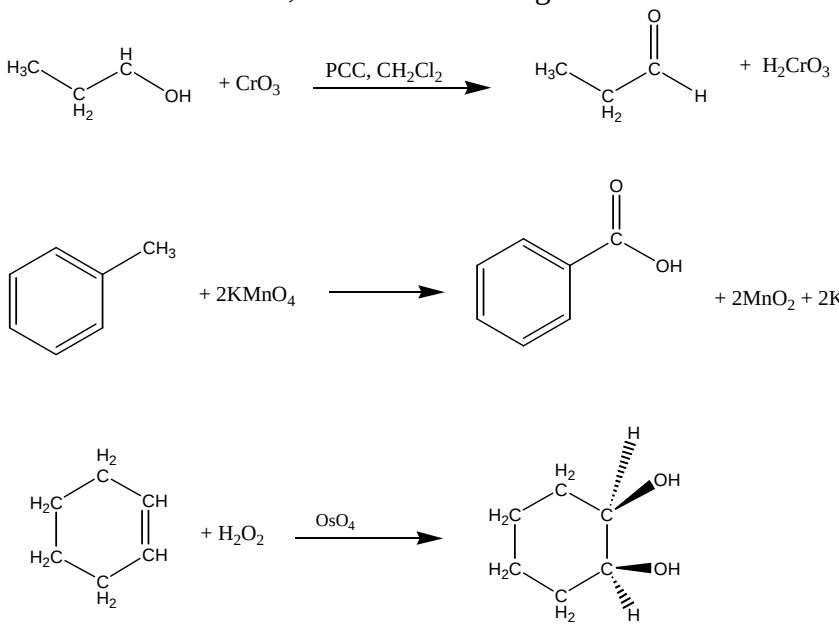
For inorganic reactions oxidation is defined as a process involving loss of electrons, as in the conversion of Fe^{+2} to Fe^{+3}. Oxidation of organic compounds also normally involves electron transfer, but because the valence of carbon usually remains at four, it is more useful to define oxidation as either (a) loss of Hydrogen atoms or (b) addition of Oxygen or other electronegative atoms to carbon. Thus, all of the following reactions are classified as oxidations:



The oxidation of alcohols provides one of the most general methods for the preparation of carbonyl compounds; oxidation of primary alcohols affords aldehydes (or carboxylic acids if oxidation is continued), while oxidation of secondary alcohols affords ketones. Tertiary alcohols cannot be oxidized without breaking carbon-carbon bonds.

The most common oxidizing agents for the conversion of alcohols to aldehydes and ketones are chromium trioxide (CrO_3) and chromate ions (CrO_4^{-2} and $Cr_2O_7^{-2}$), as well as a series of modified forms of CrO_3 such as Collins reagent, in which CrO_3 is complexed with pyridine. (Collins reagent is used in nonaqueous media, and is especially useful for oxidizing primary alcohols to aldehydes without further oxidation to the carboxylic acid.) Potassium permanganate ($KMnO_4$) can also be used to oxidize alcohols and even some alkanes.

An alternative oxidizing agent for the preparation of ketones, sodium hypochlorite (NaOCl) in acetic acid, was introduced by Stevens, Chapman and Weller (*J. Org. Chem*, **1980**, 45, 2030). This reagent offers several advantages: 1) It is cheap – sodium hypochlorite is the reagent in Clorox® and swimming pool chlorine; 2) it oxidizes secondary alcohols rapidly and in high yield, and 3) it avoids the problem of having to dispose of the toxic metallic wastes associated with chromium and manganese reagents.

The example chosen here to illustrate the oxidation of alcohols is the sodium hypochlorite oxidation of methylcyclohexanols. The identity of your ketone product will be determined by GC-FID and NMR analysis.

A. Procedure:

Dissolve 5 g of your methylcyclohexanol in 15 mL of glacial acetic acid in a 125 or 250 mL round bottom flask. Add 50 mL of Clorox (which contains about 5% of NaOCl) slowly over 10 minutes. Have an ice bath handy so that you can cool the flask to keep the internal temperature in the range of 40 to 50 ºC. After addition is complete, cover the flask with tinfoil and allow the mixture to stand at room temperature for 30 minutes with frequent swirling.

