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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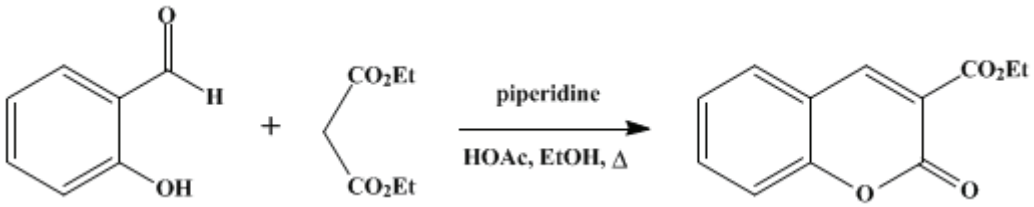
3-CARBETHOXYCOUMARIN

[2H-1-Benzopyran-3-carboxylic acid, 2-oxo-, ethyl ester]



Submitted by E. C. Horning, M. G. Horning, and D. A. Dimmig.
Checked by Richard T. Arnold and Marshall Freerks.

1. Procedure

In a 500-ml. round-bottomed flask equipped with a reflux condenser are placed 61 g. (0.50 mole) of salicylaldehyde (Note 1), 88 g. (0.55 mole) of ethyl malonate, and 200 ml. of absolute ethanol. To this mixture are added 5 ml. of piperidine (Note 2) and 0.5 ml. of glacial acetic acid, and the solution is heated under reflux for 3 hours. The hot solution is transferred to a 1-l. Erlenmeyer flask, the reaction flask is rinsed with 20 ml. of ethanol, and the ethanol rinse and 330 ml. of hot water (Note 3) are added to the solution. The product crystallizes readily as the solution cools; the mixture is stirred from time to time as crystallization proceeds and is finally stored overnight in a refrigerator. The crystalline product is collected by filtration and washed with a solution made from 80 ml. of 95% ethanol and 120 ml. of water. The material is dried in the air. The yield is 85–91 g. (78–83%) of product melting at 91–93°.

The product may be recrystallized by dissolving it in 200 ml. of hot ethanol (95%), filtering, and adding 315 ml. of hot water. The recrystallized product is washed on the filter with 200 ml. of aqueous ethanol, as before, and air-dried. The yield of white 3-carbethoxycoumarin is 79–85 g. (73–78%); m.p. 92–94°.

2. Notes

1. The yield of the final product (m.p. 92–94°) may be increased to 80–84% by the use of salicylaldehyde purified in the following manner.
Preparation of pure salicylaldehyde.[1] Two hundred and fifty grams (1 mole) of copper sulfate pentahydrate is dissolved in 500 ml. of hot water in a 1-l. Erlenmeyer flask, and 244 g. (2 moles) of salicylaldehyde (Eastman practical grade) is added. A solution of 80 g. (2 moles) of sodium hydroxide in 100 ml. of water is added slowly in small portions with intermittent vigorous shaking. The mixture is permitted to cool slowly to room temperature with intermittent shaking and is finally allowed to stand overnight. The solid is collected and washed with 200 ml. of ethanol (95%), digested with 400 ml. of ether, and again collected on a filter. Without drying, the product is treated with 1 l. of water containing 108.5 g. (59 ml., 105 moles) of 95% sulfuric acid. The mixture is shaken vigorously, and 200 ml. of ether is added to break up the oily mass that forms. The aldehyde is collected in ether and recovered by distillation of the dried (over calcium sulfate) solution. It distils at 96–97°/35 mm.; the recovery is 90%.
2. Eastman practical grade is satisfactory.
3. The water should be heated to about 60°.

3. Discussion

This compound has been prepared only by the Knoevenagel[2] condensation, with a secondary amine as a catalytic agent. The corresponding methyl ester and free acid have also been prepared by using methyl malonate[3] and malonic acid,[4] respectively, in the condensation with salicylaldehyde.

References and Notes

1. Claisen and Eisleb, *Ann.*, **401**, 95 (1914).
2. Knoevenagel, *Ber.*, **31**, 2593 (1898).
3. Werder, *Jahresber.*, **50**, 88 (1936).
4. U. S. pat. 2,338,569 [*C. A.*, **38**, 3671 (1944)].

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

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

calcium sulfate (7778-18-9)

piperidine (110-89-4)

Salicylaldehyde (90-02-8)

ethyl malonate (1071-46-1)

Malonic acid (141-82-2)

methyl malonate

3-Carbethoxycoumarin,
2H-1-Benzopyran-3-carboxylic acid, 2-oxo-, ethyl ester (1846-76-0)

copper sulfate pentahydrate (7758-99-8)