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.

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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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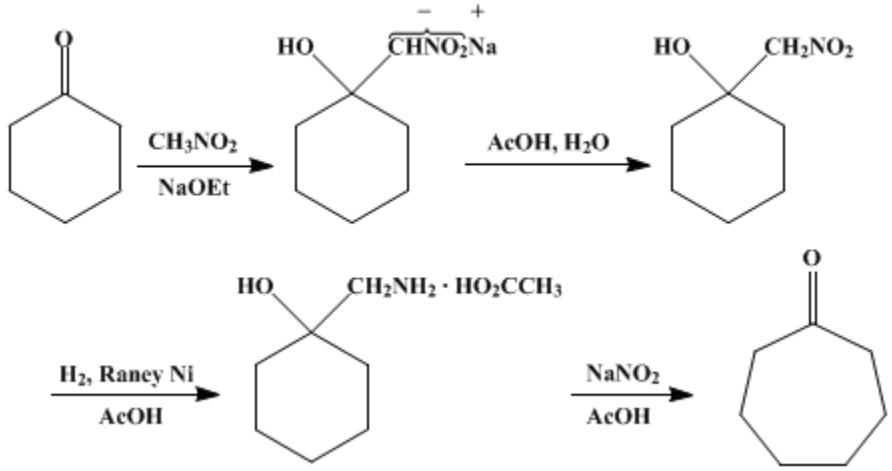
CYCLOHEPTANONE

[I. NITROUS ACID METHOD]



Submitted by Hyp J. Dauben, Jr., Howard J. Ringold, Robert H. Wade, David L. Pearson, and Arthur G. Anderson, Jr.[1].
Checked by Arthur C. Cope, Warren N. Baxter, and Robert J. Cotter.

1. Procedure

Caution! The sodium salt of 1-(nitromethyl)cyclohexanol may be an explosive (Note 1).

A solution of sodium ethoxide is prepared by adding 57.5 g. (2.5 g. atoms) of clean sodium to 1.2 l. of absolute ethanol (Note 2) in a 3-l. three-necked flask equipped with an Allihn reflux condenser fitted with a drying tube, a large sturdy sealed Hershberg stirrer, and a dropping funnel. After the sodium has dissolved, the solution is cooled to 40° and the condenser is replaced by a thermometer extending into the liquid. A mixture of 245.5 g. (258.5 ml., 2.5 moles) of redistilled cyclohexanone and 198 g. (175 ml., 3.25 moles) of redistilled nitromethane (Note 3) is added dropwise with vigorous stirring over the course of about 3 hours at a rate that maintains an internal temperature of 45 ± 3° (Note 4). After addition is complete, the white, pasty mass is stirred for an additional 3 hours without cooling or heating and then is allowed to stand overnight. The resulting suspension is cooled with an ice bath, and the white sodium salt of 1-(nitromethyl)cyclohexanol is collected on a 25-cm. Büchner funnel and dried by suction for about 1 hour (Note 1). The sodium salt cake is broken up and transferred to a 4-l. beaker equipped with a Hershberg stirrer and immersed in an ice bath. A cold solution of 184 g. (175 ml., 3 moles) of glacial acetic acid in 1250 ml. of water is added in a single portion, and the mixture is stirred for 10–30 minutes to complete dissolution. The oily layer of 1-(nitromethyl)cyclohexanol is separated, and the aqueous layer is extracted with three 100-ml. portions of ether. The ether extracts and the 1-(nitromethyl)cyclohexanol are combined, dried briefly over magnesium sulfate, and concentrated by distillation from a steam bath with a water aspirator at 20–35 mm. to remove ether and excess nitromethane. The crude, undistilled 1-(nitromethyl)cyclohexanol (Note 5) is dissolved in 450 ml. of glacial acetic acid in a 2-l. externally cooled stainless-steel hydrogenation bottle (Note 6). Three heaping teaspoonfuls of W-4 Raney nickel catalyst[2] are added, and the mixture is shaken with hydrogen at 40–45 p.s.i., with cooling to maintain the temperature below 35°, until about 90% of the theoretical amount (7.5 moles) is taken up and absorption ceases (Note 7). The catalyst is separated by filtration with suction through Filter-Cel, and the filtrate (sometimes green or tan) containing the 1-(aminomethyl)cyclohexanol is used directly in the next step (Note 8).

