A Most Simple Hydroboration Procedure

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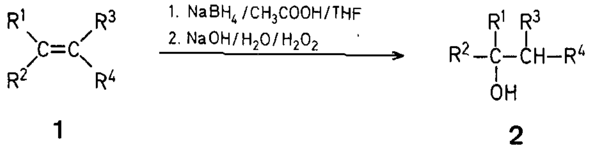
Hydroboration of alkenes to form alkylboranes and their subsequent oxidation by hydrogen peroxide to alcohols is currently one of the most widely utilized synthetic reactions. Its characteristic features are: anti-Markovnikov *cis*-hydration of the double bond, and, in the case of cycloalkenes substituted at the double bond, predominant or exclusive formation of a *trans*-alcohol[1,2]. The key reagent, diborane, can be either introduced into the reaction mixture from an external source or formed *in situ* in the reaction mixture itself. Understandably, exploitation of the latter possibility has received considerable attention[1,2,3]. Sodium borohydride in conjunction with a strong mineral acid (sulfuric, hydrochloric) or Lewis acid [boron trifluoride, aluminium chloride, titanium(IV) chloride and the like] is the most commonly utilized source of diborane for this purpose. However, hygroscopicity, corrosivity, and toxicity of these acids preclude them from being classified as attractive reagents, particularly for larger-scale preparations. This is witnessed by continuing efforts to introduce more advantageous forms and sources of diborane like dimethyl sulfide-borane[4] and tetraalkylaminium boranate[5].

In this note we present results of our study on a hydroboration procedure which by virtue of its simplicity of execution, nature of reagents applied, acceptable level of yields, and apparent generality may be superior to procedures in common use.

Ten years ago, Marshall and Johnson[6] noted that treatment of 1-hexene with sodium borohydride and acetic acid followed by alkaline hydrogen peroxide led to the formation of 1-hexanol in 75% yield. No other olefins were studied. This result, despite its practical synthetic implications has not received any further attention. We investigated its usefulness with a series of representative alkenes using the experimental procedure of Marshall and Johnson[6]. Yields of the expected alcohols formed are summarized in the Table.

However, it became apparent that the procedure had the disadvantage of requiring excessive and wasteful amounts of reagents. The hydration of 0.1 mol of olefin required 0.2 mol of sodium borohydride instead of the usual 0.033 or 0.05 mol when mineral acid (e.g. hydrochloric) is used in conjunction with borohydride[1]. Also, 0.5 mol of sodium hydroxide and 0.5 mol of hydrogen peroxide were used in the oxidation stage in contrast to the standard 0.1 mol.

We have now developed a procedure in which only equivalents or slight excess of reagents are used, similarly as in other common hydroboration procedures.

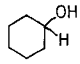
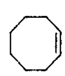
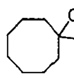
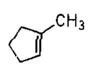
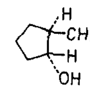
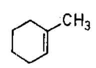
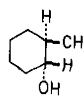
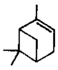
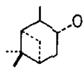


$$\underset{\mathbf{1}}{R^1R^2C{=}CR^3R^4} \xrightarrow[2.\ NaOH/H_2O/H_2O_2]{1.\ NaBH_4/CH_3COOH/THF} \underset{\mathbf{2}}{R^1R^2C(OH){-}CHR^3R^4}$$

Yields of corresponding alcohols (**2**) formed when using 0.037 mol of sodium borohydride and acetic acid for 0.1 mol of 1-hexene, cyclohexene, and cyclooctene and 0.055 mol of sodium borohydride and acetic acid for 0.1 mol of 1-methylcyclopentene, 1-methylcyclohexene and α-pinene are shown in the Table. In all cases only 0.1 mol of sodium hydroxide and 0.12 mol of hydrogen peroxide were applied in the oxidation stage. Surprisingly, these yields are higher than yields obtained when using the excess of sodium borohydride originally applied by Marshall and Johnson[6]. In addition, we found that it is unnecessary to use tetrahydrofuran distilled from lithium aluminium hydride; reagent-grade solvent dried over a molecular sieve was sufficient.

In order to obtain comparison of the present method with classical hydroboration procedures in regard to stereospecificity of product formation we subjected to G.L.C. analysis[8] crude products from the hydroboration of 1-methylcyclopentene and 1-methylcyclohexene. In the crude product from the hydroboration of the former we observed 3.1% of *cis*-2-methylcyclopentanol and 1.9% of 1-methylcyclopentanol whereas Brown et al.[7] found only "traces" of the *cis*-alcohol and 1.5% of the tertiary alcohol. Crude *trans*-2-methylcyclohexanol contained 1.5% of *cis*-2-methylcyclohexanol and 2.5% of 1-methylcyclohexanol. This compared favourably with results of Brown et al. who observed 0.8% and 1.5%, respectively. In both cases the latter authors used gaseous diborane in tetrahydrofuran. Thus, with the exception of the discrepancy between our and Brown's observation regarding *cis*-2-methylcyclopentanol it would appear that the present hydroboration procedure is capable of rendering the same degree of stereospecificity as the classical procedure utilizing gaseous diborane.

