



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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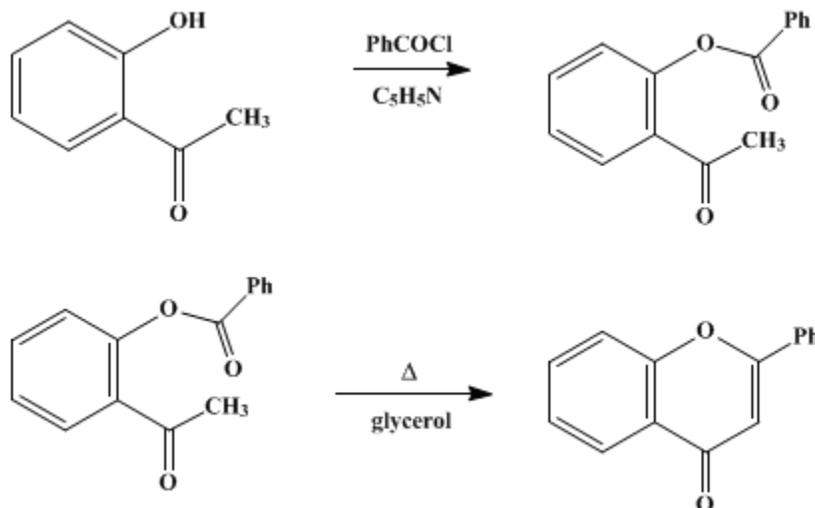
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 4, p.478 (1963); Vol. 32, p.72 (1952).

FLAVONE

[Method 1]



Submitted by T. S. Wheeler¹

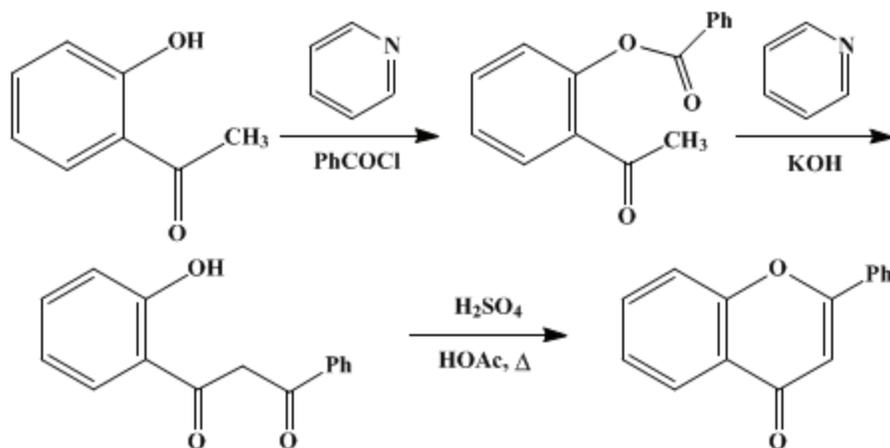
Checked by R. L. Shriner and Donald A. Scott.

1. Procedure

A. *o*-Benzoyloxyacetophenone. In a 100-ml. conical flask fitted with a calcium chloride drying tube are placed 13.6 g. (12 ml., 0.1 mole) of *o*-hydroxyacetophenone,² 21.1 g. (17.4 ml., 0.15 mole) of benzoyl chloride, and 20 ml. of pyridine (Note 1). The temperature of the reaction mixture rises spontaneously, and when no further heat is evolved (about 15 minutes) the mixture is poured with good stirring into 600 ml. of 3% hydrochloric acid containing 200 g. of crushed ice. The product is collected on a Büchner funnel and washed with 20 ml. of methanol, then with 20 ml. of water. The product is sucked as dry as possible and air-dried at room temperature. The yield of dry crude product melting at 81–87° is 22–23 g. It is recrystallized from 25 ml. of methanol, and the *o*-benzoyloxyacetophenone is obtained as white crystals; yield 19–20 g. (79–83%); m.p. 87–88°.

B. *Flavone*. In a 500-ml. round-bottomed three-necked flask, equipped with a mercury-sealed mechanical stirrer, a thermometer, and an air condenser closed with a calcium chloride drying tube in the second neck, are placed 20 g. (0.083 mole) of *o*-benzoyloxyacetophenone and 200 ml. of freshly distilled anhydrous glycerol (Note 2). A stream of nitrogen, dried by passage through a wash bottle containing sulfuric acid, is introduced through the third neck. The mixture is heated and maintained at 260° for two hours while being stirred continuously. The contents are cooled below 100° and then poured into 2 l. of water which is rendered slightly alkaline with aqueous sodium hydroxide. The mixture is stirred for 15 minutes, cooled, and kept at 0° (in a refrigerator) for 48 hours. The tan-colored crystals of flavone are collected on a filter and dried at 50°. The yield of crude product amounts to about 10 g.; m.p. 90–93°. The crude material is dissolved in 400 ml. of hot ligroin (b.p. 60–70°). Repeated partial evaporation of the solvent in stages, each followed by cooling, gives successive crops of flavone as white needles. The yield of pure flavone amounts to 8–9 g. (43–48%); m.p. 96–97°.

