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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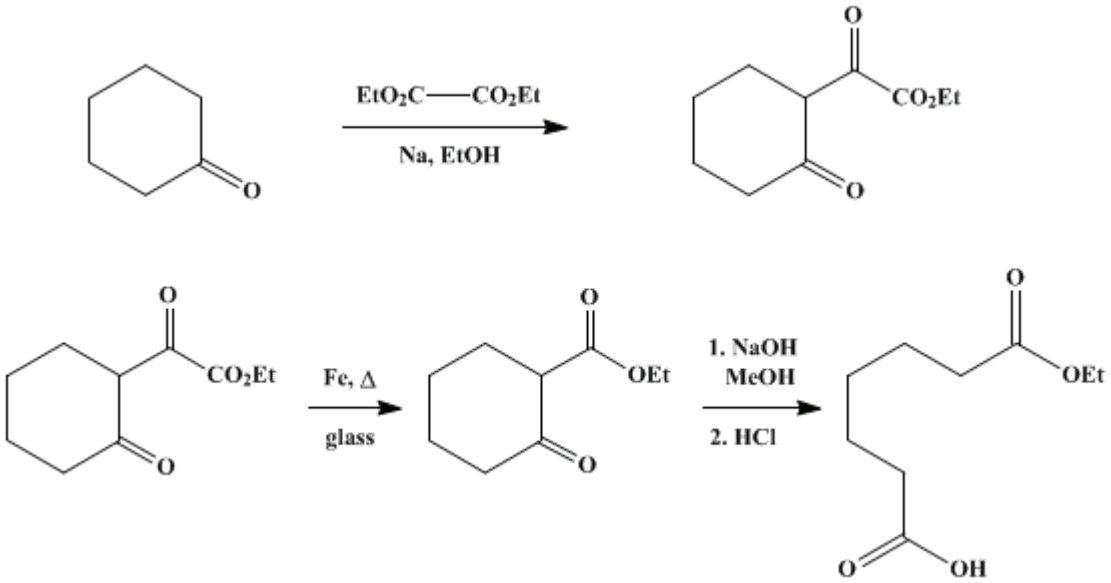
Organic Syntheses, Coll. Vol. 2, p.531 (1943); Vol. 11, p.42 (1931).

PIMELIC ACID

[(*A*) (*From Cyclohexanone*)]



Submitted by H. R. Snyder, L. A. Brooks, and S. H. Shapiro.
Checked by Lee Irvin Smith, R. T. Arnold, and John Moran.

1. Procedure

A solution of sodium ethoxide is prepared by the cautious addition of 46 g. (2 gram atoms) of clean sodium to 600 cc. of anhydrous ethyl alcohol (Note 1) in a 2-l. three-necked flask equipped with a dropping funnel, a mercury-sealed stirrer, and a reflux condenser carrying a calcium chloride tube. The flask is then immersed in an ice-salt bath and the stirrer is started. When the temperature of the solution has reached 10° (Note 2) an ice-cold solution of 196 g. (2 moles) of cyclohexanone (Note 3) in 292 g. (2 moles) of ethyl oxalate (Note 4) is added from the dropping funnel over a period of about fifteen minutes. Vigorous stirring is required to prevent complete solidification of the reaction mixture (Note 5). When the addition is complete, the ice bath is retained for an hour, and then the mixture is stirred at room temperature for about six hours.

The reaction mixture is then decomposed by the careful addition of ice-cold dilute sulfuric acid prepared by adding 56 cc. of concentrated acid (sp. gr. 1.84) to 435 g. of ice. During this neutralization the temperature of the mixture is maintained at about 5–10° by means of an ice-salt bath. The solution, which should now be acid to Congo red paper, is diluted with cold water to a volume of about 4 l. The ethyl 2-ketocyclohexylglyoxalate separates as a heavy oil and is removed. The aqueous solution is extracted with four 500-cc. portions of benzene. The crude product is combined with the extracts, and the resulting solution is washed with two 200-cc. portions of water. The benzene solution is then allowed to stand in a separatory funnel for a few minutes until it is free from suspended water.

