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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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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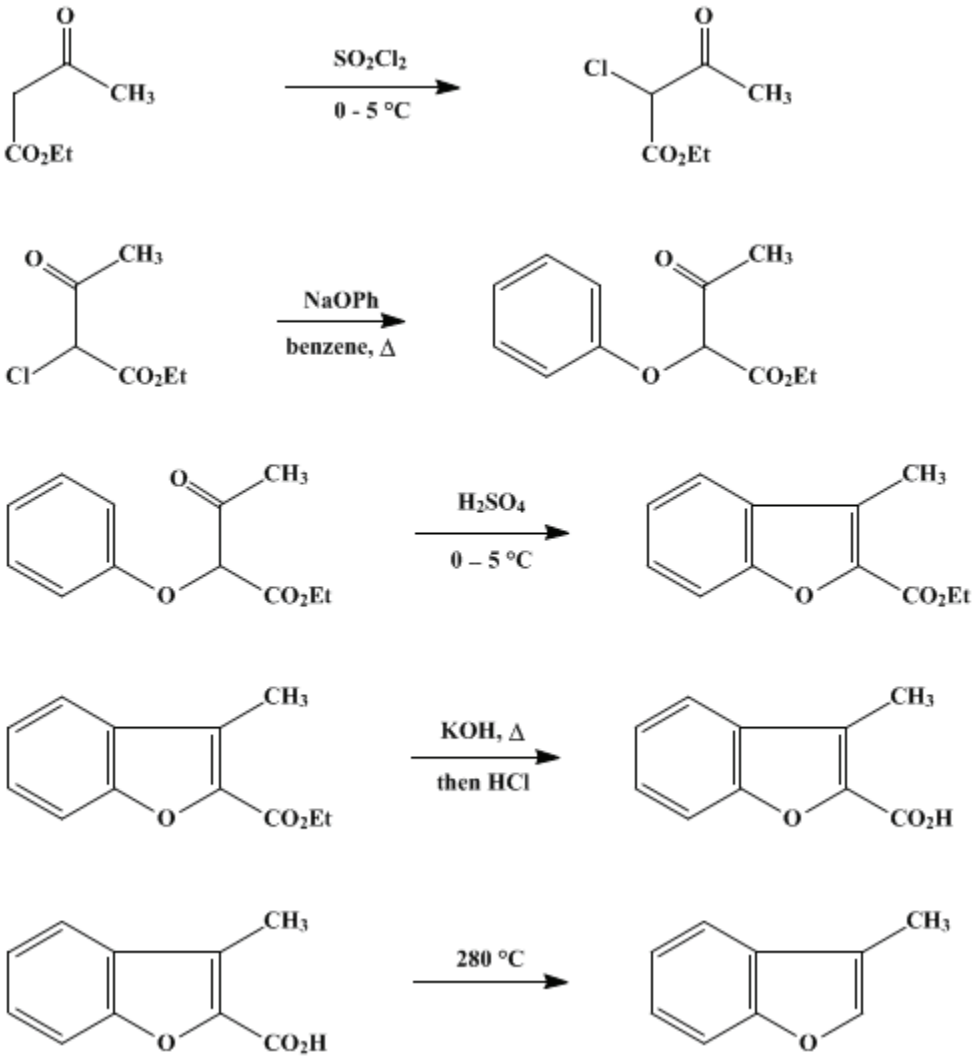
3-METHYLCOUMARONE

[Benzofuran, 3-methyl-]



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1. Procedure

A. *Ethyl 3-methylcoumarilate.* Dry sodium phenolate (116 g., 1 mole) (Note 1) and 1 l. of dry thiophene-free benzene (Note 2) are placed in a 2-l. three-necked flask fitted with mechanical stirrer, dropping funnel, and reflux condenser with drying tube. The suspension is heated to the boiling point on the steam bath, heating is moderated, and 165 g. (1 mole) of ethyl α-chloroacetoacetate (Note 3) is added with stirring through the dropping funnel at such a rate as to maintain gentle refluxing (Note 4). Refluxing and stirring are continued on the steam bath for 4 hours after the addition of the chloroester has been completed. The light brown suspension is cooled to room temperature, extracted with two 500-ml. portions of water, and dried superficially by filtration through a layer of anhydrous magnesium sulfate. The solvent is removed by distillation on the steam bath under water-aspirator vacuum. The brown oil remaining consists of crude ethyl α-phenoxyacetoacetate and weighs 188–200 g. (85–90%).

Concentrated sulfuric acid (195 ml.) is placed in a 2-l. three-necked flask immersed in an ice-salt

bath and fitted with a dropping funnel, a thermometer, and a mechanical stirrer. Ethyl α-phenoxyacetoacetate (195 g.) is added with stirring through the dropping funnel while the temperature within the flask is maintained below 5°. About 1 hour is required for the addition. The mixture, which solidifies soon after all the ester has been added, is allowed to stand in the ice bath for 1 hour longer. Ice (500 g.) and water (500 ml.) are added with stirring and external cooling. The mixture is then extracted with two 250-ml. portions of benzene. The combined extracts are washed with 100 ml. of water, then with 100 ml. of saturated aqueous sodium bi-carbonate solution, and finally are dried superficially by filtration through a layer of anhydrous magnesium sulfate. The solvent is distilled from the dried extracts, and the residue is fractionated under reduced pressure from a 250-ml. Claisen flask fitted with a short air condenser. The pale-yellow oil boils at 162–167°/16 mm. and solidifies on cooling. The product is triturated with a little petroleum ether (b.p. 35–60°) and dried at room temperature. The almost colorless rhombic plates, melting at 49–51°, weigh 60–75 g. (34–42%).

