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.

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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.

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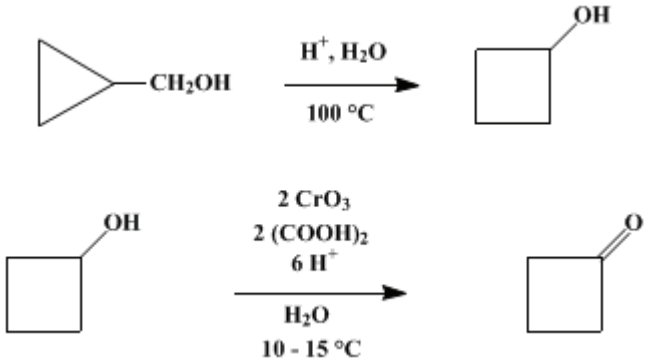
CYCLOBUTANONE



Submitted by Miroslav Krumpolc and Jan Rocek[1].
Checked by D. Seebach, R. Dammann, F. Lehr, and M. Pohmakotr.

1. Procedure

In a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser are placed 250 mL of water, 48 mL (ca. 0.55 mol) of concentrated hydrochloric acid, and 49.5 g (0.65 mol) of cyclopropylcarbinol (Note 1); the reaction mixture is refluxed for ca. 100 min. The formation of cyclobutanol can be observed nearly instantaneously, as this alcohol is only partially soluble in water and soon separates (Note 2). The flask is then immersed in an ice bath equipped with a mechanical stirrer, a thermometer, and a dropping funnel (using a three-way adapter, parallel sidearm), and the reflux condenser is replaced by an ethanol–dry ice trap connected to a U-tube immersed in an ethanol–dry ice bath to ensure condensation of the very volatile cyclobutanone. The flask is charged with an additional 48 mL (ca. 0.55 mol) of concentrated hydrochloric acid in 200 mL of water and 440 g (3.5 mol) of oxalic acid dihydrate (Note 1). The heterogeneous mixture is stirred for ca. 15 min to saturate the solution with oxalic acid. A solution of 162 g (1.62 mol) of chromium trioxide in 250 mL of water is added dropwise with stirring at such a rate that the temperature of the reaction mixture is kept between 10°C and 15°C (NaCl–ice bath, −5°C to −10°C) and the generation of carbon dioxide remains gentle. The reduction of each drop of chromic acid is practically instantaneous. As the addition of the reagent proceeds (1.5–2 hr), oxalic acid gradually dissolves and a dark-blue solution containing chromium(III) salts results (Note 3). Just before the end of the oxidation (ca. 10 mL of the chromic acid solution left), the cyclobutanone (with traces of cyclobutanol) trapped in the U-tube (a few milliliters) is added to the reaction mixture. After the oxidation is completed, the ice bath is removed and stirring is continued for ca. 1 hr to bring the reaction mixture to room temperature and to reduce the amount of carbon dioxide in the solution.

The reaction mixture is poured into a 2-L separatory funnel and extracted with four 200-mL portions of methylene chloride (Note 4). The extracts (the lower phase) are combined, dried over anhydrous magnesium sulfate containing a small amount of anhydrous potassium carbonate (to remove traces of hydrochloric acid), and filtered, and the filtrate is concentrated by distillation through a vacuum-insulated silvered column (20-cm length, 1-cm i.d.) packed with glass helices (size 2.3 mm, Lab Glass, Inc.) and equipped with an adjustable stillhead, until the pot temperature rises to 80°C (Note 5). The crude product is then transferred to a 100-mL flask and distilled through the same column (reflux ratio 10:1) to give 14–16 g (0.20–0.23 mol), 31–35% overall yield (based on pure cyclopropyl carbinol) of cyclobutanone, bp 98–99°C, d_4^{25} 0.926, n_D^{25} 1.4190 (Note 6). The product is sufficiently pure (98–99%) for most purposes (Note 5), (Note 7), (Note 8), and (Note 9).

2. Notes

1. The following compounds were used as supplied: cyclopropylcarbinol (Aldrich Chemical Company, Inc. or Fluka AG, 95% pure), hydrochloric acid (Fisher Reagent, 36.5–38%), chromium trioxide (Fisher