Add a drop of the reaction mixture to a piece of starch-iodide paper. Any unreacted hyprochlorite will cause paper to turn blue. Add saturated $NaHSO_3$ (sodium hydrosulfite) solution carefully until the starch-iodide test is negative.

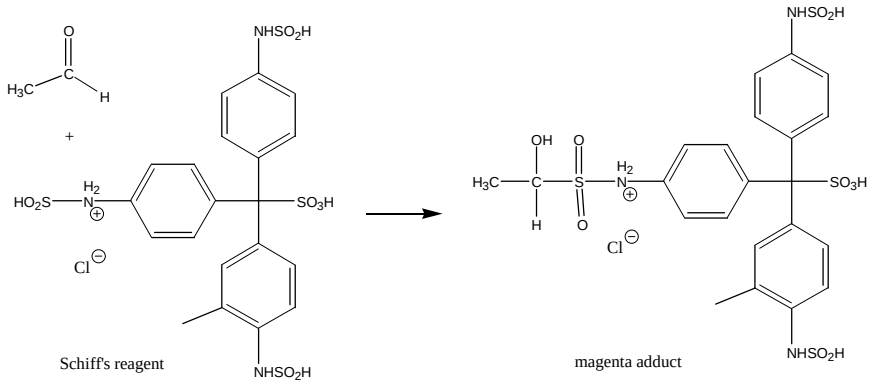
Add a 2 or 3 boiling chips to the round bottom and distill off about half of your aqueous reaction mixture.

Extract the distillate with 3 time 20 mL of dichloromethane. Combine the organic (CH_2Cl_2) layers and dry them with anhydrous Magnesium (or Sodium) Sulfate. Filter (gravity filtration) off the solid drying agent and collect the CH_2Cl_2 in a pre-weighed beaker. Boil off the CH_2Cl_2 in a hot water bath in the hood. Use a boiling stick to facilitate evaporation. Your ketone is quite volatile, so be careful not to overheat the beaker or some of the product will be lost. Obtain the final mass of the product.

B. **Qualitative tests:**

1.) Schiff's Reagent

Perform a side-by-side comparison of your product with methylcyclohexanone references. Place a drop of your liquid in a small test tube. Add 10 drops of 95% ethanol. Add 1 mL of Schiff's reagent (measure with a plastic dropper). Shake the mixture.

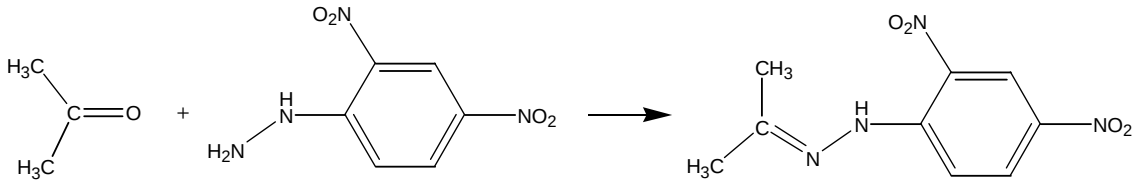


The formation of a dark violet color indicates a positive test. Most aldehydes and ketones will give a violet color immediately. However, some compounds will require up to 15 minutes, or even gentle heating, to give a color change. Aldehydes, unhindered cyclic ketones such as cyclohexanone, and unhindered methyl ketones tend to give more dramatic results than relatively more hindered carbonyls.

One could collect, dry and determine the melting point of the precipitate in order to identify the unknown. (Not required for this lab.)

2.) 2,4-dinitrophenylhydrazine reagent

Perform a side-by-side comparison of your product with methylcyclohexanone references. Place a drop of your liquid in a small test tube. Add 10 drops of 95% ethanol. Add 1 mL of the 2,4-dinitrophenylhydrazine reagent (measure with a plastic dropper). Shake the mixture.



