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ORGANOBORANES FOR SYNTHESIS. 3. OXIDATION OF ORGANOBORANES WITH AQUEOUS CHROMIC ACID. A CONVENIENT SYNTHESIS OF KETONES FROM ALKENES VIA HYDROBORATION[1,2]

HERBERT C. BROWN* and CHANDRA P. GARG[3]

Richard B. Wetherill Laboratory, Purdue University
West Lafayette, Indiana 47907 USA

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Abstract - Organoboranes react with alkaline hydrogen peroxide to provide a wide variety of alcohols. These alcohols can be taken up in ether solvent and converted without isolation into the corresponding ketones by treatment with chromic acid. Organoboranes can also be oxidized directly with chromic acid to the corresponding ketones. The chromic acid oxidation of organoboranes provides a new, convenient procedure for the synthesis of α-substituted cycloalkanones via hydroboration. The conversion of organoboranes into ketones proceeds through the intermediate alcohol. Representative cycloalkanones and α-methylcycloalkanones have been prepared from the corresponding alkenes via hydroboration, followed by chromic acid oxidation.

The rapid, quantitative addition of diborane to alkenes makes readily available a wide variety of organoboranes which are exceedingly useful in organic synthesis.[4] Alkaline hydrogen peroxide reacts quantitatively to oxidize organoboranes to alcohols under suitable conditions (eq 1).[1,4]

$$R_3B + 3\ H_2O_2 + NaOH \longrightarrow 3\ ROH + NaB(OH)_4 \qquad (1)$$

It has been reported that the hydroboration of conessine, followed by chromic acid oxidation in aqueous acetic acid, provided 3β-dimethylaminoconanin-6-one.[5] Since organoboranes are susceptible to protonolysis in the presence of acetic acid, but are stable in aqueous mineral acids,[6] we undertook to explore the utility of aqueous chromic acid for the conversion of organoboranes into ketones.

RESULTS AND DISCUSSION

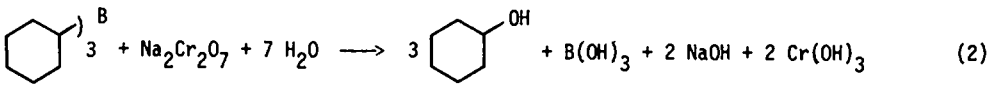
Initially, the possibility of a two-stage oxidation was investigated in which the alcohol would be produced by the oxidation of organoborane with alkaline hydrogen peroxide and then be oxidized *in situ* with chromic acid. The oxidation of secondary alcohols with chromic acid has been thoroughly examined as to the stoichiometry, effect of solvent, and of temperature.[7] Use of ethyl ether, which is also a common hydroborating solvent,[4a,8] is convenient for the chromic acid oxidation of secondary alcohols to ketones. Other ethers and ketone solvents were less satisfactory and pentane and benzene formed severe emulsions.[7]

The results with secondary alcohols indicated that the chromic acid oxidation using ethyl ether offers major advantages for the preparation of ketones capable of undergoing further oxidation or epimerization under the usual oxidation conditions. Evidently the immiscible ether layer extracts the ketone formed and protects it from further oxidation and epimerization.

Because of the excellent results realized in ethyl ether, this solvent was examined for its utility in the oxidation of organoboranes.

Two-Stage Oxidation of Organoboranes to Ketones. Cyclohexene was hydroborated in ethyl ether to the organoborane. This was oxidized by alkaline hydrogen peroxide to the alcohol.[1] Without isolation, the alcohol product was further oxidized to ketone with chromic acid. Cyclohexanone was obtained in 80% yield.

