POTASSIUM BOROHYDRIDE: IMPROVED USE AS A REDUCING AGENT FOR ORGANIC AND ORGANOMETALLIC KETONES

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Abstract:
Two improved methods for the use of potassium borohydride as reducing agent for organic and organometallic ketones have been developed and are suggested for routine use. One of these is based on the formation of *in situ* generated lithium borohydride in aqueous solution, and gives good yields for organic ketones and moderate yields for organometallic ketones. The second method is based on the stabilization of borohydride ion by basic alumina, and gives good yields for both organic and organometallic ketones (substrates which, in general, are not well reduced by alkali metal borohydrides), except for aryl ferrocenyl ketones.

Introduction:

Alkali metal borohydrides are useful reagents for the reduction of ketones and aldehydes to the corresponding alcohols. The most extensively used reagent is sodium borohydride[1-3,5,10].

If selectivity or modification of reactivity is desired, sodium borohydride may be modified, e. g. with a cyano group (cyanoborohydride)[1,2,4], reaction with alcohols to form alkoxyborohydrides [1-3] or by addition of main group or transition metal salts[1,2,12]: $ZrCl_4$, $CeCl_3$ [2], $BiCl_3$ [6], $ZnCl_2$ [7].

When a highly reactive borohydride is desired, lithium borohydride may be used[1,10].

Sodium borohydride is generally used in THF, methanol, ethanol, isopropanol, dioxane or diglyme solutions , with or without benzene or dichloromethane[2] as co-solvents. It may also be anchored to alumina or silica gel[2]. The main deficiencies of these procedures are low solubility of the reagent (diglyme and dioxane solutions) or decomposition of part of the reagent, due to slow reaction with the solvent (methanol or ethanol solutions).

A better, more facile and more currently used procedure involves reduction with an aqueous ethanol solution of sodium borohydride in presence of excess of sodium hydroxide (borohydrides are more stable in basic solutions[5]).

Although used for reduction of inorganic substrates[9], potassium borohydride is much less used in organic chemistry [6] because it does not possess the same degree of reactivity and is less soluble in organic solvents.However, it has some advantages: it is not so hygroscopic, and is much more easily stored. In our laboratory, samples are stored in a well closed vial, but without special protection against moisture (without dessicator) and are stable for years.

It is thus desirable to combine these advantages with some suitable method for augmenting the level of reactivity of potassium borohydride.

Results and Discussion:

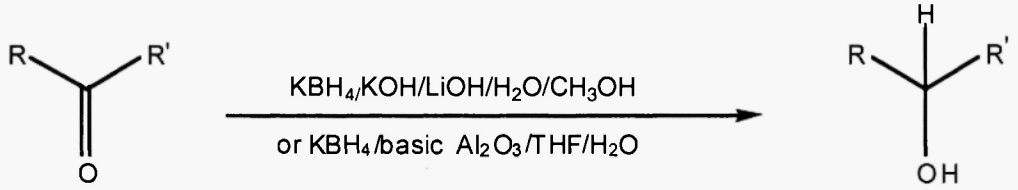
In the course of our current work on synthesis of organic and organometallic compounds, we have developed two improved procedures for the reduction of carbonyl groups, involving the use of potassium borohydride (Scheme 1)

In method I , the reactivity of potassium borohydride is increased by formation of lithium borohydride in the reaction mixture (from the potassium borohydride and lithium ions[10]). The carbonyl compound (organic ketones or aldeydes, organometallic ferrocenyl

ketones- **1** to **6**) is treated with $KBH_4/KOH/LiOH/H_2O/CH_3OH$, giving the corresponding alcohols (**7-12**) (Table I)

SCHEME 1

REDUCTION OF ORGANIC AND ORGANOMETALLIC KETONES



(1) R = CH_3 R' = Fc
(2) R = CH_2CH_3, R'= Fc
(3) R = Ph, R' = Fc
(4) R = CH_3, R' = CH_3
(5) R = Ph, R' = CH_3
(6) R = Ph, R' = Ph

(7) R = CH_3 R' = Fc
(8) R = CH_2CH_3, R'= Fc
(9) R = Ph, R' = Fc
(10) R = CH_3, R' = CH_3
(11) R = Ph, R' = CH_3
(12) R = Ph, R' = Ph