2,4-dinitrophenylhydrazine

The formation of a precipitate indicates a positive test. Most aldehydes and ketones will give a yellow to red precipitate immediately. However, some compounds will require gentle heating, to give a precipitate. Aldehydes, unhindered cyclic ketones such as cyclohexanone, and unhindered methyl ketones tend to give more dramatic results than relatively more hindered carbonyls.

C. In lab analysis:

1. Obtain the IR spectrum of the product.

D. Clean up.

1. Dispose materials in the proper containers in the waste hood.

E. Submission for GC-MS and NMR analysis.

2. Hand in a sample of your product in a properly labeled vial: Your name, date, and unknown alcohol number.

Checklist for completing the "Prelab" section:

(refer to Laboratory Syllabus for complete directions)

____ *Title*.
____ *Purpose*.
____*Physical constants*. Obtain a table of physical constants and safety data for the chemical compounds referred to in the procedure: http://domin.dom.edu/faculty/jbfriesen/chem254lab.htm

Structures and equations.
____ Write (using chemical structures) the balanced equation for this reaction using 2-methylcyclohexanol as the alcohol.
Hint: water is a product.

___ *Flowchart.* Refer to "Procedure"

___ *Calculations.*
1) Determine the number of moles of methylcyclohexanol used.
2) Determine the number of moles of NaOCl used. Use 5.25g/100 mL NaOCl in Clorox.
3) Calculate the theoretical yield (in grams) of methylcyclohexanone.
4) Calculate the atom economy of the reaction.

____ Safety Question: Look up the MSDS for Clorox <http://www.biosci.ohio-state.edu/safety/MSDS/CLOROX%20LIQUID%20BLEACH.htm> What Emergency/First Aid Procedures are advised if the product is splashed into one's eyes?

Experimental Observations and Data:

Hand in a copy of your experimental observations and data before you leave lab.
Experimental Observations.
Refer to last semester and laboratory syllabus.

Lab Report Checklist:

Results.

____ % yield of product → product mass x 100/theoretical yield

____ Interpret the IR spectrum of your ketone (obtained in lab or on the CHEM254lab website.)

____ Interpret the GC-FID chromatogram of your reaction mixture (GC-FID of standards may be obtained on the CHEM254lab website.)

____ Interpret the ^{1}H NMR spectrum for your ketone (CHEM254lab website).

____ Do the ^{13}C NMR assignments for your ketone (CHEM254lab website).

____ What is the value of the different analyses (Qual tests, IR, GC-FID, ^{1}H NMR, & ^{13}C NMR) in determining the structure of your product? What additional analyses could be (should be) done to confirm the structure of the ketone product?

Discussion and Conclusion.

____ Why would the starch-iodide paper turn blue in the presence of unreacted sodium hypochlorite? Write a chemical equation as part of your answer.

____ Why was Sodium Bisulfite added to the reaction mixture? Write a chemical equation as part of your answer.

Adapted from "Experiments in Organic Chemistry by Richard K. Hill & John Barbaro, 2nd edition, Contemporary Publishing Company of Raleigh, Inc. (2000) 0-89892-218-6

Convenient and Inexpensive Procedure for Oxidation of Secondary Alcohols to Ketones

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In connection with certain studies concerned with the total synthesis of chirally pure natural products,[1] we required large quantities of (−)-camphor. This substance can be obtained from relatively inexpensive (−)-borneol by oxidation with an almost bewildering array of reagents.[2] However, the need for repeated large-scale work forced us to consider fractors such as cost, ease of operation, and total reaction volume in the selection of an oxidation procedure. In our previous work[1] we had employed *tert*-butyl hypochlorite. However, the somewhat tedious preparation[3] of this reagent and its potentially explosive nature,[3] especially during large-scale preparations, led us to consider alternate sources of positive chlorine which might effect the same transformation. Sodium hypochlorite has been used indirectly with ruthenium tetroxide to oxidize secondary alcohols to ketones;[4] reportedly, no reaction occurs in the absence of catalyst. Sodium hypochlorite has also been used in a two-phase system with a phase-transfer catalyst to oxidize secondary alcohols to ketones in moderate yield.[5] In our hands this procedure failed to oxidize borneol to camphor and led to a complex mixture of polymeric products.