The filtrate is transferred to a 5-l. round-bottomed flask, immersed in an ice-salt mixture and

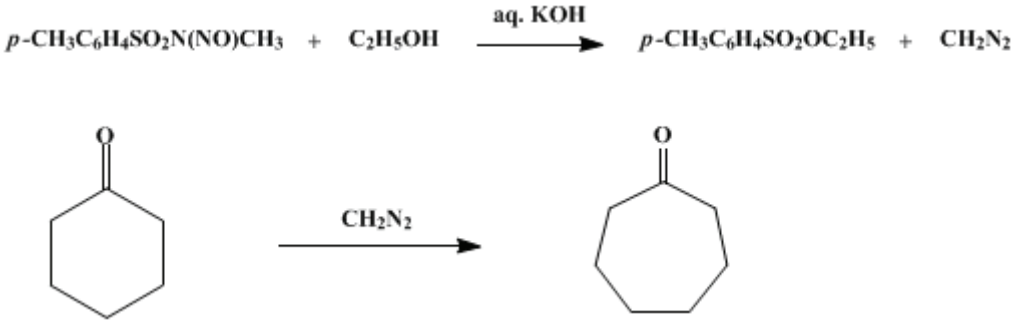
equipped with a Hershberg stirrer, a thermometer, and a dropping funnel. The solution is diluted with 2.3 l. of ice water; then an ice-cold solution of 290 g. (4.2 moles) of sodium nitrite in 750 ml. of water is added dropwise during a period of about 1 hour with stirring and cooling (ice-salt bath) to maintain the temperature at −5°. The mixture is stirred for an additional period of 1 hour and then allowed to come to room temperature overnight as the ice in the cooling bath melts. The acetic acid in the reaction mixture is neutralized by the addition of small portions of solid sodium bicarbonate, and the neutral (to litmus paper) solution is then steam-distilled until about 2 l. of distillate is collected. The oily cycloheptanone layer is separated, the aqueous layer is extracted with three 100-ml. portions of ether, and the combined organic layers are dried briefly over magnesium sulfate. Most of the ether is removed by distillation through a 17 by 2.5 cm. glass helix-packed column at atmospheric pressure (Note 9). The residue is then distilled through the same column, and the fraction boiling at 80–85°/30 mm. is collected. The yield of cycloheptanone is 112–118 g. (40–42%), n_D^{25} 1.4600 (Note 10) and (Note 11).

2. Notes

1. It has been reported[3] that when the crude product from the condensation of 2 moles of nitromethane (as the sodium salt in absolute ethanol) with 1 mole of 1,1,3,3-tetramethylcyclobutane-2,4-dione (dimethylketene dimer) was filtered, and the filter cake was dried on a porous clay plate, a violent explosion occurred upon addition of the dried powder to crushed ice.
This experience suggests that it may be inadvisable to dry completely the sodium salt of 1-(nitromethyl) cyclohexanol, and that the material should be handled with considerable caution. Also, in other procedures where salts of nitro compounds are involved, and the extent of the reaction and the nature of the products are not known with certainty, the salts probably should not be filtered, but should be neutralized in the reaction mixtures and the free nitro alcohols separated by suitable means.
2. Commercial absolute ethanol is used without additional drying. The submitters state that the use of absolute ethanol may be avoided by employment of the alternative condensation procedure of Wood and Cadorin[4] using 5 mole per cent of sodium hydroxide in aqueous methanol at 15–20° for 6 hours, but the yield of 1-(nitromethyl)cyclohexanol is appreciably lower (51%).
3. Cyclohexanone is dried over magnesium sulfate or calcium sulfate (Drierite) for 1 day and distilled; the fraction boiling at 152.5–154° (uncor.) is used. Nitromethane is dried in the same manner and distilled; small quantities of acidic impurities are removed in the fore-run, and the fraction boiling at 101.5–102.5° (uncor.) is used. Drying is frequently unnecessary when good grades of cyclohexanone and nitromethane are used.
4. Efficient stirring of the pasty reaction mixture is necessary to obtain maximum yield.
5. Removal of residual amounts of acetic acid in the crude product is unnecessary; their presence is actually preferable to the presence of traces of bases, such as any sodium bicarbonate remaining from neutralization, which reverse the condensation on attempted distillation of 1-(nitromethyl) cyclohexanol.[4] The submitters state that, in preparations conducted on twice the scale specified, fractional distillation of the residue yielded 620–670 g. (78–84%) of 1-(nitromethyl)cyclohexanol, b.p. 129–132°/19 mm., n_D^{25} 1.4835.
6. A Pyrex bottle can be used; it must be enclosed to prevent possible injury by fragments of glass in case of explosion.
7. Catalytic hydrogenation of 1-(nitromethyl)cyclohexanol in acetic acid solvent is a markedly exothermic reaction, and, unless the temperature is moderated to about 35°, low yields of 1-(aminomethyl)cyclohexanol result owing to hydrogenolysis and deactivation of the catalyst. Cooling can be accomplished by running cold water through a copper coil surrounding the hydrogenation bottle or by periodically adding ice to the container in which the bottle is placed. Considerable cooling is necessary during initial stages of the hydrogenation, but cooling below 25° greatly retards the reduction. Absorption of hydrogen is usually complete in 15–18 hours under these conditions, but longer times may be required, depending on the temperature and pressure and on the amount and activity of the catalyst.
8. 1-(Aminomethyl)cyclohexanol can be isolated as its acetic acid salt by the addition of 2 volumes of ether to the acetic acid solution or to the residue after removal of the acetic acid under reduced pressure, followed by trituration and refrigeration overnight. After filtration of the first crop of crystals, m.p. 118–121°, a second crop of the salt, m.p. 113–116°, is obtained on removal of the dissolved nickel from an aqueous solution of the concentrated filtrate by saturation with hydrogen sulfide, concentration, and

