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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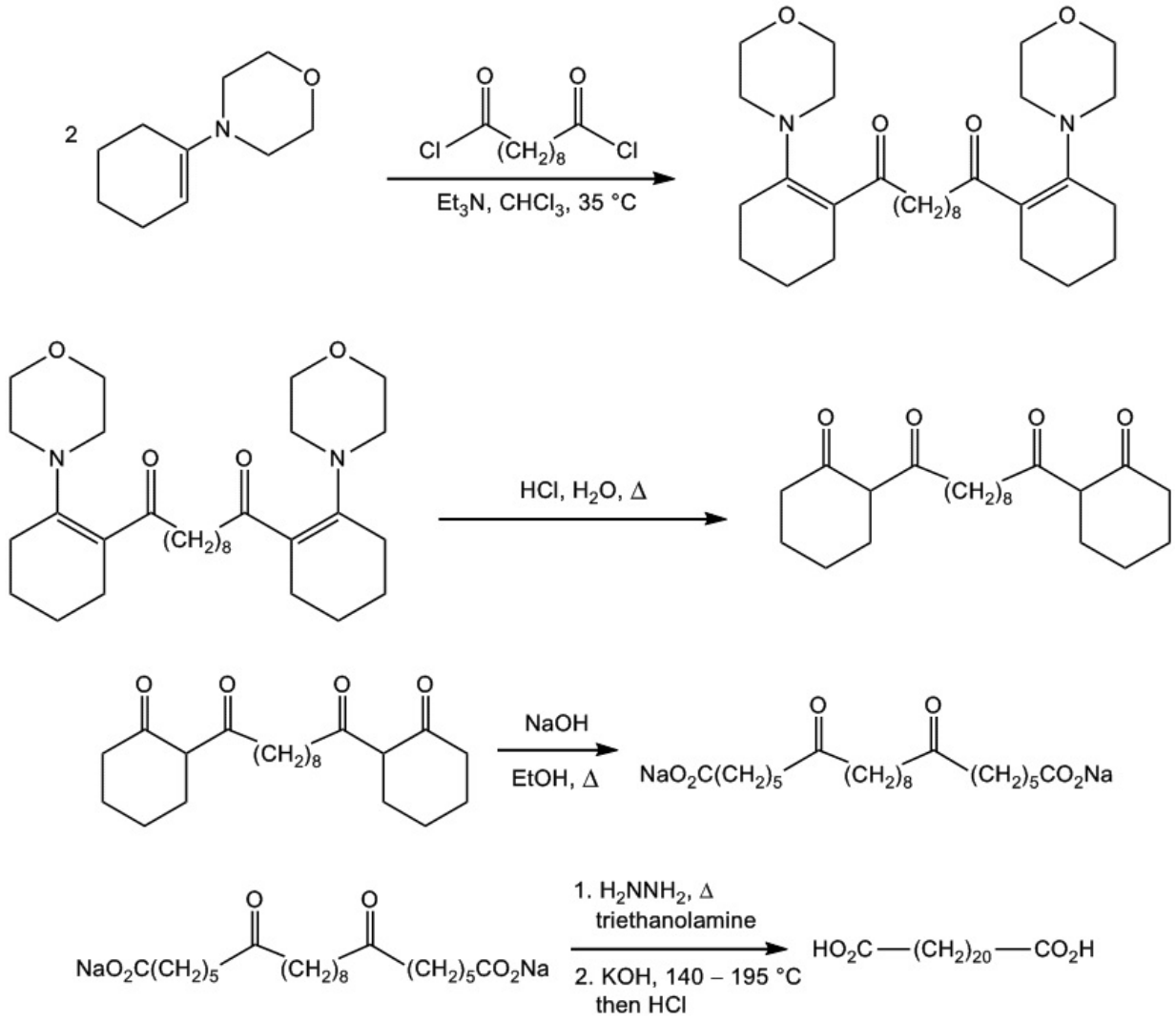
DOCOSANEDIOIC ACID



