



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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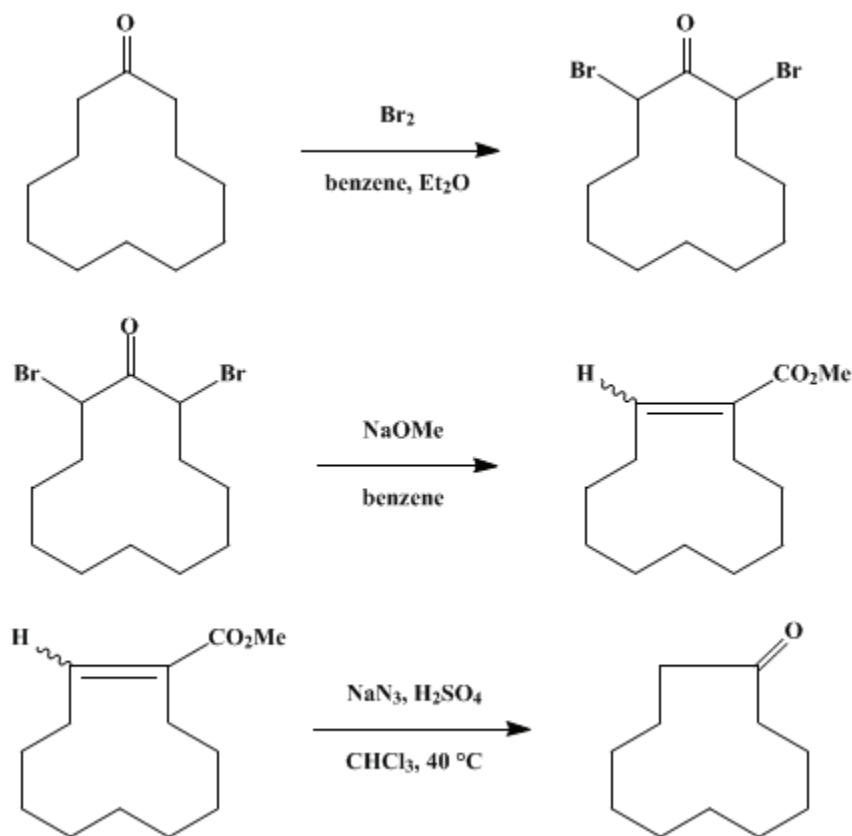
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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RING CONTRACTION *via* A FAVORSKII-TYPE REARRANGEMENT: **CYCLOUNDECANONE**



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1. Procedure

Caution! Hydrazoic acid, which is used in Part C of this procedure, is very toxic. Consequently, the conversion of methyl 1-cycloundecenecarboxylate to cycloundecanone by the Schmidt degradation, including hydrolysis and subsequent steam distillation, should be conducted in a well-ventilated hood.

Pure hydrazoic acid in a condensed state has been reported in several instances to explode violently without apparent inducement, but explosions during Schmidt reactions do not seem to have been observed. Nevertheless, it is recommended that this reaction be carried out behind a safety shield.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *2,12-Dibromocyclododecanone.* A 3-l., three-necked, round-bottomed flask is fitted with a magnetic stirrer (Note 1), a pressure-equalizing dropping funnel, a thermometer, and a gas-outlet tube. The outlet tube is connected by Tygon tubing to a calcium chloride drying tube, which is placed near an

exhaust port of a hood. The flask is charged with 182 g. (1.00 mole) of **cyclododecanone** (Note 2), 1.4 l. of dry **benzene** (Note 3), and 150 ml. of anhydrous **diethyl ether**, and the funnel with 320 g. (2.00 moles) of **bromine** (Note 4). The reaction vessel is immersed in a water bath, stirring is initiated, and **bromine** is added at such a rate that the **bromine** in solution is consumed before the addition of each new drop; the addition requires 20–30 minutes. Ice is added to the water bath, as required, to hold the reaction temperature at 20–25°. The gas-outlet tube is then connected to a water aspirator, the dropping funnel is replaced with a stopper, and the water bath is filled with warm water. While stirring is continued, the pressure in the reaction flask is gradually decreased to evaporate the **hydrobromic acid** formed (together with most of the ether and some of the **benzene**) until the aspirator water is neutral to indicator paper (Note 5). Approximately 1 l. of solution remains in the flask, and this is used directly for the next step.

B. *Methyl 1-cycloundecenecarboxylate*. The **benzene** solution of **2,12-dibromocyclododecanone** prepared in Part A is stirred and treated with 125 g. (2.31 moles) of powdered **sodium methoxide** (Note 6), which is added in portions over 30–40 minutes. Ice is added to the water bath, as required, to hold the reaction temperature at 25–30°. After being stirred at 25–30° for another 20 minutes, the reaction mixture is extracted successively with 500-ml. portions of water, 5% **hydrochloric acid**, and saturated aqueous **sodium chloride**. The aqueous phases are combined, extracted with 400 ml. of **ether**, and discarded. The combined organic phases are filtered through anhydrous **sodium sulfate**, the solvents are evaporated under reduced pressure, and the residual oil is distilled through a 7-cm., insulated Vigreux column (0.4 mm.). Collection of the fractions boiling below 104° provides 191–196 g. (91–93%) of **methyl 1-cycloundecenecarboxylate** (Note 7) as a pale yellow oil, most of which distils at 83–87° (0.4 mm.). This ester is sufficiently pure for use in the next step.