treatment with ether. Total yields of the air-dried crude acetic acid salt of 1-(aminomethyl)cyclohexanol obtained from 100–350 g. lots of 1-(nitromethyl)cyclohexanol in this manner ranged from 69% to 94%.
9. Distillation of the product from a modified Claisen flask and collection of the fraction boiling at 67–77°/20 mm. (largely 69–72°) gave 140–149 g. of impure cycloheptanone, n_D^{25} 1.4570–1.4590, containing about equal amounts (10–15 g.) of lower-boiling and higher-boiling (mainly 1-(nitromethyl) cyclohexanol) contaminants, which were separated by distillation through the glass helix-packed column.
10. The submitters state that the yields of cycloheptanone obtained from 60- to 700-g. quantities of the crude acetic acid salt of 1-(aminomethyl)cyclohexanol (isolated by the procedure of ((Note 8)) were 57–65%.
11. Small quantities of cycloheptanone are prepared more conveniently by the diazomethane method[5] or by dry distillation of suberic acid salts[6,7,8] or suberic acid admixed with iron filings and barium hydroxide.[9]

[II. DIAZOMETHANE METHOD]



Submitted by Th. J. de Boer and H. J. Backer[10].
Checked by James Cason, John B. Rogan, and Wm. G. Dauben.

1. Procedure

Caution! Diazomethane is very toxic; therefore the operations must be carried out in a well-ventilated hood. (See p. 250.)

In a 500-ml. round-bottomed flask, provided with a mechanical stirrer (Note 1), a thermometer, and a dropping funnel, are placed 49 g. (0.5 mole) of cyclohexanone (Note 2), 125 g. (0.58 mole) of *p*-tolylsulfonylmethylnitrosamide (p. 943), 150 ml. of 95% ethanol, and 10 ml. of water (Note 3). The nitroso compound is largely undissolved. The stirrer is adjusted so that only the upper portion of solution is stirred and the precipitate moves slightly. The thermometer bulb is placed in the liquid.

The reaction mixture is cooled to about 0° with an ice-salt bath; then with gentle stirring a solution of 15 g. of potassium hydroxide in 50 ml. of 50% aqueous ethanol is added dropwise very slowly from the dropping funnel. After the addition of 0.5–1 ml. of the alkaline solution a brisk evolution of nitrogen commences and the temperature rises. The rate of addition is adjusted so that the temperature is maintained at 10–20° (Note 4). The addition of the alkali requires about 2 hours, during which the nitroso compound gradually disappears. The orange-yellow solution is stirred for an additional 30 minutes, then 2*N* hydrochloric acid (about 50 ml.) is added until the solution is acidic to litmus paper.

A solution of 100 g. of sodium bisulfite (Note 5) in 200 ml. of water is added as stirring is continued. After a few minutes a thick precipitate separates. The mixture is stirred or preferably shaken mechanically at room temperature with exclusion of air for 10 hours. The bisulfite addition product is separated by suction filtration, washed with ether until colorless, and decomposed in a flask with a lukewarm solution of 125 g. of sodium carbonate in 150 ml. of water. The ketone layer is separated, the aqueous layer is extracted with four 25-ml. portions of ether, and the combined organic layers are dried over anhydrous sodium sulfate. Most of the ether is removed by distillation at atmospheric pressure, and

the residual oil is distilled at reduced pressure (Note 6).

After a few drops of fore-run, practically all the liquid distils at 64–65°/12 mm. The yield of cycloheptanone is 18.5–20.2 g. (33–36%) (Note 6).