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1. Procedure

A. *2,2'-Sebacoyldicyclohexanone*. A solution of 167 g. (1.00 mole) of 1-morpholino-1-cyclohexene[2] and 101 g. (139 ml., 1.00 mole) of anhydrous triethylamine in 500 ml. of dry chloroform (Note 1) is put in a 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser. Tubes of calcium chloride are inserted in the open ends of the dropping funnel and reflux condenser. The reaction flask is immersed in a water bath at 35°, and a solution of 120 g. (0.50 mole) of sebacoyl chloride (Note 2) in 200 ml. of dry chloroform is added to the well-stirred reaction mixture over a period of about 1.5 hours. The reaction mixture gradually assumes an orange to red color, and a solid precipitates. The reaction mixture is stirred for an additional 3 hours at 35°, 500 ml. of 20% hydrochloric acid is added, and the mixture is boiled under reflux for 5 hours with vigorous stirring. The reaction mixture is cooled to room temperature, and the chloroform layer is separated and extracted with six 150-ml. portions of water. The washings and the aqueous phase are combined, adjusted to a pH of 5–6 with 25% sodium hydroxide solution, and extracted with five 100-ml. portions of chloroform. The chloroform extracts are combined with the chloroform layer, and the chloroform is

removed by distillation on a steam bath. The residue gradually congeals to an oily solid on standing at room temperature under a pressure of 10–50 mm. The yield of crude 2,2'-sebacoyldicyclohexanone is 181–192 g. (100–106%) (Note 3).

B. *Disodium 7,16-diketodocosanedioate*. A mixture of 120 g. (3.00 moles) of sodium hydroxide and 1.4 l. of commercial absolute ethanol is refluxed with mechanical stirring in a 5-l. round-bottomed flask until all the sodium hydroxide is dissolved (about 2 hours). The solution is cooled to room temperature, and a warm solution of the crude 2,2'-sebacoyldicyclohexanone from Step A in 300 ml. of absolute ethanol is added. The mixture is brought to a boil on a water bath or steam bath in the course of about 15 minutes and is then refluxed for 1 hour. Colorless disodium 7,16-diketodocosanedioate separates during the heating. The reaction mixture, now a thick mush, is cooled to room temperature, and the salt is collected on a 25-cm. Büchner funnel and pressed as dry as possible, preferably with the aid of a rubber dam. The moist salt is suspended in 1 l. of absolute ethanol with mechanical stirring and is then collected on the Büchner funnel as before. After being dried in air, the crude colorless disodium 7,16-diketodocosanedioate weighs 248–255 g. (112–115%, based on 1-morpholino-1-cyclohexene). It is pure enough for the following reduction to docosanedioic acid (Note 4).

C. *Docosanedioic acid*. All the crude disodium 7,16-diketodocosanedioate of Step B is added to 1 l. of triethanolamine in a 5-l. round-bottomed flask equipped with a reflux condenser, a thermometer, a mechanical stirrer, and a deep oil bath. The mixture is heated under reflux until all the salt dissolves (about 15 minutes). The solution is cooled to 130°, 610 ml. (10 moles) of 82% hydrazine hydrate is added through the reflux condenser, and the mixture is refluxed for 4 hours (Note 5).

Potassium hydroxide (168 g., 3.0 moles) is dissolved in 400 ml. of triethanolamine by heating the mixture to boiling in a 1-l. Erlenmeyer flask (about 15 minutes is required). At the end of the reflux period, the hot reaction mixture is transferred to a good hood if it is not already in one, the condenser is removed, and the hot potassium hydroxide solution is added cautiously but rapidly to the stirred reaction mixture (Note 6). The open reaction mixture is at least two-thirds immersed in the oil bath to help prevent foaming over and is heated strongly and rapidly in order to drive off water and excess hydrazine hydrate. After 2–3 hours the temperature inside the flask reaches about 140°, and decomposition of the bis-hydrazone begins, with evolution of nitrogen and considerable foaming. Foaming over is prevented by judicious regulation of the heating, good stirring, and occasional addition of a little silicone oil, which is a good antifoaming agent (Note 7). The temperature is raised as rapidly as possible to 195° (about 2 hours is needed) and held at this temperature for 6 hours. The final oil bath temperature is 200–220°.