We now report that secondary alcohols are cleanly oxidized to ketones with sodium hypochlorite in acetic acid in the absence of catalyst. Inexpensive concentrated solutions of sodium hypochlorite are sold commercially as "swimming pool chlorine".[6] Dropwise addition of this reagent to a solution of the alcohol in acetic acid at room temperature leads to an exothermic reaction which is usually complete 15 min after the end of the addition. Ketones are isolated in excellent yield (see Table I) by diluting the mixture with water and collecting the products by filtration (solids) or extraction (liquids). We have repeatedly used this procedure for the oxidation of borneol to camphor without incident.[8]

Other secondary alcohols are oxidized equally efficiently (see Table I). The reaction appears to be relatively insensitive to geometric or steric constraints (e.g., compare Table I entries 1 and 2, 4 and 5). Methyl ketones are formed without undergoing a subsequent haloform reaction (entry 9). Primary aliphatic alcohols react sluggishly, leading to dimeric esters, presumably via hemiacetal intermediates (entry 10).[9] We have made use of this difference in reactivity to oxidize a secondary alcohol in the presence of a primary alcohol (entry 11). The use of this reagent as a selective oxidant and applications of the ester-forming reaction will be the subject of a future paper.

(1) R. V. Stevens and F. C. A. Gaeta, *J. Am. Chem. Soc.*, **99**, 6105 (1977).

(2) For leading references, see "Compendium of Organic Synthetic Methods", (I. T. Harrison and S. Harrison, Vol. I and II; L. G. Wade, Vol. III), Wiley-Interscience, New York.

(3) Preparation: (a) "Organic Syntheses", Wiley, New York: Collect. Vol. 4, 1963, p 125; Collect. Vol. 5, 1973, p 184. Use as an oxidant: (a) C. A. Grob and H. J. Schmid, *Helv. Chim. Acta*, **36**, 1763 (1953); D. Ginsburg, *J. Am. Chem. Soc.*, **75**, 5489 (1953); G. S. Fonken, J. L. Thompson and R. H. Levin, *ibid.*, **77**, 172 (1955).

(4) S. Wolfe, S. K. Hasan, and J. R. Campbell, *J. Chem. Soc. D*, 1420 (1970).

(5) G. A. Lee and H. H. Freedman, *Tetrahedron Lett.*, 1041 (1976); S. L. Regen, *J. Org. Chem.*, **42**, 875 (1977).

(6) We used Sani-Chlor Pool Sanitizer (General Pool Supply, Los Angeles, CA 90045) which is sold as a 12.5% solution by weight. As sold, these solutions were found to be 1.8–2.0 M by means of a simple titration procedure.[7] On standing at room temperature in their original containers, these solutions decreased in concentration by about 20% per month. For most applications an excess of the reagent can be used with the stated concentration as a guide. For more precise work the simple titration procedure[7] is recommended. Our cost was $0.95/gal or about 13¢/mol.

(7) I. M. Kolthoff and R. Belcher, "Volumetric Analysis", Interscience, New York, 1957, pp 262–6.

(8) We have experienced no difficulties in working with this reagent. However, as with all strong oxidants, care should be taken due to the potential for formation of peroxides.

(9) (a) Preparation of esters from aldehydes via hemiacetals has been described previously: P. Sundararaman, E. C. Walker, and C. Djerassi, *Tetrahedron Lett.*, 1627, (1978). (b) Oxidation of primary benzylic alcohols by hypochlorites has been described previously: C. Y. Meyers, *J Org. Chem.*, **26**, 1041 (1961).