Direct Oxidation of Organoboranes With Chromic Acid. It was of interest to explore the possibility of avoiding the intermediate step of oxidation with hydrogen peroxide. An attempted oxidation of tricyclohexylborane in tetrahydrofuran with an excess (10% excess over the quantity required to oxidize the borane to ketone) of sodium dichromate (without added sulfuric acid) for 1 h at 35-40°C afforded cyclohexanol in 25% yield (eq 2). Apparently such oxidation reaction was very slow. Consequently, the emphasis was placed on the chromic acid oxidation.



$$3 + Na_2Cr_2O_7 + 7\ H_2O \longrightarrow 3 + B(OH)_3 + 2\ NaOH + 2\ Cr(OH)_3 \qquad (2)$$

The reaction of trialkylborane with a stoichiometric amount of chromic acid, just enough to produce alcohol, provided a mixture of alcohol and ketone, indicating that organoboranes are transformed to ketones via alcohols and also that the reaction cannot be stopped cleanly at the alcohol stage. Since the rapid oxidation of organoboranes with alkaline hydrogen peroxide affords nearly quantitative yields of the corresponding alcohols without any difficulty (eq 1), the possibility of oxidizing organoboranes to alcohols using sodium dichromate or chromic acid was not explored further. It has been proposed that the oxidation of organoboranes with chromic acid at pH 3-7 can be stopped cleanly at the alcohol stage.[9]

In view of the successful oxidation of secondary alcohols to ketones in ether medium with aqueous chromic acid, representative organoboranes were oxidized under similar conditions (eq 3).

$$(RR'CH)_3B + 2\ Na_2Cr_2O_7 + 8\ H_2SO_4 \longrightarrow 3\ RR'C{=}O + B(OH)_3 + 2\ Cr_2(SO_4)_3 + 2\ Na_2SO_4 + 8\ H_2O \qquad (3)$$

The results are summarized in Table 1.

Table 1. Oxidation of Organoboranes With Aqueous Chromic Acid in Ethyl Ether at 25-30°C

Alkene	Alkylborane	Ketone	Yield,[a] %
cyclopentene	R_3B	cyclopentanone	62
cyclohexene	R_3B, R_2BH	cyclohexanone	62-63
cyclooctene	R_2BH	cyclooctanone	49
norbornene	R_3B	norcamphor	51
1-methylcyclopentene	R_2BH	2-methylcyclopentanone	83
1-methylcyclohexene	R_2BH	2-methylcyclohexanone	87(78)
1-methylcyclohexene[b]	R_2BH	2-methylcyclohexanone	85
1-phenylcyclohexene	RBH_2	2-phenylcyclohexanone	60[c](55)
α-pinene	R_2BH	isopinocamphone	72[d](65)

[a] Determined by GC; values in parentheses indicate the isolated yields. [b] The hydroboration was carried out using sodium borohydride and a catalytic amount of zinc chloride. [c] 12% of 1-phenylcyclohexene was present. [d] 10-12% of the epimer, pinocamphone, was present.

It should be noted that simple cycloalkenes were transformed to the corresponding cycloalkanones in 49-63% yields. On the other hand, 2-methylcycloalkanones were obtained in distinctly superior yields (80-87%). The difference in yields can be attributed to the possible further oxidation of cycloalkanones with chromic acid, whereas, such a reaction is resisted by the steric effect of α-methyl group in the case of 2-methylcycloalkanones.

Mechanism of Chromic Acid Oxidation. The oxidation of organoboranes with alkaline hydrogen peroxide has proven to be of immense value.[4] The mechanism of this reaction has been established based on kinetic data.[10]

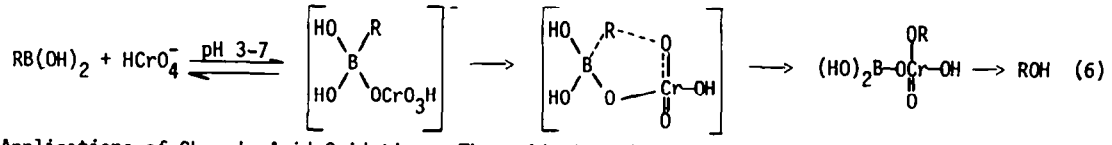
Chromic acid has been used as an oxidizing agent for well over a century and the most acceptable mechanism is that proposed by Westheimer.[11] According to this mechanism, chromic acid oxidation involves a rapid, reversible, acid-catalyzing esterification of the alcohol, followed by a slow oxidation step. Accordingly, a two-step oxidation of organoborane with chromic acid to ketone via the intermediate alcohol can be postulated as shown in eq 4. The oxidation of alcohol to ketone then proceeds according to Westheimer's mechanism (eq 5).[11]