The reaction mixture is cooled to about 100° (Note 5), washed out of the flask with 5 l. of hot water (Note 8), and acidified to a pH between 2 and 3 with 1.4 l. of 12*N* hydrochloric acid. The mixture is cooled to room temperature, and the docosanedioic acid that has precipitated is collected on a 25-cm. Büchner funnel and pressed as dry as possible (Note 9). The filter cake is suspended in 5 l. of water with mechanical stirring and collected on the Büchner funnel as before. The moist filter cake is dissolved in 700 ml. of hot 2-methoxyethanol, the hot solution is filtrate through a fluted paper in a heated funnel, and the filtrate is gradually cooled to 0–5°. The docosanedioic acid that crystallizes out is separated on a Büchner funnel, pressed as dry as possible, and suspended in 500 ml. of 95% ethanol with mechanical stirring. The acid is collected on a Büchner funnel, washed with a little 95% ethanol, dried in air, and pulverized. The colorless docosanedioic acid thus obtained weighs 127–133 g. (69–72%, based on 1-morpholino-1-cyclohexene) and is nearly pure; m.p. 124–126°; neutralization equivalent 181–184 (calculated, 185) (Note 10) and (Note 11).

2. Notes

1. Satisfactory chloroform is obtained by washing 2 l. of commercial chloroform with two 100-ml. portions of 2*N* sodium carbonate solution and two 200-ml. portions of water and distilling it until no more water codistils and the boiling point is 61°. The material remaining in the distillation pot is used without distillation.
2. Satisfactory sebacoyl chloride can be purchased from the Eastman Kodak Co., Rochester, New York. The submitters prepared it as follows. A mixture of 150 g. (0.74 mole) of sebacic acid and 150 ml. of thionyl chloride is heated in a water bath at 60°. The acid gradually goes into solution with evolution of

sulfur dioxide and hydrogen chloride. When gas evolution ceases, the mixture is distilled as rapidly as possible under reduced pressure. The yield of sebacoyl chloride, b.p. 171–175°/15 mm., is about 140 g. (79%). *Caution! Toward the end of the distillation, spontaneous decomposition of the residue with formation of a voluminous black foam frequently occurs.*

3. The tetraketone can be obtained in a pure form by recrystallizing it first from ether with the addition of decolorizing carbon and then from *n*-butanol; yield 50–58%; m.p. 68–72°.

4. The submitters obtained pure 7,16-diketodocosanedioic acid by the following procedure. A solution of 300 ml. of 12*N* hydrochloric acid in 3 l. of water is stirred into a warm solution of 250 g. of the crude disodium 7,16-diketodocosanedioate in 3 l. of water. The resultant suspension of the diketo acid is boiled for a few minutes to make the acid easier to filter, then cooled to room temperature and collected on a Büchner funnel. The filter cake is suspended in 3 l. of water with mechanical stirring and collected on a Büchner funnel, and this procedure is repeated. The moist well-pressed filter cake is recrystallized from 600 ml. of 2-methoxyethanol. The recrystallized acid is suspended in 500 ml. of 95% ethanol, separated on a Büchner funnel, and dried in air. About 120 g. (61%) of pure 7,16-diketodocosanedioic acid is obtained; m.p. 127–129°; equivalent weight 196 ($-CO_2H$), 200

$$(>C=O)$$

(calculated, 199).

5. One may interrupt the procedure at this point and allow the mixture to stand overnight at room temperature.

6. It is essential for good results that the procedure not be interrupted from the time that the potassium hydroxide solution is added until the time that the 6-hour heating at 195° is completed.

7. Additional security against foaming over is provided by a glass tube that projects into the neck of the flask and is attached to a water pump. The checkers found it helpful to use a Hershberg stirrer with two wire blades; the upper blade was adjusted so that its ends extended above the surface of the reaction mixture and into the foam.

8. The aqueous mixture is not clear because the sodium salt is sparingly soluble in water.

9. The precipitate can be more rapidly separated by means of a centrifuge.

10. Very pure docosanedioic acid can be obtained by another recrystallization from about 450 ml. of 2-methoxyethanol. The recrystallized acid is collected on a Büchner funnel, and the well-pressed filter cake is suspended in 200 ml. of 95% ethanol, refiltered, and dried in air; weight 112 g. (61%); m.p. 126–127°; neutralization equivalent, 185–187.

11. The checkers found it slightly more convenient to recrystallize the moist crude docosanedioic acid from 1 l. of methyl ethyl ketone. The hot solution is filtered and cooled, and the acid is collected on a Büchner funnel, washed with methyl ethyl ketone, and dried in air.