Table I. Oxidation of Alcohols with NaOCl

entry	alcohol	product	% yield[a]
1	(−)-borneol	(−)-camphor	95
2	(±)-isoborneol	(±)-camphor	91
3	(−)-menthol	(−)-menthone	94
4	cyclohexanol	cyclohexanone	96
5	2,2,5-trimethylcyclohexanol	2,2,5-trimethylcyclohexanone	90
6	9-cyanoisoborneol[b]	9-cyanocamphor	94
7	5α-androstane-3β,17β-diol	5α-androstane-3,17-dione	96
8	norborneol	norcamphor	92
9	2-octanol	2-octanone	96
10	1-decyl alcohol	decyl decanoate	89
11	2-ethyl-1,3-hexanediol	2-ethyl-1-hydroxy-3-hexanone	85

[a] All yields represent isolated, pure products. Known products were identified by comparison with authentic samples. New compounds were characterized by their ^1H and ^{13}C NMR, IR, and exact mass spectra. [b] The synthesis of this compound will be described in a future paper.

Experimental Section

General Procedures. Sodium hypochlorite solutions[6] and glacial acetic acid (Mallinckrodt, analytical reagent) were used as received. Starting alcohols were purified by distillation or crystallization, as appropriate; purity was established by vapor-phase or thin-layer chromatography prior to use. Infrared spectra were recorded on a Beckman IR 4210 infrared spectrophotometer. NMR spectra were taken on Varian T-60, Bruker WP-200, and Varian CFT-20 spectrometers in dilute deuteriochloroform solutions with tetramethylsilane as internal standard. Mass spectra were recorded on an AEI-MS 9 mass spectrometer. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter.

Oxidation of (−)-Borneol. (−)-Borneol (502 g, 3.26 mol, $[\alpha]^{25}_D$ ($CHCl_3$) −35.3°) was dissolved in glacial acetic acid (1.5 L) in a 5-L 3-neck flask fitted with a mechanical-stirring apparatus and thermometer. Aqueous sodium hypochlorite solution (2 L of 2.0 M solution, 4.0 mol) was added dropwise over 2.5 h. The mixture was cooled in an ice bath as necessary to keep the internal temperature in the range 15–25 °C. The mixture was stirred for 1 h after completion of the addition, at which time a positive potassium iodide–starch test was obtained. Saturated aqueous sodium bisulfite solution (200 mL) was added until the color of the mixture changed from yellow to white and the potassium iodide–starch test was negative. The mixture was then poured over an ice–brine mixture (10 L), and the resulting white solid was collected on a Buchner funnel and washed with saturated aqueous sodium carbonate solution until foaming was no longer evident. The solid product was pressed as dry as possible and dissolved in petroleum ether (2 L, bp 20–60 °C), and the aqueous and organic layers were separated. The aqueous layer was extracted twice with petroleum ether and discarded. The organic layers were combined and dried over anhydrous calcium chloride. The mixture was concentrated by rotary evaporation until most of the petroleum ether was removed and a white slurry remained. The remainder of the petroleum ether was then removed by high-vacuum rotary evaporation with the condensor cooled to −78 °C to prevent sublimation of camphor, leaving 475 g (95.8%) of (−)-camphor as a free-flowing white powder, mp 175.5–176.5 °C, $[\alpha]^{25}_D$ ($CHCl_3$) −42.1°. The ^1H NMR and IR spectra and VPC retention time of this product were identical with those of an authentic sample.

Oxidation of Cyclohexanol. Cyclohexanol (99.0 g, 0.988 mol) was dissolved in glacial acetic acid (660 mL) in a 2-L 3-neck flask fitted with a mechanical-stirring apparatus and thermometer. Aqueous sodium hypochlorite (660 mL of 1.80 M solution, 1.19 mol) was added dropwise over 1 h. The reaction was cooled in an ice bath to maintain the temperature in the 15–25 °C range. The mixture was stirred for 1 h after the addition was complete. A potassium iodide–starch test was positive. Saturated aqueous sodium bisulfite solution (3 mL) was added until the color of the reaction mixture changed from yellow to white and the potassium iodide–starch test was negative. The mixture was then poured into an ice–brine mixture (2 L) and extracted six times with ether. The organic layer was washed with aqueous sodium hydroxide (5% by weight) until the aqueous layer was basic (pH test paper). The aqueous washes were then combined and extracted five times with ether. The ether layers were combined and dried over magnesium sulfate. The ether was distilled through a 30-in. Vigreux column until less than 300 mL of solution remained. The remainder was fractionally distilled through a 12-in. Vigreux column. After a forerun of ether, cyclohexanone (bp 155 °C) was distilled to give 92.9 g (95.8%) of a colorless liquid which had ^1H NMR and IR spectra and VPC retention time identical with those of an authentic sample.

