Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

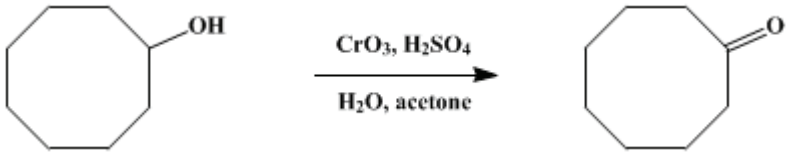
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.045.0028

Organic Syntheses, Coll. Vol. 5, p.310 (1973); Vol. 45, p.28 (1965).

CYCLOÖCTANONE



Submitted by E. J. Eisenbraun[1]
Checked by E. J. Corey and Ernest Hamanaka.

1. Procedure

The chromic acid oxidizing reagent is prepared by dissolving 67 g. of chromium trioxide in 125 ml. of distilled water. To this solution is added 58 ml. of concentrated sulfuric acid (sp. gr. 1.84), and the salts which precipitate are dissolved by addition of a minimum quantity of distilled water; the total volume of the solution usually does not exceed 225 ml.

A solution of 64 g. (0.5 mole) of cycloöctanol (Note 1) in 1.25 l. of acetone (Note 1) is added to a 2-l. three-necked flask fitted with a long-stem dropping funnel, a thermometer, and a powerful mechanical stirrer (Note 2). The vigorously agitated solution is cooled in a water bath to about 20°. The chromic acid oxidizing reagent is added from the dropping funnel as a slow stream, and the rate of addition is adjusted so that the temperature of the reaction mixture does not rise above 35° (Note 3). The addition is continued until the characteristic orange color of the reagent persists for about 20 minutes (Note 4) and (Note 5). The volume of reagent added is about 120 ml.

The stirrer is removed, the mixture is decanted into a 2-l. round-bottomed flask, and the residual green salts are rinsed with two 70-ml. portions of acetone. The rinsings are added to the main acetone solution and additional oxidizing agent is added, if necessary, to ensure complete reaction. The stirrer is replaced and isopropyl alcohol is added dropwise until the excess chromic acid is destroyed (Note 6). In small portions and with caution there is added 63 g. of sodium bicarbonate, and the suspension is stirred vigorously until the pH of the reaction mixture tests neutral (Note 7). The suspension is filtered and the filter cake is washed with 25 ml. of acetone. The filtrate is concentrated by distillation through a 75-cm. length of Vigreux column until the pot temperature rises to 80° and a water film begins to develop in the lower portions of the distillation column (Note 8). The cooled pot residue (about 110 ml.) is transferred to a 1-l. separatory funnel, 500 ml. of saturated sodium chloride solution is added, and the mixture is extracted with two 150-ml. portions of ether. The ether extracts are combined, washed with a total of 25 ml. water in several portions, dried over anhydrous magnesium sulfate, filtered, and the ether distilled at atmospheric pressure. The pot residue is distilled under reduced pressure, b.p. 76–77° (10 mm.) (Note 9). The yield of cycloöctanone is 58–60 g. (92–96%), m.p. 40–42°.

An additional 2.2 g. (4%) of cycloöctanone may be obtained by addition of 250 ml. of water to the green salts formed during the reaction (Note 10), extraction of the mixture with ether, distillation of the ether, and addition of 12 ml. of acetone. To the acetone solution there is added sufficient chromic acid oxidizing reagent to permit the orange color of the reagent to persist (Note 11), and the mixture is processed as above.

2. Notes

1. Cycloöctanol is available from Aldrich Chemical Company, Inc. A redistilled solvent grade of acetone is satisfactory.
2. The submitter has also carried out this preparation starting from 2 moles of cycloöctanol. An 8-l. Pyrex® bottle, Corning No. 1595, is ideally suited for this scale. A round-bottomed flask is less desirable because it is necessary to see into the reaction vessel. Vigorous stirring is essential; a Lightnin Model L stirrer fitted with two 2-in., three-blade propellers is adequate for the larger-scale run. A cold-water bath for the 8-l. bottle may be conveniently constructed from an open-top 5-gallon solvent can by cutting a

