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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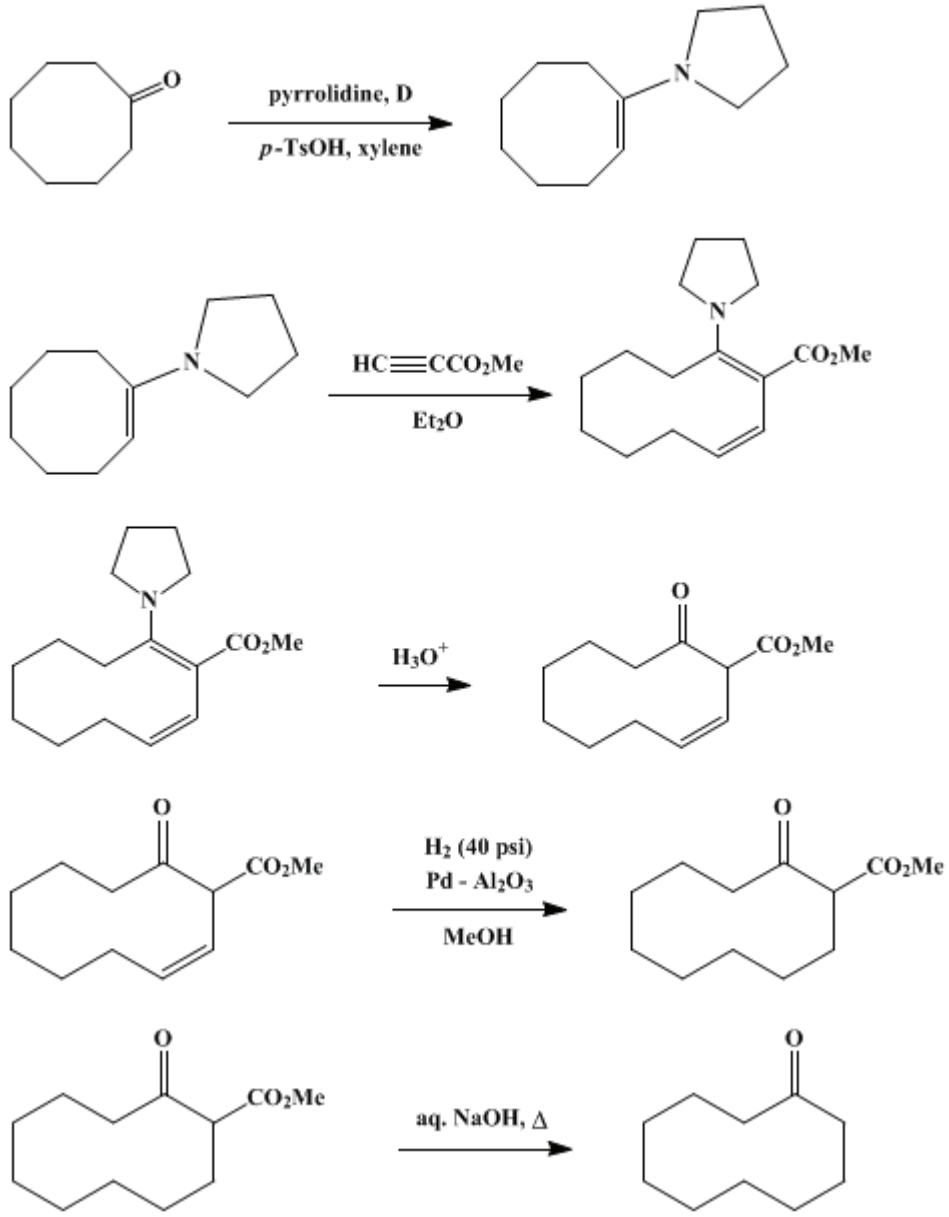
CYCLODECANONE



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1. Procedure

To a 500-ml. round-bottomed flask fitted with a 25- to 30-cm. column packed with glass helices to which is attached a water separator[2] filled with hexane (Note 1) are added 126 g. (1.00 mole) of cyclooctanone (Note 2), 100 g. (1.4 moles) of pyrrolidine, 100 ml. of xylene, and 0.5 g. of *p*-toluenesulfonic acid. The solution is heated under reflux until the separation of water ceases (Note 3). The water separator is replaced by a distillation head, and the reaction mixture is distilled through the column under reduced pressure to remove solvent and unreacted starting materials. When the head temperature reaches 50° (1 mm.), distillation is stopped, and the residue of almost pure N-(1-cycloocten-1-yl)pyrrolidine (152–161 g.) is used in the next step without further purification (Note 4).