Certified), oxalic acid dihydrate (Fisher Certified), methylene chloride (Fisher Certified).
2. At this point cyclopropylcarbinol has been completely converted into a mixture of products containing ca. 80% cyclobutanol, 8% 3-butene-1-ol, and several additional products observable by GLC analysis in varying amounts. About 95–97% pure cyclobutanol (60–65% yield) can be obtained if the reaction mixture is neutralized with sodium hydroxide and sodium bicarbonate, saturated with magnesium sulfate, extracted with ether, and fractionally distilled on an efficient distillation column. The remaining impurities are extremely difficult to remove.
3. Oxalic acid is used in excess to ensure a rapid oxidation of the alcohol and to destroy the excess chromic acid when the cooxidation process is over. Part of the oxalic acid is consumed by chromium (III) to form oxalatochromium(III) complexes.
4. As cyclobutanone is considerably soluble in water, a thorough and vigorous agitation is recommended to ensure good extraction of the aqueous layer by methylene chloride. Oxalic acid is insoluble in this solvent.
5. The checkers used a silvered, vacuum-insulated column 30 cm in length with 1.5-cm i.d., filled with 4-mm × 4-mm helices; distillation of CH_2Cl_2 was first done from a 250-mL, two-necked flask with dropping funnel from which the dried extraction solution was continuously added. When ca. 50-mL total volume of solution remained (bath temperature ca. 90°C), it was transferred into a 100-mL, one-necked flask. Eight fractions of the cyclobutanone were collected at a 15–20:1 reflux ratio: bp/g/% purity of ketone (by VPC): 80–90/1.17/37, 90–95/4.3/53, 95–96/1.71/99.5, 96–97/1.41/—, 96–97.5/1.2/99.9, 97.5–98/3.95/99.9, 98/3.76/100, 98/1.78/99.8. The $n_D^{20.5}$ of fraction 7 was 1.4210.
6. The reported physical constants of cyclobutanone[2] are bp 99–100°C, d_4^{24} 0.924, n_D^{25} 1.4188.
7. Gas-liquid chromatography [1/8-in. × 6-ft, 10% diethylene glycol succinate (LAC-728) column, 70° C] of cyclobutanone (99.2% pure) revealed the presence of small amounts of methylene chloride (0.6%) and cyclobutanol (0.2%). No cleavage product, 4-hydroxybutyraldehyde, was found. The traces of water, detected by NMR spectroscopy using CD_3COCD_3 as a solvent, can be removed by drying over molecular sieves.
8. ^{1}H NMR (CCl_4) δ: 1.98, degenerate quintet (2 H, J = 8 Hz); 3.03, t (4 H, J = 8 Hz). IR (liquid film on KBr plates) cm^{-1}: 1783 (strong, C=O).
9. If the preparation of cyclobutanone from cyclopropylcarbinol is carried out in two steps, with cyclobutanol isolated first, somewhat higher yields can be achieved (70–80% based on cyclobutanol, 45–50% overall yield, purity 98–99%).

3. Discussion

Cyclobutanone has been prepared (1) by pyrolysis of 1-hydroxycyclobutane-1-carboxylic acid[3] (15% yield), (2) by reaction of diazomethane with ketene[4,5,6] (36% overall yield based on precursors used for the generation of both components[6]), (3) from pentaerythritol, the final step being the oxidative degradation of methylenecyclobutane[7,8] (30–45% overall yield), (4) by oxidation of cyclobutanol with chromic acid–pyridine complex in pyridine[9] (no yield is given), (5) by oxidative cleavage of 5,9-dithiaspiro[3.5]nonane, prepared via 2-(ω-chloropropyl)-1,3-dithiane[10,11] from 1,3-propanedithiol[12] (40% overall yield), (6) via solvolytic cyclization of 3-butyn-1-ol[13,14] (30% yield), (7) by epoxidation of methylenecyclopropane followed by ring expansion of resulting oxaspiropentane[15,16,17] (28% overall yield), (8) from 1,3-dibromopropane and methyl methylthiomethyl sulfoxide via cyclobutanone dimethyl dithioacetal *S*-oxide[18] (75% overall yield), and (9) from 4-chlorobutyraldehyde cyanohydrin, the final step being hydrolysis of cyclobutanone cyanohydrin[19] (45% overall yield).

The present procedure offers a simple and fast (2–3 days are required) preparation of pure cyclobutanone from cyclopropylcarbinol. The synthesis is carried out in one operation, without isolating the intermediate cyclobutanol. The first reaction, acid-catalyzed rearrangement of cyclopropylcarbinol, has been described by Caserio, Graham, and Roberts.[9] The novel feature is the preparation of cyclobutanone from cyclobutanol in the presence of oxalic acid. It is based on rapid cooxidation of two substrates proceeding via a three-electron oxidation–reduction mechanism[20,21] in which chromium (VI) is reduced directly to chromium (III). In the absence of oxalic acid the chromic acid oxidation of cyclobutanol gives along with cyclobutanone ca. 30–40% of 4-hydroxybutyraldehyde,[2] as the alcohol undergoes extensive carbon–carbon cleavage by chromium (IV).[2,21,22] The participation of oxalic acid in the reaction process serves to suppress the formation of a chromium (VI) intermediate; the only by-product formed is carbon dioxide.

Cyclobutanone is a versatile starting material used for numerous synthetic and theoretical studies in the chemistry of small rings. The preparation of this compound by the cooxidation process illustrates the synthetic utilization of three-electron oxidation–reduction reactions.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 117

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

oxalatochromium(III) complexes

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

1,3-dibromopropane (109-64-8)

Oxalic acid (144-62-7)

carbon dioxide (124-38-9)

pyridine (110-86-1)

chromic acid (7738-94-5)

Ketene (463-51-4)

methylene chloride (75-09-2)

Pentaerythritol (115-77-5)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Diazomethane (334-88-3)

oxalic acid dihydrate (6153-56-6)

Cyclobutanone (1191-95-3)

cyclopropylcarbinol,
cyclopropyl carbinol (2516-33-8)

3-butene-1-ol (627-27-0)

Cyclobutanol (2919-23-5)

3-butyn-1-ol (927-74-2)

1,3-propanedithiol (109-80-8)

methylenecyclobutane (1120-56-5)

5,9-dithiaspiro[3.5]nonane (15077-16-4)

Methylenecyclopropane (6142-73-0)

Oxaspiropentane (157-41-5)

2-(ω-chloropropyl)-1,3-dithiane

chromium(III),
chromium (III)

4-hydroxybutyraldehyde (25714-71-0)

1-hydroxycyclobutane-1-carboxylic acid

methyl methylthiomethyl sulfoxide (33577-16-1)

4-chlorobutyraldehyde cyanohydrin

cyclobutanone cyanohydrin

chromium (VI)

chromium (IV)

cyclobutanone dimethyl dithioacetal S-oxide