1.5-cm. hole 5 cm. from the bottom and a 2.8-cm. hole 5 cm. from the top. These holes are respectively fitted with a rubber inlet tube (11/16 in. O.D. by 3/8 in. I.D.) and a rubber outlet tube (1¼ in. O.D. by 1 in. I.D.). The rubber tubing fits directly in the holes without adapter or nipples.
3. The temperature is kept below 35° to avoid the use of a condenser.
4. The characteristic end point orange color can be demonstrated by addition of a slight excess of the chromic acid oxidizing reagent to a few milliliters of acetone containing a few drops of isopropyl alcohol.
5. The course of the reaction can conveniently be followed by gas chromatography. A sample of the reaction mixture is withdrawn at intervals, neutralized with solid sodium bicarbonate, dried over magnesium sulfate, and injected directly into a gas chromatography column consisting of 15% phenyldiethanolamine succinate (PDEAS) substrate coated on 60/80 mesh, acid-washed fire brick contained in a ¼ in. by 5 ft. spiral-shaped copper tube. A Wilkens Instrument and Research, Inc., gas chromatography apparatus, Model A-90-P, operating at column temperature of 155°, 80 ml. per min. helium flow, was used. Complete separation of peaks (5.9 minutes for cycloöctanone, 7.0 minutes for cycloöctanol) is observed, and the reaction is considered complete when a peak for cycloöctanol can no longer be observed in the gas chromatogram.
6. The reaction mixture must be slightly acidic for the oxidation to proceed. On one occasion it was necessary to add a few drops of sulfuric acid to consume the oxidizing agent completely.
7. Calcium carbonate has also been used to remove residual acid.
8. If additional runs are contemplated, the recovered acetone may be used again.
9. A heat lamp may be used to prevent solidification during distillation.
10. The chromium salts formed during the oxidation are quite sticky and tend to occlude product as well as starting material.
11. The material freed from the chromium salts should be checked for completeness of reaction by gas chromatographic analysis to ensure the absence of starting material.

3. Discussion

Cycloöctanone has been prepared by distilling the calcium and thorium salts of azelaic acid,[2] by heating azelaic acid with barium oxide in the presence of iron,[3] by the action of nitrous acid on 1-(aminomethyl)-cycloheptanol,[4] by Dieckman cyclization of azelaic acid dimethyl ester[4] and diethyl ester,[5] and by ring expansion of cycloheptanone with diazomethane.[6,7]

4. Merits of the Preparation

This preparation illustrates a general and convenient way of oxidizing secondary alcohols to ketones in high yield. This procedure, usually called the Jones oxidation or oxidation by use of the Jones reagent,[8] offers the advantage of almost instantaneous oxidation of the alcohol under mild conditions. The reagent rarely attacks unsaturated centers; using this procedure an 81% yield of 2-cyclohexenone can be obtained from 2-cyclohexenol. The present example illustrates how this reagent can be utilized for a large-scale preparation. The major limitation of the reaction is the low solvent power of acetone. Another example of the Jones oxidation is given on p. 863 of this volume.

An attractive alternative to the Jones oxidation is oxidation with chromic acid in the two-phase system, water-ether, the details of which were reported recently.[9] By this procedure cyclooctanone was obtained in 93% yield (as determined by gas-liquid chromatography). Although the yield of isolated yields of ketones from other secondary alcohols were very good, particularly when a 100% excess of chromic acid was used at 0°.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 866
- Org. Syn. Coll. Vol. 7, 177
- Org. Syn. Coll. Vol. 7, 402

References and Notes

1. Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma. Work done at Aldrich Chemical Co., Milwaukee, Wisconsin.
2. L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, **9**, 339 (1926).
3. A. I. Vogel, *J. Chem. Soc.*, 721 (1929).
4. F. F. Blicke, J. Azuara, N. J. Doorenbos, and E. B. Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).
5. N. J. Leonard and C. W. Schimelpfenig, *J. Org. Chem.*, **23**, 1708 (1958).
6. E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).
7. S. J. Kaarsemaker and J. Coops, *Rec. Trav. Chim.*, **70**, 1033 (1951).
8. A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).
9. H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem.*, **36**, 387 (1971).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

calcium and thorium salts of azelaic acid

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium bicarbonate (144-55-8)

iron (7439-89-6)

sodium chloride (7647-14-5)

barium oxide

nitrous acid (7782-77-6)

calcium carbonate (471-34-1)

acetone (67-64-1)

isopropyl alcohol (67-63-0)

chromic acid (7738-94-5)

Azelaic acid (123-99-9)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Diazomethane (334-88-3)

Cycloheptanone (502-42-1)

helium (7440-59-7)

Cyclooctanone (502-49-8)

azelaic acid dimethyl ester (1732-10-1)

2-cyclohexenol

2-Cyclohexenone (930-68-7)

phenyldiethanolamine succinate

1-(aminomethyl)-cycloheptanol

cyclooctanol