The crude enamine is dissolved in 450 ml. of ether, and the solution is transferred to a 1-l. three-necked flask equipped with a sealed stirrer, a 250-ml. dropping funnel, and a two-necked adapter fitted with a calcium chloride tube and a thermometer immersed in the solution. A solution of 71–76 g. (0.85–0.90 mole) (Note 5) of methyl propiolate *(Caution! Methyl propiolate is a severe lachrymator and should be handled only in the hood.)* in 150 ml. of ether is added dropwise. During the addition the temperature of the mixture is maintained at 25–30° by periodic cooling of the reaction flask in a dry ice-acetone bath. When the addition is almost complete, a white solid begins to separate. The mixture is stirred at 25–30° for an additional hour, cooled to 0°, and filtered to remove the solid. This is dissolved in 700 ml. of 6% hydrochloric acid (Note 6), the acidic solution is warmed at 55–60° for 1 hour, and the mixture is cooled and extracted with two 100-ml. portions of ether. The ether is removed on a steam bath, and the residue of crude methyl 10-oxocyclodec-2-ene-1-carboxylate is dissolved in 300 ml. of methanol and hydrogenated over 5 g. of 5% palladium-on-alumina catalyst at 40 p.s.i. pressure and room temperature.

The catalyst is filtered, 200 g. (155 ml.) of 25% aqueous sodium hydroxide is added to the filtrate, and the mixture is heated under reflux for 1 hour. The condenser is replaced by a short Vigreux column and distillation head, and the heating is continued until most of the methanol has distilled. The two-phase residue is cooled and extracted with two 100-ml. portions of ether. The ether is removed on a steam bath, and the residue is distilled through a 20-cm. Vigreux column to yield 68–77 g. (44–50%) of cyclodecanone, b.p. 94–98° (10 mm.), m.p. 20–22° (Note 7).

2. Notes

1. If hexane is not used in the trap, an excessive amount of pyrrolidine is lost in the aqueous layer.
2. Cyclooctanone from Aldrich Chemical Co., methyl propiolate from Farchan Research Laboratories, and pyrrolidine from Eastman Organic Chemicals were used as received.
3. The reaction is usually complete after 3–6 hours at reflux. Owing to dissolved pyrrolidine, the aqueous layer amounts to 35–45 ml., and thus its volume is not a good measure of the extent of reaction.
4. Pure N-(1-cycloocten-1-yl)pyrrolidine, b.p. 76–78° (1 mm.), may be isolated by distillation through a Vigreux column.
5. The amount used should be adjusted to be equimolar with the amount of crude enamine.
6. This solid intermediate is reasonably stable to storage under nitrogen; however, the yield in the acid hydrolysis step is better when freshly prepared material is hydrolyzed immediately.
7. The same reaction sequence may be used to convert cyclododecanone to cyclotetradecanone. Preparation of the pyrrolidine enamine of cyclododecanone requires 2–3 days at reflux, and reaction of the enamine with methyl propiolate is best carried out in refluxing hexane. The enamine-propiolate reaction may also be used to convert cycloheptanone to cyclononanone. In this case the procedure must be modified to provide for partial hydrogenation of the intermediate amino ester without prior hydrolysis.[3] The reduced intermediate is saponified as described in the present procedure.

3. Discussion

Cyclodecanone has been obtained together with other products in the pyrolysis of the thorium or yttrium salts of nonanedioic acid.[4] It has also been prepared by reduction of sebacoin with zinc and hydrochloric acid,[5,6] by dehydration of sebacoin followed by catalytic hydrogenation,[7] by ring enlargement of cyclononanone with diazomethane[8,9] and of cyclooctanone with diazomethane in the presence of a Lewis acid catalyst,[9] by hydroboration of 1,2-cyclodecadiene followed by oxidation of the organoborane,[10] and by the present procedure.[3]

4. Merits of the Preparation

The chief merits of this preparation are its simplicity and the high purity of the product. Although the synthesis involves several steps, each step is a simple operation, and all intermediates may be used in the subsequent steps without purification. The purity of even the crude product is high, and any impurities which may be present are readily removed by a simple distillation.

The overall yield of cyclodecanone is comparable to the overall yield obtained by conversion of

dimethyl sebacate to sebacoin[11] and subsequent reduction to cyclodecanone.[6] In addition, the present procedure does not require the use of a high-speed stirrer, the rigorous exclusion of air, and the high dilution that are necessary in preparing sebacoin.

References and Notes

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

Sebacoin

palladium-on-alumina

enamine-propiolate

thorium or yttrium salts of nonanedioic acid

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

zinc (7440-66-6)

xylene (106-42-3)

Diazomethane (334-88-3)

pyrrolidine (123-75-1)

hexane (110-54-3)

Cyclodecanone (1502-06-3)

cyclononanone (3350-30-9)

Cycloheptanone (502-42-1)

dimethyl sebacate (106-79-6)

Cyclooctanone (502-49-8)

cyclododecanone (830-13-7)

methyl propiolate (922-67-8)

N-(1-cycloocten-1-yl)pyrrolidine

methyl 10-oxocyclodec-2-ene-1-carboxylate

cyclotetradecanone (3603-99-4)

pyrrolidine enamine

1,2-cyclodecadiene

p-toluenesulfonic acid (104-15-4)