B. *3-Methylcoumarilic acid.* Ethyl 3-methylcoumarilate (70 g.) and 500 ml. of 10% aqueous potassium hydroxide solution are refluxed for 1 hour. The clear yellowish solution is acidified while hot (Note 5) with a slight excess of concentrated hydrochloric acid to precipitate the 3-methylcoumarilic acid. The suspension is cooled to room temperature, and the colorless solid is filtered with suction. The filter cake is resuspended in 500 ml. of cold water, stirred vigorously for several minutes, and filtered again with suction. The colorless powder, after being dried in a desiccator under reduced pressure, weighs 54–57 g. (90–95%) and melts at 192–193°.

C. *3-Methylcoumarone*. Dry 3-methylcoumarilic acid (50 g.) is distilled from a 250-ml. Claisen flask fitted with a long air condenser and immersed in a Wood's metal bath heated slowly to 280°. Carbon dioxide is evolved, and a cloudy liquid distils at 190–220°. The crude product is purified by redistillation through a Vigreux column (Note 6). The clear colorless distillate, weighing 31.5–33 g. (84–88%), boils at 195–197°, n_D^{25} 1.5520.

2. Notes

1. Sodium phenolate may be prepared *in situ* by evaporating molar equivalents of phenol and sodium hydroxide solution in the reaction flask on the steam bath under reduced pressure and drying the residue by heating the flask for several hours longer on the steam bath under reduced pressure. The solid cake of dry sodium phenolate breaks up in the succeeding step of the synthesis.
2. Benzene is conveniently dried by slowly distilling about 20% of it and cooling the residue with protection from atmospheric moisture by use of a calcium chloride tube.
3. Ethyl α-chloroacetoacetate is prepared by the general method of Allihn.[2] *Caution! Since the substance is a severe lachrymator and gases evolved during the preparation are difficult to absorb, the entire preparation should be carried out in a hood.* In a 1-l. three-necked flask fitted with dropping funnel, a thermometer, and a mechanical stirrer, and connected to a gas-absorption trap,[3] is placed 260 g. (2 moles) of technical grade ethyl acetoacetate. Sulfuryl chloride (270 g., 2 moles) is added slowly with stirring and external cooling, the temperature being maintained between 0° and 5°. About 3 hours is required for the addition. The solution is allowed to stand overnight at room temperature, and hydrogen chloride and sulfur dioxide are removed at 40–50° under water-aspirator vacuum. The residual dark-amber liquid is distilled through a short Vigreux column at reduced pressure. After a small fore-run, the ethyl α-chloroacetoacetate distils at 85–89°/17 mm. The yield of colorless liquid is 308–321 g. (93–97%). The checkers, using a 12-cm. unheated Vigreux column, obtained this yield only after redistilling the combined fore-run and after-run. Ethyl α-chloroacetoacetate is currently available from Distillation Products Industries, Rochester, New York.
4. The time of addition is 20–30 minutes. Some external heating is usually necessary to maintain reflux during the addition.
5. If the solution is allowed to cool much below 70° the potassium salt of 3-methylcoumarilic acid crystallizes in the form of colorless needles.
6. The checkers used an 18-in. Podbielniak column with simple wire spiral, heated jacket, and partial-reflux head.

3. Discussion

3-Methylcoumarone has been prepared by the cyclization of ethyl α-phenoxyacetoacetate followed by hydrolysis and de-carboxylation of the resulting ethyl 3-methylcoumarilate,[4] by debromination and rearrangement of 3,4-dibromo-4-methyl-coumarin to 3-methylcoumarilic acid followed by decarboxylation,[4,5] by cyclization of phenoxyacetone with concentrated sulfuric acid,[6] and by treatment of 3-coumaranone with methyl-magnesium iodide followed by dehydration of the resulting carbinol.[7]

The procedure described is a modification of the method of Hantzsch.[4]

References and Notes

1. The National Drug Company, Philadelphia, Pennsylvania.
2. Allihn, *Ber.*, **11**, 567 (1878).
3. *Org. Syntheses Coll. Vol.* **2**, 4 (1943).
4. Hantzsch, *Ber.*, **19**, 1290 (1886).
5. Peters and Simonis, *Ber.*, **41**, 832 (1908).
6. Stoermer, *Ber.*, **28**, 1254 (1895).
7. Stoermer and Barthelmes, *Ber.*, **48**, 67 (1915).

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

sulfuric acid (7664-93-9)

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

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sulfur dioxide (7446-09-5)

carbon dioxide (124-38-9)

sulfuryl chloride (7791-25-5)

potassium hydroxide (1310-58-3)

methyl-magnesium iodide (917-64-6)

Ethyl acetoacetate (141-97-9)

sodium phenolate

magnesium sulfate (7487-88-9)

3-Methylcoumarone,

Benzofuran, 3-methyl- (21535-97-7)

ethyl α-chloroacetoacetate (609-15-4)

ethyl α-phenoxyacetoacetate

sodium bi-carbonate

3,4-dibromo-4-methyl-coumarin

phenoxyacetone (621-87-4)

3-coumaranone (7169-34-8)

Ethyl 3-methylcoumarilate (22367-82-4)

3-Methylcoumarilic acid (24673-56-1)

potassium salt of 3-methylcoumarilic acid