Oxidation of 2-Ethyl-1,3-hexanediol. 2-Ethyl-1,3-hexanediol (Eastman, 10.12 g, 0.068 mol) was dissolved in glacial acetic acid (50 mL) in a 250-mL 3-neck flask equipped with a thermometer and magnetic stirring bar. Aqueous sodium hypochlorite (49 mL of 1.48 M solution, 0.072 mol) was added dropwise over 1 h. The reaction was cooled in an ice–water bath as necessary to maintain the temperature between 20 and 25 °C. The mixture was stirred for 30 min after completion of the addition, after which a potassium iodide–starch test was negative. The reaction mixture was poured into ice–brine (300 mL), and the resulting mixture was extracted five times with ether. The combined ether extract was washed three times with saturated aqueous sodium carbonate solution and twice with aqueous sodium hydroxide solution (5% by weight). The aqueous washes were combined and extracted three times with ether. The ether extracts were then combined, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give a colorless oil (9.64 g). Vacuum distillation in a short-path apparatus gave 8.42 g (85%) of 2-ethyl-1-hydroxy-3-hexanone as a colorless oil:[10] ^1H NMR (200 MHz) δ 3.73 (2 H, ddd, J = 6, 11, 11 Hz, CH_2OH), 2.65 (1 H, m, O=C**H**Et), 2.49 (2 H, t, J = 7 Hz, $CH_2CH_2C{=}O$), 2.12 (1 H, t, J = 6 Hz, CH_2OH, exchanges with D_2O), 1.40–1.80 (4 H, m, CH_2), 0.85–1.05 (6 H, superimposed t, CH_2CH_3); ^{13}C NMR δ 215.0 (C=O), 62.9, 55.8, 45.2, 21.5, 16.8, 13.8, 11.8; IR (CCl_4) 3450 (br, OH), 2950 (s, CH), 2920 (m, CH), 2864 (m, CH), 1703 cm^{-1} (s, C=O); exact mass, m/e found 144.1146, calculated for $C_8H_{16}O_2$ 144.1151.

Acknowledgment. We are grateful to the National Science Foundation (NSF CHE78-27084) and the National Institutes of Health (AM 20398) for generous financial support of this work. We are also grateful to the National Institutes of Health for a National Research Service Award (1 F32 CA 06455 01) to H.N.W. We thank Dr. M. E. Jung for kindly providing samples of the diols used in this work.

Registry No. (−)-Borneol, 464-45-9; (±)-isoborneol, 24393-70-2; (−)-menthol, 2216-51-5; cyclohexanol, 108-93-0; 2,2,5-trimethylcyclohexanol, 73210-25-0; 9-cyanoisoborneol, 73210-26-1; 5α-androstane-3β,17β-diol, 571-20-0; norborneol, 1632-68-4; 2-octanol, 123-96-6; 1-decyl alcohol, 112-30-1; 2-ethyl-1,3-hexanediol, 94-96-2; (−)-camphor, 464-48-2; (±)-camphor, 21368-68-3; (−)-menthone, 14073-97-3; cyclohexanone, 108-94-1; 2,2,5-trimethylcyclohexanone, 933-36-8; 9-cyanocamphor, 56906-71-9; 5α-androstane-3,17-dione, 846-46-8; norcamphor, 497-38-1; 2-octanone, 111-13-7; decyl decanoate, 1654-86-0; 2-ethyl-1-hydroxy-3-hexanone, 27970-80-5.

(10) I. I. Lapkin and F. G. Saitkulova, *Zh. Org. Khim.*, 6, 450, (1970).