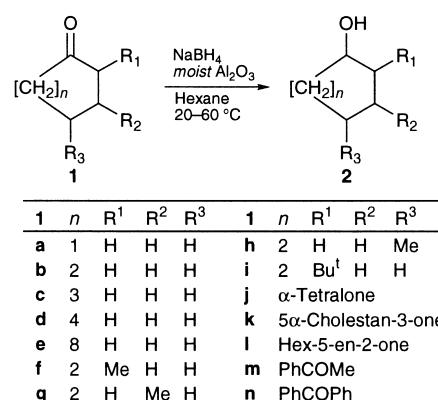
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A combination of NaBH₄ and alumina preloaded with a small amount of water is a highly efficient reducing agent for cycloalkanones, substituted cyclohexanones and unsaturated and aromatic ketones in hexane, affording the corresponding alcohols in excellent yields under mild conditions (20–60 °C).

There are many reagents and methodologies available for the catalytic and stoichiometric reduction of a broad range of functional groups.¹ Sodium tetrahydroborate (NaBH₄) is one of the most extensively employed hydride donors,² owing to its mild reducing capability and versatility. In addition, its insensitivity to moisture and relatively easy exchangeability of the Na⁺ ion for other cations (Li⁺, Ca²⁺, Ba²⁺, Zn²⁺, Al³⁺, Sn⁴⁺)² to produce agents with different reducing power, chemo- and/or stereo-selectivities make NaBH₄ very attractive as a major laboratory synthetic reagent.^{2,3}

Recently, we have observed that *in situ* generated alumina-supported reagents can be successfully used for the selective oxidation of sulfides,^{4a–c} alcohols,^{4d,e} and ketones^{4f} and the regioselective nuclear monochlorination of activated arenes^{4g,h} in water-free media. The remarkable ability of alumina to catalyse the reactions under mild conditions led us to investigate the reduction of organic compounds with a combination of NaBH₄ and alumina. Although alumina-supported NaBH₄ reagents are known to effect reductions^{5,6} and some of these are now available from commercial sources (Aldrich, Fluka, etc.), their preparation is time-consuming (*i.e.* a few hours' thorough mixing of alumina and aqueous NaBH₄, followed by overnight drying *in vacuo*)^{5b} and commercial reagents are rather expensive. Consequently, it is of value to provide a convenient reduction method based on the use of NaBH₄ under solid-solution biphasic conditions by taking advantages of our *in situ* method.^{4,7}

The reduction of a ketone **1** was carried out instantly by efficiently stirring a heterogeneous mixture of NaBH₄, **1**, and hexane under a dry atmosphere in the presence of chromatographic neutral alumina preloaded with the optimum amount of water (moist alumina; *vide infra*). The reaction was clean and did not suffer from the formation of any by-product, and therefore essentially pure alcohol **2** was obtained simply by filtration of the insoluble materials and removal of the solvent from the combined filtrate and washings. The applicability of the NaBH₄/moist alumina system for typical ketones is summarised in Scheme 1 and Table 1. Thus, simple C₅–C₁₂ alicyclic ketones **1a–e** (Entries 1–5), substituted cyclohexanones **1f–j** (Entries 6–10), and aromatic ketones **1m** and **1n** (Entries 13 and 14, respectively) were readily reduced to afford the corresponding alcohols in excellent to quantitative yields under optimum conditions. Successful reduction of the steroidal ketone **1k** (Entry 11) and the unsaturated ketone **1l** (Entry 12) might extend the utility of the current procedure. Independent reactions of



Scheme 1

cyclohexanone **1b**, 2-methylcyclohexanone **1f**, and 2-*tert*-butylcyclohexanone **1i** under the conditions of Entry 2 showed that their conversions were 100, 78, and 44%, respectively, clearly indicating that their apparent reactivities towards NaBH₄ decrease as the substituents adjacent to the

Table 1 Reduction of ketones to the alcohols with NaBH₄ and moist alumina in hexane^a