The benzene solution, without drying, is transferred in portions of about 500 cc. to a 1-l. Claisen flask connected to a water-cooled condenser. The flask is heated on the steam bath until the benzene no longer distils. The steam bath is then replaced by an oil bath and the system is gradually evacuated to a pressure of 10–12 mm. while the oil bath is held at about 90°. When all the benzene, unchanged ester, and ketone have distilled (Note 6) the temperature of the oil bath is increased. When the temperature of the distillate reaches 105°/10–12 mm. the receiver is changed. The bath temperature is immediately raised to 175° and all material distilling between 105° and 165° at 10–15 mm. is collected. This requires one-half to one hour. During this time the bath temperature is slowly increased to 200° to obtain the last

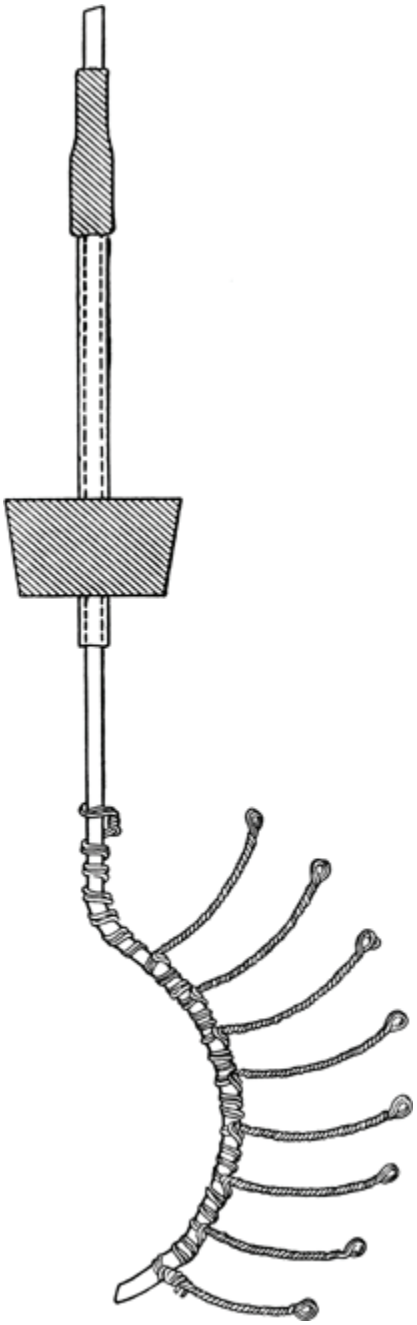
portions. The yield is 250–265 g. (63–67 per cent of the theoretical amount). The distillate is transferred to a 500-cc. modified Claisen flask, and a trace of iron powder and some finely ground soft glass are added (Note 7). The mixture is distilled at 40 mm. with the bath temperature maintained at 165–175° (Note 8). Carbon monoxide is evolved and the distillate is collected between 125° and 140°. About one and a half to two hours is required for the pyrolysis. The yield of ethyl 2-ketohexahydrobenzoate is 200–210 g. (59–62 per cent of the theoretical amount based on cyclohexanone). This product, whose refractive index at 25° varies from 1.476 to 1.479, is sufficiently pure for use in the next step without redistillation.

