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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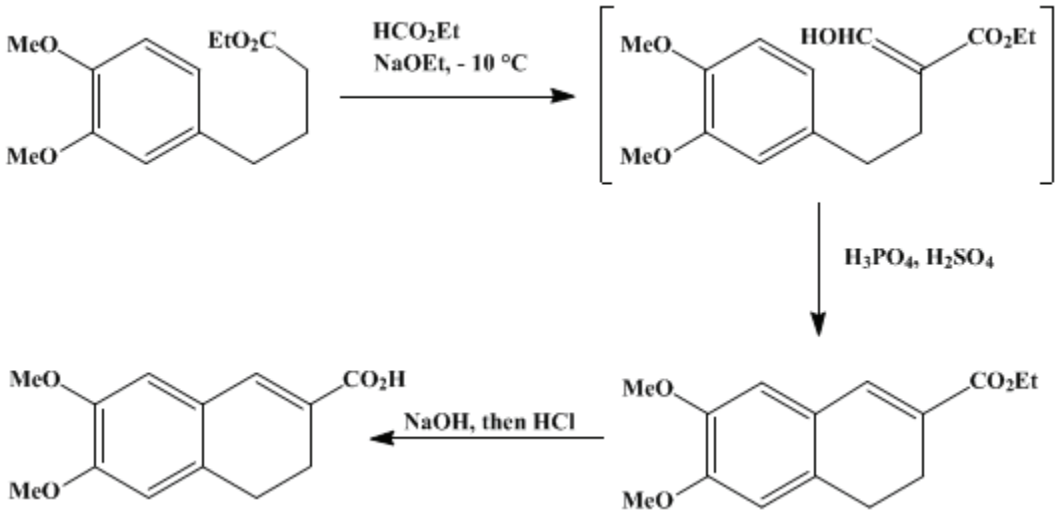
Organic Syntheses, Coll. Vol. 3, p.300 (1955); Vol. 26, p.28 (1946).

6,7-DIMETHOXY-3,4-DIHYDRO-2-NAPHTHOIC ACID

[2-Naphthoic acid, 3,4-dihydro-6,7-dimethoxy-]



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1. Procedure

A. *Ester condensation*. A suspension of 9.40 g. (0.41 gram atom) of powdered sodium[1] in 100 ml. of absolute ether is placed in a 1-l. three-necked flask (Note 1) fitted with a reflux condenser, dropping funnel, and a calcium chloride tube. A solution of 23.8 ml. (0.41 mole) of absolute ethanol (Note 2) in 50 ml. of absolute ether is added through the dropping funnel, and the mixture is refluxed on a steam bath for 10–11 hours. The reflux condenser is replaced by a mercury-seal stirrer. A thermometer and a calcium chloride tube are fitted into the third neck of the flask. The suspension of sodium ethoxide in absolute ether is cooled to −10° to −15° in an ice-hydrochloric acid bath, and a solution of 47.85 g. (0.19 mole) of ethyl γ-veratrylbutyrate (Note 3) and 29.6 g. (0.40 mole) of ethyl formate in 100 ml. of absolute ether is added dropwise through the dropping funnel with vigorous stirring (Note 4). The mixture is kept at −10° for 4 hours, and then the thermometer and calcium chloride tube are removed and the stirrer is replaced by a reflux condenser equipped with a calcium chloride tube. The mixture is allowed to come to room temperature and stand for 72 hours. During this time a gas is evolved and a pale yellow solid separates.

On digestion of this solid mass with 1 l. of ice and water, the sodium salt of the enol dissolves in the water, and the unreacted ester is removed by extracting the aqueous layer with two 200-ml. portions of ether (Note 5). The formyl derivative settles out as an oil upon acidification of the aqueous layer with dilute sulfuric acid. The oil is extracted with three 200-ml. portions of ether, and the ethereal extract is washed several times with water and dried over anhydrous sodium sulfate. The ether is distilled, and, to remove traces of ethyl formate, the oil is heated on a steam bath under a pressure of 20–30 mm. for 1 hour. The remaining yellow formyl derivative weighs 27–29 g. (Note 6).