$$R_3B + HCrO_4^- \rightleftharpoons \left[R_2\overset{R}{\underset{|}{B}}{-}OCrO_3H\right]^- \longrightarrow R_2B{-}OR \xrightarrow{H_2O} ROH + R_2BOH \qquad (4)$$

$$RR'CHOH + HCrO_4^- + 2\ H^+ \rightleftharpoons RR'CHOCrO_3H_2 + H_2O \xrightarrow{:B} RR'C{=}O + BH^+ + H_2CrO_3 \qquad (5)$$

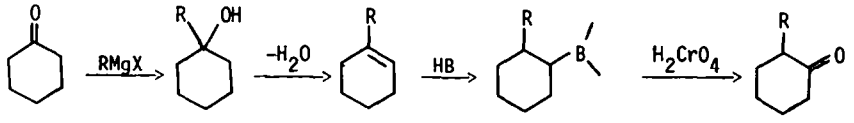
The formation of alcohols via chromic acid oxidation of organoboranes proceeds with the retention of configuration, as was realized by the controlled oxidation of bis(*trans*-2-methylcyclohexyl)-borinic acid to *trans*-2-methylcyclohexanol. This is consistent with the retention of configuration analogous to that observed in the hydrogen peroxide oxidation of organoboranes.[10] More recently, the chromic acid oxidation of alkylboronic acids has been studied by Ware and Traylor[9] from the

kinetic and mechanistic point of view. These workers report that the reaction proceeds through a mechanism similar to that of the hydrogen peroxide oxidation (eq 6).



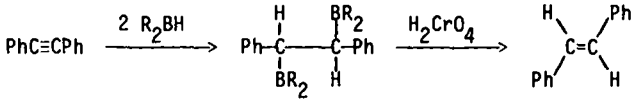
Applications of Chromic Acid Oxidation. The oxidation of secondary alcohols with chromic acid in ether medium provides the corresponding ketones in high yields and excellent purities. This procedure offers special promise for the synthesis of ketones susceptible to epimerization during the usual oxidation conditions.

The chromic acid oxidation of organoboranes provides a convenient method for the preparation of α-alkyl- or α-arylcycloalkanones from cyclic ketones, thus providing a new regiospecific method for the α-alkylation of ketones (eq 7).



The chromic acid oxidation of organoboranes has already been employed for organic synthesis. Thus, *cis*-bicyclo[4.2.0]oct-7-ene has been converted into the corresponding ketone.[12] The method has also been successfully applied for the synthesis of 3β,20β-diacetoxypregnan-6-one[13] and the C_{16} musk compound, 8-cyclohexadecen-1-one.[14] The conversion of norbornene to norbornanone proceeds without rearrangement,[15] whereas, hydroboration-chromic acid oxidation of norbornadiene is not clean. However, norborn-5-ene-2-one could be obtained by a two-stage oxidation.[16] Likewise, the direct oxidation of the organoborane obtained from α-pinene afforded isopinocamphone containing a considerable amount (10-12%) of its epimer (pinocamphone) (Table 1). This difficulty was circumvented by following the two-stage oxidation procedure.[7] A relatively large-scale application (1 mol) of this one-stage hydroboration-oxidation has been described. *endo*-5,6-Trimethylene-8-norbornene has been hydroborated and oxidized to a mixture of *endo*-5,6-trimethylene-9-norbornanone and -8-norbornanone, readily separated with sodium bisulfite.[17]

The organoborane obtained from diphenylacetylene provides *trans*-stilbene instead of the expected diketone upon treatment with chromic acid (eq 8).[18]



CONCLUSIONS

The present study reports a simple procedure for the conversion of secondary alcohols conveniently obtained via the hydroboration of alkenes, followed by alkaline hydrogen peroxide oxidation into the corresponding ketones. Alternatively, organoboranes can be directly oxidized by chromic acid in ethyl ether to ketones. This method has proven valuable, especially in the synthesis of cycloalkanones. The reaction sequence shown in eq 7 represents a regiospecific synthesis of α-alkyl or α-aryl ketones.