In a 2-l. three-necked flask equipped with a dropping funnel, a reflux condenser, and a special stirrer (Note 9) is placed 100 g. (2.5 moles) of sodium hydroxide and 300 cc. of anhydrous methyl alcohol. The stirred mixture is heated for one hour in an oil bath held at 120° in order to effect solution of most of the sodium hydroxide. Stirring and heating are continued while 100 g. (0.59 mole) of ethyl 2-ketohexahydrobenzoate is added over a period of two hours. The resulting mixture is heated for one hour longer with the bath temperature at 120°. It is then diluted with 600 cc. of water and the condenser is arranged for distillation. The methyl alcohol is removed by distillation until a thermometer immersed in the boiling solution reads 98–100°. The residual aqueous solution is vigorously stirred, and exactly 210 cc. of concentrated hydrochloric acid (sp. gr. 1.18) is carefully added drop by drop from a dropping funnel (Note 10). The hot acid solution is treated with 2–4 g. of Darco and is filtered through a heated Büchner funnel. The filtrate is cooled in an ice bath. The pimelic acid is collected on a Büchner funnel and is crystallized from 100 cc. of boiling water for each 45 g. of acid. After drying in the air the acid melts at 103.5–104° and weighs 65–73 g. The mother liquors from the hydrolysis and recrystallization are combined and evaporated to dryness on a steam bath. The resulting solid is extracted with two 500-cc. portions of acetone. The acetone is distilled from a steam bath, and the residual crude pimelic acid is recrystallized from the minimum quantity of benzene, yielding an additional 10–12 g. of pure material. The total yield is 75–83 g. (80–88 per cent of the theoretical amount based on ethyl 2-ketohexahydrobenzoate; 47–54 per cent based on cyclohexanone).

2. Notes

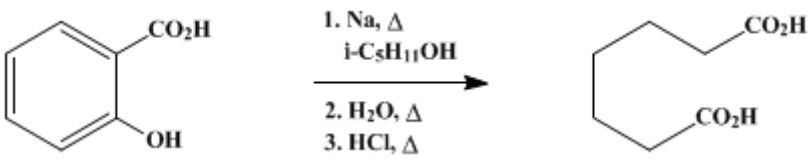
1. Dry sodium methoxide can be used with good results. One hundred eight grams (2 moles) of sodium methoxide (Matheson Alkali Company) and 400 cc. of anhydrous ethyl alcohol are used instead of the sodium ethoxide solution.
2. The dropping funnel may be replaced with a cork carrying a thermometer during this part of the procedure.
3. Commercial cyclohexanone was redistilled through a 20-in. column packed with Carborundum. The fraction boiling at 154°/746 mm. is of sufficient purity.
4. Commercial ethyl oxalate was redistilled from a modified Claisen flask, and the fraction boiling at 83–86°/25 mm. was used.
5. A precipitate usually appears within an hour or two after addition of the reagents. If the solution is orange in color and no precipitate forms, it may still be worked up with fair results.
6. The last portions of this distillate are tested with ferric chloride. A red or violet color indicates ethyl 2-ketohexahydrobenzoate.
7. More than a milligram of iron, although increasing the rate of pyrolysis, leaves behind a hard residue difficult to remove. Ordinary soft glass is ground in a mortar; from 0.5 to 1 g. is sufficient.
8. If the bath temperature is too high, the unpyrolyzed ester will distil. A high refractive index indicates the presence of unchanged ester.
9. The stirrer (Fig. 17) is constructed by wrapping a double strand of copper magnet wire around a semicircular glass stirring rod. At intervals a loop of the wire is twisted to make a projection which extends about 2" in. from the glass rod. The stirrer is introduced into the center neck of the three-necked flask. The projections are arranged so that they touch the sides of the flask when the stirrer is in use. This adjustment is made by a steel or glass rod introduced through one of the side necks. The scraping of the sides of the flask by the copper wire prevents the deposition of the salt on the walls, with consequent moderation of bumping. With an ordinary stirrer the yield in this step is at least 10 per cent less.

Fig. 17



10. The solution becomes almost clear when sufficient acid has been added.

[(*B*) (*From Salicylic Acid*)]



Submitted by Adolf Müller
Checked by Reynold C. Fuson, J. R. Little, and Wesley Fugate.