2. Notes

1. If it is desired to determine the amount of nitrogen evolved, then it is necessary to use a sealed stirrer and a discharge tube for the nitrogen; however, observing the amount of nitrogen evolved affords no particular advantage. The temperature exerts sufficient control on the reaction rate, and dissolution of the nitroso compound indicates the progress of the reaction.
2. Cyclohexanone was distilled before use, b.p. 154–155°.
3. The water keeps in solution the potassium *p*-toluenesulfonate, which is formed by partial saponification of the ester.
4. In some experiments, the temperature was allowed to rise temporarily to 35° without mishap, but the lower temperature is preferred for reasons of safety.
5. Cycloöctanone, which is a by-product, is removed at this stage since it does not form an adduct with bisulfite.
6. The checkers found it desirable to distil the product through a fractionating column in order to effectively remove the small fore-run and a smaller after-run. The pattern obtained in a 50-cm. column of the simple Podbielniak type follows: fraction 1, 1.13 g., b.p. up to 63°/12 mm., n_D^{25} 1.4549; fraction 2, 19.44 g., b.p. 63–64°/12 mm., n_D^{25} 1.4592; fraction 3, 0.55 g., b.p. > 64°/12 mm., n_D^{25} 1.4604. A center cut of fraction 2 had n_D^{25} 1.4590.

3. Discussion

Cycloheptanone has been prepared by variations of two general routes, ring closure and ring enlargement. Ring-closure methods that have been employed are: (*a*) dry distillation of calcium[6] (35–50% yield), thorium[7] (45% yield), cerium[7] (45% yield), and zinc or magnesium[8] (55–60% yield) salts of suberic acid; (*b*) pyrolysis of a mixture of suberic acid, iron filings, and barium hydroxide[9] (40% yield) or pyrolysis of suberic acid in the presence of catalytic amounts of thorium oxide;[11] (*c*) Dieckmann condensation of diethyl suberate with sodium ethoxide in ether[12] or potassium *tert*-butoxide in xylene under high dilution conditions;[13] (*d*) Thorpe-Ziegler condensation of suberonitrile using preferably sodium methylanilide in ether by a high-dilution technique followed by hydrolysis and decarboxylation (80–85% yield);[14] and (*e*) dehydrohalogenation of suberyl chloride using triethylamine by a high-dilution technique (33% yield).[15] Ring-enlargement methods that have been used are: (*a*) diazomethane on cyclohexanone (33–36% yield)[5] and (*b*) catalytic reduction of cyclohexanone cyanohydrin[16] or electrolytic reduction of 1-(nitromethyl)cyclohexanol[17] and treatment of the resulting 1-(aminomethyl) cyclohexanol with nitrous acid, and hydrogenation of tetrahydrobenzonitrile (from acrylonitrile and butadiene) to cyclohexylmethylamine which then is caused to react with nitrous acid.[18]

Procedure I represents an improved modification of the procedure of Dauben, Ringold, Wade, and Anderson,[19] and Procedure II is a modification of earlier diazomethane methods and employs the relatively stable *p*-tolylsulfonylmethylnitrosamide (p. 943).

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

Drierite

acetic acid salt of 1-(aminomethyl)cyclohexanol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

iron (7439-89-6)

Cyclohexanone (108-94-1)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

sodium bisulfite (7631-90-5)

thorium oxide

calcium sulfate (7778-18-9)

nickel (7440-02-0)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

calcium (7440-70-2)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

barium hydroxide (17194-00-2)

xylene (106-42-3)

Nitromethane (75-52-5)

magnesium sulfate (7487-88-9)

butadiene (106-99-0)

Diazomethane (334-88-3)

Cerium (7440-45-1)

acrylonitrile (107-13-1)

thorium (7440-29-1)

Cycloheptanone (502-42-1)

1-(Nitromethyl)cyclohexanol (3164-73-6)

1-(aminomethyl)cyclohexanol (4000-72-0)

1,1,3,3-tetramethylcyclobutane-2,4-dione (933-52-8)

suberic acid (505-48-6)

diethyl suberate (2050-23-9)

suberonitrile (629-40-3)

sodium methylanilide

suberyl chloride (10027-07-3)

triethylamine (121-44-8)

cyclohexanone cyanohydrin (931-97-5)

tetrahydrobenzonitrile

cyclohexylmethylamine (3218-02-8)

Cyclooctanone (502-49-8)

potassium p-toluenesulfonate

potassium tert-butoxide (865-47-4)

p-Tolylsulfonylmethylnitrosamide

sodium salt of 1-(nitromethyl)cyclohexanol