B. *Cyclization*. The above oil is poured dropwise into a well-stirred mixture of 110 ml. of 90% phosphoric acid (sp. gr. 1.75) and 23.4 ml. of sulfuric acid (sp. gr. 1.83) which is kept at −10°. The temperature is allowed to rise to 0–10°, and the stirring is continued for 2 hours. The viscous reaction mixture is poured into 500 ml. of ice and water, and the acid is partially neutralized with 300 ml. of 40% sodium hydroxide solution with efficient cooling. The viscous cream-colored oil is extracted with three 150-ml. portions of ether; the ether extract is washed well with water and sodium bicarbonate solution to remove the last traces of acid and then dried over anhydrous sodium sulfate. The cyclized ester, after

removal of the ether, is a red oil which solidifies upon cooling. The yield is 23–24 g.

C. *Saponification*. The ester is saponified by refluxing for 5 hours with 75 ml. of a 10% sodium hydroxide solution containing 3 ml. of ethanol; it is then poured into 150 ml. of water and decolorized with Norit. Upon acidification of the alkaline solution with dilute hydrochloric acid, 18–19 g. (40–43%) (Note 7) and (Note 8) of acid is obtained, melting at 191–193° (cor.).

2. Notes

1. It is suggested that a flask with a ground-glass joint be employed for the condensation as it leads to less discoloration of the formylation product.
2. The absolute ethanol employed in the condensation was refluxed over calcium oxide for 20 hours and finally distilled from magnesium ethoxide.
3. The ethyl γ-veratrylbutyrate, b.p. 203–207°/20 mm., is obtained in 80% yield by esterification of γ-veratrylbutyric acid by the Fischer-Speier method. The γ-veratrylbutyric acid is prepared by the method of E. L. Martin[2] from β-(3,4-dimethoxybenzoyl) propionic acid.
4. The ethereal solution of the two esters should be added at such a rate that the addition is complete in about 1 hour.
5. On distillation, after removal of the ether, 18–20 g. of the ethyl γ-veratrylbutyrate is recovered.
6. The formylation product is too sensitive to purify by distillation even at pressures of 1–2 mm. of mercury.
7. In a similar manner, 3,4-dihydro-2-naphthoic acid, m.p. 111–114° (cor.), and 7-methoxy-3,4-dihydro-2-naphthoic acid, m.p. 149–150.5° (cor.), have been obtained in 35% yields.
8. 6,7-Dimethoxy-3,4-dihydro-2-naphthoic acid can be dehydrogenated[3] to give 6,7-dimethoxy-2-naphthoic acid. The yield of the latter was 85% after distillation and crystallization from ethanol.

3. Discussion

This method of preparation is essentially that used by Robinson and Crowley[4] for the preparation of 6-methoxy-3,4-dihydro-2-naphthoic acid. They first used concentrated sulfuric acid but found that this reagent caused sulfonation.

References and Notes

1. *Org. Syntheses*, **18**, 25 (1938); Coll. Vol. **2**, 195 (1943).
2. E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1440 (1936); *Org. Syntheses*, **17**, 97 (1937); Coll. Vol. **2**, 499 (1943).
3. *Org. Syntheses*, **18**, 59 (1938); Coll. Vol. **2**, 423 (1943).
4. Robinson and Crowley, *J. Chem. Soc.*, **1938**, 2003.

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

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

mercury (7439-97-6)

Norit (7782-42-5)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

sodium ethoxide (141-52-6)

calcium oxide

ethyl formate (109-94-4)

γ-veratrylbutyric acid

6,7-Dimethoxy-3,4-dihydro-2-naphthoic acid,
2-Naphthoic acid, 3,4-dihydro-6,7-dimethoxy- (53684-50-7)

ethyl γ-veratrylbutyrate

magnesium ethoxide (2414-98-4)

β-(3,4-dimethoxybenzoyl) propionic acid

3,4-dihydro-2-naphthoic acid

7-methoxy-3,4-dihydro-2-naphthoic acid

6,7-dimethoxy-2-naphthoic acid

6-methoxy-3,4-dihydro-2-naphthoic acid

sodium salt (824-79-3)