C. *Cycloundecanone*. In a well-ventilated hood a 3-l.; three-necked, round-bottomed flask is fitted with a magnetic stirrer (Note 1), a thermometer, a reflux condenser protected by a calcium chloride tube, and a rubber stopper. Concentrated **sulfuric acid** (600 ml.) is placed in the flask, stirred slowly, and cooled to 5° with an ice bath. **Methyl 1-cycloundecenecarboxylate** (191–196 g., 0.91–0.92 mole) is added through a long-stemmed funnel, the rate of stirring is increased until the mixture becomes a homogeneous solution, and 500 ml. of **chloroform** is added. The resulting mixture is heated to 35° by immersion in a warm water bath. Vigorous stirring is continued while 78 g. (1.2 moles) of **sodium azide** (Note 8) is added in small portions over a 30–50-minute period, the reaction temperature being maintained at $40 \pm 2^\circ$ by adding ice to the water bath. *Caution! This operation should be performed behind a safety shield.* After an additional 10–15 minutes of stirring at 35–40°, the reaction mixture is cooled to 5°, poured onto 1 kg. of ice, and transferred together with 1.5–2 l. of water to a 5-l., three-necked flask set up for steam distillation. The **chloroform** is distilled off and saved, and the **cycloundecanone** is steam distilled with 3.5–4.0 kg. of steam. The steam distillate is extracted with the recovered **chloroform**, then with 500 ml. of **ether**. After the ethereal extract has been washed with concentrated aqueous **sodium chloride**, the organic phases are filtered through anhydrous **sodium sulfate**, combined, and concentrated under reduced pressure. Vacuum distillation of the residual oil affords 139–143 g. (83–85%) of **cycloundecanone** as a colorless or pale yellow oil, b.p. 84–85° (2 mm.), n_D^{25} 1.4794–1.4796 (Note 8).

2. Notes

1. A Thomas Magne-Matic Stirrer Model 15 (available from the Arthur H. Thomas Company, Philadelphia, Pennsylvania, was used in conjunction with a 5-cm., Teflon-coated, egg-shaped magnet.
2. **Cyclododecanone** was obtained from the Aldrich Chemical Company, Inc., and used without purification.
3. Solvent grade **benzene** was dried over **sodium** wire prior to use. If a voluminous sludge forms on drying, the solvent should be distilled from **sodium**.
4. Various brands and grades of **bromine** were used without noticeable difference (however, *cf.* reference ²). **Bromine** was added until a light orange color persisted for more than 2 minutes, which occasionally required the addition of a few drops in excess of the theoretical amount.
5. At this stage, the addition of a small amount of anhydrous **potassium hydrogen carbonate** powder to the residual reaction mixture should not cause evolution of **carbon dioxide** gas.
6. The submitters used the reagent as supplied by Mallinckrodt Chemical Works. The checkers have

occasionally found that commercially available sodium methoxide has deteriorated on storage over an extended period, unless the reagent has been properly protected from moisture. Therefore, it was prepared in the following manner. A 2-l., three-necked, round-bottomed flask was equipped with a magnetic stirrer and a reflux condenser and flushed with dry nitrogen through a gas bubbler attached to the top of the condenser. Into this flask was distilled approximately 600 ml. of absolute methanol (dried with magnesium methoxide), and then 69 g. of sodium was added in 1–3-g. portions. After all of the sodium had dissolved, the methanol was distilled, first at atmospheric and then at reduced pressure. The resulting mass of sodium methoxide was powdered under nitrogen and dried under vacuum at 150° for 8 hours. Titration of the reagent against 0.1311 N hydrochloric acid showed it to be 97.5% pure.

7. GC analysis of the product showed two major peaks (relative intensity, 5:1), and the mass spectrum of each peak revealed a molecular ion at m/e 210. The ¹H NMR spectrum of the mixture showed that the two products were geometrically isomeric esters.

8. Practical grade sodium azide was obtained from Eastman Organic Chemicals, and lumps were broken up with a spatula. Care was taken to avoid contact of sodium azide with the skin.

9. The cycloundecanone solidified on cooling and melted at 16.2–16.6°. GC analysis of the product showed a single peak [1.5 m. by 3.2 mm. column, 5% SE-30 on Chromosorb W, at 125° (submitters); 1.5 m. by 3.2 mm. column, UC-W98, 150°, retention time 10.25 minutes (checkers)]. ¹H NMR (CDCl₃), δ (multiplicity, number of protons): 1.3–2.1 (m, 16H), 2.4–2.7 (m, 4H); IR (neat) cm⁻¹: 1700, very strong.

3. Discussion

Cycloundecanone has been prepared in several ways: (a) pyrolysis of the thorium salt of dodecanedioic acid,³ (b) reduction of 2-hydroxycycloundecanone,^{4,5} (c) ring expansion of several lower homologs of cycloundecanone,⁶ (d) Curtius degradation of 1-cycloundecenecarboxylic acid,² and (e) hydrolysis of 1-methoxycycloundecene.⁷

The present method, a modification of a procedure described previously by the submitters,⁸ gives higher yields and is less expensive and more expeditious than the previously published methods. This route, involving a Favorskii-type rearrangement, has the potential of being widely applicable for the preparation of the lower homolog of a ketone having at least one hydrogen atom at each α-position. For example, cyclodecanone has been prepared in 77% yield from cycloundecanone by essentially the same procedure.⁸

References and Notes

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Appendix

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

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

magnesium methoxide

sodium azide (26628-22-8)

Cyclodecanone (1502-06-3)

Cycloundecanone (878-13-7)

Methyl 1-cycloundecenecarboxylate (3667-72-9)

2,12-Dibromocyclododecanone (24459-40-3)

2-hydroxycycloundecanone

1-cycloundecenecarboxylic acid

1-methoxycycloundecene

potassium hydrogen carbonate (298-14-6)

cyclododecanone (830-13-7)

thorium salt of dodecanedioic acid