EXPERIMENTAL SECTION

Materials. Tetrahydrofuran and diglyme were distilled from lithium alumimum hydride. Sodium dichromate and ethyl ether (from Mallinckrodt) were used as received. Other solvents and reagents were purified as described elsewhere.[19] Sodium borohydride (98%) and lithium borohydride (95%) from Metal Hydrides, Inc. were used without further purification.

Methods. The techniques used in handling air-sensitive materials are described elsewhere.[19] All reactions involving hydride and organoboranes were carried out under the atmosphere of nitrogen. GC analyses were carried out on a F&M-500 gas chromatograph using 6 ft x 1/4 in columns.

One-Stage Hydroboration-Chromic Acid Oxidation. The alkene was hydroborated in ethyl ether with boron trifluoride etherate and lithium borohydride or with sodium borohydride in the presence of catalytic quantities of zinc chloride.[20] Ether was used to facilitate the oxidation to ketone and recovery of the ketone. However, the reaction can also be carried out in tetrahydrofuran or diglyme.[17] The following procedure is representative. The usual hydroboration apparatus is assembled using a 200-mL flask, magnetic stirrer, condenser, pressure-equalizing addition funnel, thermometer and bubbler. The system is flushed with nitrogen and maintained under a static pressure of nitrogen through the oxidation stage. In the flask are placed 0.5 g (22.5 mmol, 20% excess) of lithium borohydride in 30 mL of ethyl ether and 4.8 g (0.050 mole) of 1-methylcyclohexene. The flask is

immersed in a water bath at 25°C. To the flask is added 0.95 mL (0.0075 mole, 20% excess) of boron trifluoride etherate over a period of 15 min at 25-30°C. After 2 h, 5 mL of water is added to destroy excess residual hydride. The chromic acid solution (10% excess), prepared from 11.0 g (39.6 mmol) of sodium dichromate dihydrate and 8.25 mL (148.3 mmol) of 96% sulfuric acid and diluted with water to 45 mL, is added to the stirred solution over a period of 15 min, maintaining the temperature at 25-30°C. The mixture is then heated under reflux for 2 h. The upper layer is separated and the aqueous phase is extracted with two 10-mL portions of ether. GC examination indicates an 87% yield of 2-methylcyclohexanone. Distillation gives 4.36 g (78% yield) of 2-methylcyclohexanone, bp 63-64° (24 mm), $n^{20}D$ 1.4487.

Partial Oxidation of bis-*trans*-2-Methylcyclohexylborinic Acid. 1-Methylcyclohexene (50 mmol) was hydroborated as described above in ethyl ether with lithium borohydride and boron trifluoride etherate. The excess hydride was destroyed with 5 mL of water. The chromic acid solution, prepared from 5.0 g (16.8 mmol) of sodium dichromate dihydrate and 3.75 mL (67 mmol) of 96% sulfuric acid and diluted to 45 mL, was added to the stirred solution over a period of 15 min, maintaining the temperature at 35-37°C. After heating under reflux for 2 h, the upper layer was separated and the aqueous layer was extracted with ether (2 x 25 mL). The combined ether extracts were washed with saturated sodium bicarbonate solution, then with water. Gas chromatographic analysis indicated 6% of 2-methylcyclohexanone and 54.8% of *trans*-2-methylcyclohexanol. Analysis of the aqueous layer with standard sodium thiosulfate revealed that 94% of the sodium dichromate was used for the oxidation.

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