Table. Hydroboration of Alkenes (**1**) with Sodium Borohydride and Acetic Acid in Tetrahydrofuran

	Alkene **1**[a]	Alcohol **2**	Yield[b] (%) A[c]	B[d]
a	n-C_4H_9–CH=CH_2	n-C_6H_{13}–OH	75[e]	82
b			77	85
c			78	92
d			63	76[f]
e			72	78[f]
f	 α-pinene	 isopinocampheol	68	77

[a] All starting materials were of commercial origin. Their quality was established by G.L.C.[8] and where necessary they were purified by distillation to a purity of 97% or better.

[b] Reported yields refer to isolated, purified (distillation), identified (b.p., m.p. N.M.R.), and analyzed (G.L.C.) substances. In most cases, standard samples from other sources were available for comparison. Yields estimated by G.L.C. of crude products were in the 90–95% range.

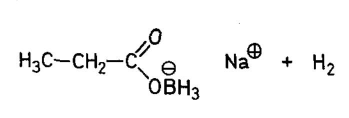
[c] Yields obtained using the procedure of Marshall and Johnson, see Ref.[6].

[d] Yields obtained by the present procedure.

[e] Yield reported by Marshall and Johnson[6].

[f] For a detailed discussion of stereochemistry of product formation, see text of paper.

Nature of the reactive species involved in this method of hydroboration remains unclear. Brown and Subba Rao[9] have suggested that in diglyme sodium borohydride and propanoic acid most probably react as follows.



$$H_3C{-}CH_2{-}COOH + NaBH_4 \longrightarrow H_3C{-}CH_2{-}C(=O){-}\overset{\ominus}{O}BH_3\ Na^{\oplus} + H_2$$

According to Marshall and Johnson[6], this species could either add directly to the olefin, convert into another species capable of the same, or, finally, generate free diborane. The first possibility is not easily reconciled with the orbital symmetry-allowed mechanism of hydroboration proposed recently[10]. Regarding the third possibility, Brown et al.[11] have shown that free diborane reacts fast with free carboxylic acids even at 0°; however, very little is known about the mechanism and its intermediates[12]. If under the present experimental arrangement free diborane was indeed involved one would expect acetic acid to compete with the alkene (**1**) for diborane available in solution and this would, most probably, lead to a substantially lower yield of alcohol (**2**).

Also, we found that the present procedure is strongly solvent dependent. We thought that the use of diglyme, in which borohydride is better soluble than in tetrahydrofuran, would enable a homogeneous reaction system and better control during the hydrogen evolution period. Surprisingly, when the hydroboration of α-pinene was carried out in diglyme under conditions successfully applied with tetrahydrofuran, only a ~15% yield of the expected isopinocampheol was obtained.

Hydroboration of Alkenes; General Procedure:
All equipment to be used is oven-dried. So is sodium borohydride, usually 2–3 h are sufficient. Starting alkene and tetrahydrofuran are dried over a molecular sieve, 3A or 4A. Other methods may be applied, however. Acetic acid is kept anhydrous by the addition of 2% of acetic anhydride. The starting olefin (0.1 mol) is placed in a flask equipped with a magnetic stirrer, calcium chloride tube, nitrogen inlet, and dropping funnel. Sodium borohydride (0.037 or 0.055 mol, depending on the starting olefin, see Ref.[4]) is placed in the flask and tetrahydrofuran (250 ml) is added at once. The dropping funnel is charged with a solution of acetic acid (0.037 or 0.055 mol, corresponding to the amount of borohydride) in tetrahydrofuran (50 ml). The flask is placed in a water-ice bath and throughout the reaction sequence the temperature is kept in the 10–20° range. The flask is continuously purged with dry nitrogen and a careful addition of the acetic solution is started. Addition of the solution is completed within 1 h and the reaction mixture is stirred for another 2 h. A solution of sodium hydroxide (4 g) in water (20 ml) is cautiously added, followed by a 30% solution of hydrogen peroxide (14 ml). Stirring is continued for another 2 h during which period the reaction mixture separates into two layers. The organic layer is separated and the lower aqueous phase is extracted with ether (3 × 25 ml). The ether extract is added to the tetrahydrofuran layer and the combined phase is dried with sodium sulfate. The solvents are evaporated and the residue obtained is distilled in vacuo to give the product. Generally, major portions of the *cis* and tertiary alcohols formed from methylcyclopentene and methylcyclohexene are easily removed in the forerun.

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[8] The accuracy of our G.L.C. analysis was estimated to be ±0.3%; column 1/8″ × 15′, 10% diglycerol on Chromosorb P, 30–60 ml nitrogen/min at 90–120°. Starting materials were analyzed under similar conditions using 10% Carbowax 20 M on Chromosorb P.

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