1. Procedure

Four hundred cubic centimeters of freshly distilled isoamyl alcohol (b.p. 128–132°) is heated to 90–100° on an oil bath in a 5-l. two-necked flask fitted with a dropping funnel and reflux condenser. Two hundred forty grams (10.4 gram atoms) of clean sodium is then added, and the temperature of the oil bath is raised rapidly until the alcohol is brought to vigorous boiling (Note 1). A solution of 100 g. (0.73 mole) of salicylic acid in 2 l. of isoamyl alcohol is allowed to flow into the flask at the rate of 100 cc. every four minutes, so that the entire amount is added over a period of eighty minutes. The dropping funnel is then rinsed with 100 cc. of isoamyl alcohol. The solution in the flask is clear at first, then becomes cloudy with the addition of the salicylic acid. The temperature of the oil bath is regulated so that the alcohol refluxes rapidly throughout the course of the experiment. The sodium goes completely into solution in seven to eight hours.

The flask is then allowed to cool to 100°, and 800 cc. of hot water is added with vigorous shaking (Note 2). The hot mixture is transferred to a 5-l. separatory funnel, the flask being rinsed with 200 cc. of hot water (Note 3). The mixture is shaken well and the layers separated. The isoamyl alcohol layer is extracted with four or five 200-cc. portions of nearly boiling water (Note 4). The combined aqueous extracts are then steam-distilled in order to remove any isoamyl alcohol from the aqueous solution of the sodium salt. About 500 cc. of distillate is collected (Note 5).

The flask is allowed to cool, and 920 cc. of hydrochloric acid (sp. gr. 1.19) is added. The unchanged salicylic acid is then steam-distilled from the mixture. The flask is strongly heated, so that its contents are concentrated and, towards the end of the distillation, sodium chloride begins to precipitate. The removal of salicylic acid is practically complete when about 10–12 l. of distillate has come over, although the distillate still gives a ferric chloride test for salicylic acid. The solution in the flask is allowed to cool overnight and is finally chilled in an ice bath.

The crystalline precipitate, which is a mixture of sodium chloride and pimelic acid, is then collected on a suction filter without washing. The product is dried in an evaporating dish on the water bath for several hours, with frequent stirring, whereby the brown mass is partially melted. The mass, after cooling, is transferred to a 500-cc. Soxhlet thimble. The Soxhlet apparatus is mounted over a hot plate and the solid extracted with about 650 cc. of benzene. Complete extraction is indicated when the liquid in the siphon is no longer turbid (Note 6). The extraction is complete when evaporation of a small quantity of the solution in the extractor leaves no residue (two to three hours). After the extraction is complete, the benzene solution is concentrated to about 300 cc. and the pimelic acid allowed to crystallize. The crystals are collected on a filter, washed with cold benzene, and dried in the air. The product melts at 104–105° and weighs 50–58 g. (43–50 per cent of the theoretical amount).

2. Notes

1. The yield of pimelic acid is materially reduced if the alcohol is not refluxing rapidly at this point.
2. The water must be added slowly and with thorough shaking at first, since traces of unchanged sodium may still be present.
3. Unless hot water (85–90°) is used for the extractions troublesome emulsions are likely to form. If such emulsions do form they may be broken by passing steam into the solution while in the separatory funnel.
4. A large portion of the isoamyl alcohol may be recovered for use in subsequent preparations. The moist alcohol from the water extractions is directly distilled, and a fraction boiling at 128–135° collected. The alcohol layer in the fore-run may be separated from the water layer and redistilled with the moist alcohol from the following run.
5. Ethyl pimelate may be prepared by proceeding as follows: The combined aqueous extracts, instead of being subjected to steam distillation, are evaporated on a steam bath until the thick crystalline magma which forms has only a faint odor of isoamyl alcohol. The magma is dissolved in 600 cc. of water, and 800 cc. of concentrated hydrochloric acid is added. The mixture is cooled to room temperature and filtered, and 170 cc. of concentrated hydrochloric acid is added to the filtrate. The acid mixture is extracted with three 400-cc. portions of ether—a continuous extractor such as that shown in Org. Syn. Coll. Vol. I, **1941**, 277, can be used to advantage—and the ether is removed from the extract by distillation. Upon cooling the residue in an ice bath, crystals separate; they are cooled thoroughly, collected on a Büchner funnel, and pressed on a porous plate. The filtrate, after the addition of a few

pieces of porous plate, is left overnight in a vacuum desiccator over concentrated sulfuric acid. The crystals which separate are collected on a filter, pressed on a porous plate, and added to the rest of the product. The total weight is 60–70 g.