TABLE I

REDUCTION OF ORGANIC AND ORGANO-METALLIC KETONES WITH $KBH_4/KOH/LiOH/H_2O/CH_3OH$ - METHOD 1

Ketone (mmol)	Reducing agent (mmol of KBH_4)	Product number	Yield (%)	M.p. or B.p. (°C)
1 (2)	2-6[a]	**7**	36-65[c]	77 (lit. 78-79[11,15], 70-72[15], 77-78 and 81[23])
2 (2)	2-6[a]	**8**	42-58[c]	liq. b.p. not determined (lit. liq.,b.p. 80-90, 0,4 mm/Hg)[24]
3 (2)	2-6[b]	**9**	62-64[c]	77-79 (lit. 78-80, 81-82)[15]
4 (5)	2.5[b]	**10**	84	liq., b.p. 55-56 (lit. 56)[22]
5 (5)	2.5[b]	**11**	99	liq. b.p. 84-85,15 mm/Hg (lit. 204, 760 mm/Hg, m.p. 20.7)[22]
6 (10)	5-10.4[b]	**12**	98-100[d]	64-67(lit. 69)[22]

[a]Slight to large excess
[b]Stoichiometric or slight excess
[c]Dependent on the quantity of the reducing agent
[d]Several runs

For ferrocenyl ketones as substrates, the yields are lower then in other cases, though still moderate to high (≅ 65%). Maximum yields of alcohols are obtained, only if excess of reducing agent is used. However, they are comparable (20-64%) or better then the results obtained with sodium borohydride reported in other studies[13,15]. Indeed, it has been generally accepted that borohydrides are not good reducing agents for ferrocenyl ketones[11,16] There is only one report of a high yield reduction of an aryl ferrocenyl ketone by a large excess of sodium borohydride[14] but it was not confirmed by other workers[15].

Considering the various reports, our technique using the $KBH_4/KOH/LiOH/H_2O/CH_3OH$ system for the reduction of organometallic ketones is valuable.

Furthermore, our results with organic ketones as substrates are very satisfactory, giving high to almost quantitative yields of alcohols.

The second method (method II) involves stabilisation of potassium borohydride with basic alumina. The organic or organometallic ketones (**1** - **6**) are treated with potassium borohydride and basic alumina, suspended in aqueous THF, for 36 hs., at room temperature, giving the corresponding alcohols (**7**-**12**, Table II).

TABLE II
REDUCTION OF ORGANIC AND ORGANOMETALLIC KETONES WITH KBH_4 (BASIC ALUMINA/THF/H_2O) - METHOD II

Ketone (mmol)	Reducing agent (mmol of KBH_4)	Product number	Yield (%)	M.p. or B.p. °C
1 (4)	5.6[a]	**7**	82	77 (lit. 78-79[11,15], 70-72[15], 77-78 and 81[23])
2 (2)	2.8[a]	**8**	85	liq. b.p. not determined (lit. liq.,b.p. 80-90, 0,4 mm/Hg)[24]
3 (2)	2.8[a]	**9**	-[b]	-[b]
4 (5)	7.0[a]	**10**	97	liq., b.p. 54-56 (lit. 56)[22]
5 (5)	7.0[a]	**11**	91	liq. b.p. 82-86,15 mm/Hg (lit. 204, 760 mm/Hg, m.p. 20.7)[22]
6 (4)	5.6[a]	**12**	97-100[c]	64-68, 65-67(lit. 69)[22]

[a]Ketone/KBH_4 molar ratio 1:1.4, mass of alumina = mass of ketone
[b]Starting material recovered unchanged.
[c]Several runs

The yields are excellent, even better than with method I and with classical $NaBH_4$ techniques: up to 99 %. However the method is not applicable to aryl ferrocenyl ketones: They were not reduced even at reflux temperature.

These two procedures are routinely used in our laboratory.

It is convenient to add some recent results obtained during the preparation of this manuscript. (β-Dimethylaminoethyl)(4-chlorophenyl)ketone was reduced in 97% yield, by the KBH_4/KOH/LiOH/H_2O/CH_3OH system (method I) during a research project for new synthetic methods for histamine antagonists. Also, citronellal (an aldehyde from citronella oil) was converted to the corresponding alcohol, citronellol, in 70 % yield (based on the starting quantity of citronella oil) during a project of research on new insecticides. A third example involves the reduction of ferrocenyl aldehyde using method II, in 96% yield.

These examples demonstrate the general applicability of our procedures.

We recommend the use of one or both procedures for routine reductions of organic ketones and aldehydes; the procedure of KBH_4 / alumina / THF /H_2O (method II) for alkyl ferrocenyl ketones and ferrocenyl aldehydes. For the aryl ferrocenyl ketones, the method of KBH_4/ KOH/ LiOH/ H_2O/CH_3OH gives moderate yields, but in our hands, they are better reduced by $LiAlH_4$ [11,16,17,20] or modified aluminum hydrides (DIBAL-H, Red-Al)[11], in very high yields (up to 95%) in THF and almost quantitative yields (92-100%) in ethyl ether. The $LiAlH_4$ reduction is, in this case, a complementary procedure. The protocol is based on the Harimoto & Haven[16], Hamilton[20] and Gokel & Ugi[11] methods, but acetone is used to decompose the excess hydride in place of water or ethyl acetate. The yields in THF are slighly lower than in ethyl ether.