Entry	Ketone	NaBH ₄ (mmol)	T/°C	t/h	moist Al ₂ O ₃ /g	Alcohol (%) ^b
1	1a	0.3	20	1	0.5	2a (97)
2	1b	0.3	20	1	0.5	2b (92)
3	1c	0.3	20	3	0.5	2c (quant.)
4	1d	0.5	30	3	1.0	2d (quant.)
5	1e	0.6	60	3	0.5	2e (98)
6	1f	0.4	30	3	1.0	2f (87)
7	1g	0.3	20	1	0.5	2g (93)
8	1h	0.3	20	1	0.5	2h (91)
9	1i	0.8	40	3	1.5	2i (quant.)
10	1j	0.5	30	3	1.0	2j (quant.)
11	1k	0.3	40	3	0.5	2k (96)
12	1l	0.3	40	3	0.5	2l (quant.)
13	1m	0.3	40	3	0.5	2m (98)
14	1n	0.4	60	3	0.5	2n (98)
15 ^c	1n	16	60	3	10	2n (quant.)

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^aKetone **1** mmol, hexane 10 ml. ^bIsolated yield of **2** based on the starting **1**. ^cBenzophenone **1n**: 40 mmol (7.28 g), hexane 50 ml, and ether washing (5 × 30 ml) were used.

carbonyls (R^1 in Scheme 1) increase in size. This fact might suggest that the steric hindrance of the alkyl groups plays an important role in determining the reactivities of the ketones. The current procedure can favorably be compared to the reduction with the preformed alumina-supported NaBH_4 reagent.^{5b} Indeed, the reduction of benzophenone **1n** gave benzhydrol **2n** in superior yield (98%) to that obtained by the earlier procedure, in which crude **2n** was obtained in 88% yield.^{5b} Finally, an attempted reduction of **1n** on a large (40 mmol) scale was accomplished successfully (Entry 15).

In conclusion, the *in situ* generated alumina-supported NaBH_4 reagent serves as a convenient, inexpensive and high-yielding reduction system for various ketones under mild conditions.

Experimental

General.—The ^1H NMR spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer for solutions using deuteriochloroform with TMS as an internal standard. Analytical gas chromatography was performed on a Shimadzu GC-14B instrument with a 2 m \times 4 mm diameter column packed with 5% PEG-20 M on Chromosorb WAW-DMCS, with temperature programming. Mass spectra were determined on a JEOL SX-102A mass spectrometer coupled to a Hewlett-Packard GC5890 Series II GC apparatus via a heated capillary column.

Starting Materials.—Hexane was rigorously dried (CaCl_2), distilled and stored over molecular sieves. Commercial NaBH_4 was ground to a fine powder in a dry-box and stored in a desiccator. Ketones **1a–n** were available from commercial sources and used without further purification. Moist alumina (water content 10 wt%) was prepared by adding deionised water (0.05 g) to predried (500 °C, 6 h) alumina (ICN BIOMEDICALS, Alumina N, Super I; 0.45 g) in portions, followed by vigorous shaking of the mixture on every addition for a few minutes until a free-flowing powder was obtained, which was immediately used for the reduction.

Typical Reduction Procedure.—A heterogeneous mixture of benzophenone **1n** (1 mmol; 0.182 g), hexane (10 ml), finely ground NaBH_4 (0.4 mmol; 0.151 g) and freshly prepared moist alumina (0.5 g) in a 30 ml round-bottom flask was vigorously stirred for 3 h at 60 °C. The cooled reaction mixture was transferred onto a sintered glass funnel, and the filter cake thoroughly washed with portions of dry diethyl ether (*ca.* 60 ml). Removal of the solvent from combined clear filtrate on a rotary evaporator gave satisfactorily pure (GC, NMR, and TLC) benzhydrol **2n** in 98% yield (0.180 g); mp 63.2–63.8 °C (lit.,⁸ mp 65–67 °C).

The reductions of ketones **1a–m** with the NaBH_4 /moist alumina system were performed under conditions determined in terms of their reactivity and the yield of **2**, followed by the normal work-up, afforded alcohols **2a–m**, which were fully characterised by spectroscopic comparisons (IR, NMR, and MS) with commercial authentic samples. It is noteworthy that although certain ketones and alcohols have only limited solubilities in hexane under the conditions employed, the reduction of the ketones and work-ups of the products were readily achieved. A large-scale reduction of **1n** was

carried out under the conditions indicated in Entry 15 to afford **2n** quantitatively.

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