3. Discussion

Docosanedioic acid has been prepared by Wolff-Kishner reduction of 6,17-diketodocosanedioic acid, formed by reaction of the half-ester acid chloride of adipic acid with the αω-cadmium derivative of decane (%26 overall yield).[3] Reduction of ω-[5-(ω-carboxy-*n*-octyl)-2-thenoyl]caprylic acid by the Wolff-Kishner method, followed by simultaneous reduction and desulfurization with Raney nickel of the 2,5-bis(*w*-carboxyoctyl)thiophene produced, is reported to yield docosanedioic acid in 68% overall yield.[4] Other routes to docosanedioic acid include electrolysis of the monomethyl ester of dodecanedioic acid (43% yield);[5] oxidative coupling of 10-undecynoic acid to docosa-10,12-diynedioic acid (90% yield) and reduction of this intermediate with a palladium catalyst;[6] and reaction of α,ω-diiodoeicosane with potassium cyanide followed by hydrolysis of the dinitrile produced.[7]

The present method of making docosanedioic acid has been described by Hünig and Lücke.[8] The Wolff-Kishner reduction of the diketonic intermediate is an application of the modification of Gardner, Rand, and Haynes.[9]

4. Merits of the Preparation

The present procedure has been used to convert suberoyl chloride to eicosanedioic acid (44%), and it is probably a general method for increasing by twelve carbon atoms the chain length of dicarboxylic

acids whose chain length is eight or more carbon atoms.[8] A variant of the method, in the first step of which the ester chloride of a dicarboxylic acid is condensed with 1-morpholino-1-cyclohexene, has also been used to prepare dicarboxylic acids. Thus the mono-ester acid chloride of succinic acid has been converted to sebacic acid (48%), that of suberic acid to tetradecanedioic acid (34%), and that of sebacic acid to hexadecanedioic acid (32%).[8] A general method of increasing the chain length of a carboxylic acid by six carbon atoms is to employ a monoacyl chloride in the present procedure; overall yields of acids from nonanoic to tetracosanoic are 42–48%.[10] 1-Morpholino-1-cyclopentene[11] can be used in the same sort of syntheses as 1-morpholino-1-cyclohexene; thus, by starting with it and lauroyl chloride, heptadecanoic acid can be obtained in 60% yield.[12] Similarly, an enamine of cyclododecanone has been used to lengthen the chain of monocarboxylic acids by twelve carbon atoms, and of dicarboxylic acids by twenty-four; for instance, stearic acid has been converted to triacontanoic acid (70%), and suberic acid to pentatricontanedioic acid (40%).[13]

How to decide whether the enamine method or some other method is better for preparing a given mono- or dicarboxylic acid is discussed in two papers.[8,10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 808

References and Notes

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

αω-cadmium derivative of decane

Raney nickel of the 2,5-bis(w-carboxyoctyl)thiophene

ethanol (64-17-5)

hydrogen chloride,
hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

Adipic acid (124-04-9)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

Succinic acid (110-15-6)

n-butanol (71-36-3)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

palladium (7440-05-3)

hydrazine hydrate (7803-57-8)

methyl ethyl ketone (78-93-3)

sebacic acid (111-20-6)

stearic acid (57-11-4)

lauroyl chloride (112-16-3)

2-methoxyethanol (109-86-4)

suberic acid (505-48-6)

suberoyl chloride (10027-07-3)

triethylamine (121-44-8)

1-Morpholino-1-cyclohexene (670-80-4)

10-Undecynoic acid (2777-65-3)

cyclododecanone (830-13-7)

Docosanedioic acid (505-56-6)

2,2'-Sebacoyldicyclohexanone (17343-93-0)

sebacoyl chloride (111-19-3)

disodium 7,16-diketodocosanedioate (134507-60-1)

triethanolamine (102-71-6)

7,16-diketodocosanedioic acid

6,17-diketodocosanedioic acid

dodecanedioic acid (693-23-2)

docosa-10,12-diynedioic acid (28393-02-4)

eicosanedioic acid (2424-92-2)

tetradecanedioic acid (821-38-5)

hexadecanedioic acid (505-54-4)

1-Morpholino-1-cyclopentene

triacontanoic acid (506-50-3)

pentatricontanedioic acid

ω-[5-(ω-carboxy-n-octyl)-2-thenoyl]caprylic acid

Heptadecanoic acid (506-12-7)

α,ω-diiodoeicosane