The crude material, which is a mixture of pimelic and salicylic acids, is esterified by boiling for four hours with 520 cc. of absolute ethyl alcohol and 6 cc. of concentrated sulfuric acid. Two-thirds of the alcohol is then removed by distillation. To the residue, 600 cc. of water and 400 cc. of ether are added, the mixture is shaken, and the aqueous layer is drawn off. The ether solution is shaken with two 200-cc. portions of 2 *N* sodium hydroxide solution to remove ethyl salicylate, and then with water until the disappearance of an alkaline reaction. The ether is evaporated and the residue is distilled under reduced pressure. Ethyl pimelate boils at 153–156°/24 mm.; 148–152°/22 mm. The yield is 54–60 g. (35–38 per cent of the theoretical amount based upon the salicylic acid).

In this procedure it is important to remove the brown sludge formed by partial acidification of the alkaline solution of the sodium salts. If all the hydrochloric acid is added at once, ether extraction of the entire precipitate is tedious because of the slow separation of the aqueous and ether layers. It is also important to wash the ether solution of ethyl pimelate and ethyl salicylate carefully with sodium hydroxide solution in order to avoid loss of product by hydrolysis. (Private communication by Adolf Müller and Erich Rölz. Checked by W. H. Carothers and W. L. McEwen.)

6. During some runs the pimelic acid begins to crystallize in the siphon. This difficulty may be minimized by fashioning an asbestos jacket around the extraction chamber. Occasionally it is necessary to pass steam over the siphon.

3. Discussion

Pimelic acid has been obtained as a by-product of the reaction between trimethylene bromide and sodium cyanoacetic ester;[1] by the action of carbon dioxide upon pentamethylene-1,5-dimagnesium bromide;[2] by hydrolysis of pentamethylene cyanide;[3] by the action of sodium and amyl alcohol upon salicylic acid, guaiacol carboxylic acid,[4] or anthranilic acid;[5] and from 2-cyanocyclohexanone.[6]

The preparation of pimelic acid from cyclohexanone, described in Part (*A*) above, and from salicylic acid, described in Part (*B*) above,[7] are new procedures in Organic Syntheses. The older directions for preparing ethyl pimelate[8] are given as Note 5 on p. 536.

References and Notes

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3. Hamonet, ibid. **139**, 60 (1904); Bull. soc. chim. (3) **33**, 532 (1905); v. Braun, Ber. **37**, 3591 (1904).
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8. Müller and Rölz, ibid. **48**, 734 (1927); Org. Syn. **11**, 42.

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

Ethyl 2-ketocyclohexylglyoxalate

pimelic and salicylic acids

sodium cyanoacetic ester

pentamethylene-1,5-dimagnesium bromide

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

iron,
iron powder (7439-89-6)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

Trimethylene bromide (109-64-8)

salicylic acid

carbon dioxide (124-38-9)

acetone (67-64-1)

sodium methoxide (124-41-4)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ferric chloride (7705-08-0)

Anthranilic Acid (118-92-3)

Ethyl oxalate

isoamyl alcohol (123-51-3)

amyl alcohol (71-41-0)

Pimelic acid (111-16-0)

Ethyl 2-ketohexahydrobenzoate (1655-07-8)

Ethyl pimelate (33018-91-6)

ethyl salicylate (118-61-6)

pentamethylene cyanide (646-20-8)

2-cyanocyclohexanone

guaiacol carboxylic acid (6324-11-4)