Materials and Methods - Experimental:

Potassium borohydride (Aldrich), neutral alumina (Merck, type: Aluminum oxide 600 neutral for thin layer cromatography), lithium hydroxide (Merck), potassium hydroxide, organic ketones are commercial products, used without purification.

Ferrocene (Aldrich) was recrystallized from 95 % ethanol, prior to use.

Organometallic ferrocenyl ketones (aryl and alkyl) were prepared by an improved $AlCl_3$ catalysed Friedel δ Crafts acylation[18] or by a new technique developed by us, using Friedel & Crafts acylation, catalysed by BF_3 etherate[19].

A - Basic Alumina:

Neutral alumina (Al_2O_3) was stirred for 12 hs. with 2% sodium hydroxide solution and washed with water until the washings were free of hydroxide ion; filtered off under vacuum and dried in air, then activated by heating in an oven at 100°C for 4 hs.

This method of treatment of alumina gives especially good results, though commercial grades of basic alumina may be used, with slighly lesser yields. Neutral alumina was not effective.

B - Procedure for Reductions Using $KBH_4/KOH/LiOH/CH_3OH/H_2O$ System (Method I):

Lithium hydroxide monohydrate (0.1 g) and 5 mmol of KBH_4 were added to a solution of 30 mmol of KOH in 20ml of water. The resulting solution contained 1 mmol of KBH_4 in 4 ml.

To the appropriate amount of this reduction mixture (Table I), the ketone (**1-6**) was added, previously dissolved in 1 ml of methanol for each mmol.

After stirring at room temperature for 4 hrs., the excess of hydride was destroyed with acetone (water was used for compound **4**), and the product was extracted with ethyl ether. The organic extracts were washed with water, dried over sodium sulphate and evaporated (this was omitted in the case of the highly volatile compound **10**) The residue was distilled, if liquid, or recrystallized if solid.

By this procedure we have prepared: methyl ferrocenyl carbinol (**7**), ethyl ferrocenyl carbinol (**8**) phenyl ferrocenyl carbinol (**9**), isopropanol (**10**), 1-phenyl-1-hydroxyethane (**11**), benzhydrol (**12**).

C- Procedure for Reduction Using the KBH_4/basic alumina/THF/ water (Method II):

To a suspension of basic alumina (prepared as in A) in THF/H_2O 4:1 v.v. (4 ml of solvent for each gram of alumina), solid KBH_4 was added (Table II), followed by the appropriate amount of the ketone (**1-6**). The quantity of alumina used was the same as that of the ketone. The mixture was stirred for 36 hrs, , the solid was filtered off, washed with THF/H_2O 4:1 mixture, acetone was added(water for compound **4**), organic solvents were removed under vacuum and the alcohol extracted with ethyl ether. After a work up, similar to that described in B, the following products were isolated: methyl ferrocenyl carbinol (**7**), ethyl ferrocenyl carbinol (**8**), isopropanol (**10**), 1-phenyl-1-hydroxy ethane (**11**), benzhydrol (**12**). Compound **9** was not obtained by this method. The starting ketone (**3**) was recovered unchanged, even when the reaction was carried out under reflux.

D- Reduction of Aryl Ferrocenyl Ketones with $LiAlH_4$:

For ferrocenyl ketones, technique B and conventional reduction with $NaBH_4$ give only moderate yields. Procedure C is better, but does not reduce aryl ferrocenyl ketones.

For this type of ketone we recommend the following modification of reported procedures[11,16,20]. 4 mmol of the ketone (**3**) was dissolved in 7-10 ml of anhydrous ether (THF is also satisfactory, but gives somewhat lesser yields) and cooled in ice. To this solution, 1-2 mmol of solid $LiAlH_4$ was added. The mixture was allowed to attain ambient temperature and stirred for 3-4 hs, then cooled, acetone was added in order to decompose excess of hydride, the mixture was then poured into saturated NH_4Cl solution. The alcohol was isolated by extraction with ethyl ether, the organic extracts dried over anhydrous $MgSO_4$ and vacuum evaporated. 92-100% yields of the practically pure phenyl ferrocenyl carbinol (**9**) were obtained.

E - Characterization of the structure of the compounds obtained:

All the compounds obtained are known, but are important. For example, ferrocenyl carbinols are starting materials for ferrocenyl catalysts and benzhydrol is an intermediate in synthesis of the anti-histaminic Diphenylhydramine and related compounds. The synthesis of these known compounds demonstrates the generality of our methods.

All the compounds gives IR, ^1H - NMR, ^{13}C - NMR spectra in accordance with the expected structure and with literature data.[11, 14-17,20-32]

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