[Method 2]



1. Procedure

A. *o*-Benzoyloxyacetophenone. This is prepared as in Method 1.

B. *o*-Hydroxydibenzoylmethane. A solution of 20 g. (0.083 mole) of *o*-benzoyloxyacetophenone in 75 ml. of pyridine (Note 1) is prepared in a 300-ml. beaker and warmed to 50°. To the solution is added 7 g. of hot pulverized 85% potassium hydroxide (Note 3), and the mixture is mechanically stirred for 15 minutes, during which time a copious precipitate of the yellow potassium salt of *o*-hydroxydibenzoylmethane forms (Note 4). The mixture is cooled to room temperature and acidified with 100 ml. of 10% acetic acid. The diketone separates as a light-yellow precipitate which is collected on a filter and sucked dry (Note 5). The yield of crude *o*-hydroxydibenzoylmethane is 16–17 g. (80–85%); m.p. 117–120°.

C. Flavone. To a solution of 16.6 g. (0.069 mole) of the crude diketone in 90 ml. of glacial acetic acid, contained in a 250-ml. conical flask, is added, with shaking, 3.5 ml. of concentrated sulfuric acid. The mixture is heated under a reflux condenser on a steam bath for 1 hour with occasional shaking and is then poured onto 500 g. of crushed ice with vigorous stirring. After the ice has melted, the crude flavone is collected on a filter, washed with water (about 1 l.) until free from acid, and finally dried at 50°. The yield of product is 14.5–15 g. (94–97%); m.p. 95–97°. The over-all yield of flavone based on *o*-hydroxyacetophenone is 59–68%. The product may be recrystallized from ligroin as in Method 1.

2. Notes

- Commercial pyridine is dried over solid sodium hydroxide and distilled through a fractionating column.
- Glycerol is twice distilled under reduced pressure and used immediately in the reaction.
- The potassium hydroxide is pulverized rapidly in a mortar previously heated at 100°.
- The mixture usually becomes so thick and pasty that hand stirring is necessary.
- o*-Hydroxydibenzoylmethane can be crystallized from 95% ethanol and forms crystals melting at 120°, which give a strong enol reaction with ferric chloride. Crystallization is not necessary here.

3. Discussion

o-Benzoyloxyacetophenone has been prepared by the action of benzoyl chloride on a pyridine solution of *o*-hydroxyacetophenone.³ The rearrangement of *o*-benzoyloxyacetophenone to *o*-hydroxydibenzoylmethane by alkali has been described.^{4,5} The latter diketone has been made by the base-catalyzed condensation of ethyl benzoate with *o*-hydroxyacetophenone.⁶ The cyclization of *o*-hydroxydibenzoylmethane described in Method 2 is based on the work of Doyle, Gogan, Gowan, Keane, and Wheeler.⁵ Cyclization has also been effected by use of glacial acetic acid containing hydrogen chloride or sodium acetate.⁴

Other methods of preparing flavone include: the action of ethanolic alkali on 2'-acetoxy- α,β -dibromochalcone;⁷ Claisen condensation of ethyl *o*-ethoxybenzoate and acetophenone, and cyclization of the resulting 1,3-diketone with hydriodic acid;⁸ and treatment of 3-bromoflavanone with potassium hydroxide in ethanol.⁹ Flavone has also been prepared from ethyl phenylpropiolate by condensation with sodium phenoxide and subsequent cyclization with phosphorus pentachloride in benzene;¹⁰ by fusing *o*-hydroxyacetophenone with benzoic anhydride and sodium benzoate;¹¹ by the dehydrogenation of 2'-hydroxychalcone with selenium dioxide;¹² by the action of alkali on flavylum chloride;¹³ by the acid hydrolysis of 3-benzoyl-4-hydroxycoumarin;¹⁴ by the condensation of benzamide with 2-hydroxyacetophenone;¹⁵ and by heating β -morpholino-2-chlorochalcone which cyclizes to 4-morpholinoflavylum chloride, and which in turn may be hydrolyzed to flavone.¹⁶

Method 1 is a new procedure for the direct production of flavone from *o*-benzoyloxyacetophenone and has been successfully applied to the synthesis of other flavones. Method 2, which involves the Baker-Venkataraman transformation, is recommended because of its high over-all yield and the reproducibility of the results. Mozingo and Adkins' method⁶ is satisfactory, but the yield of *o*-hydroxydibenzoylmethane is variable.

References and Notes

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Appendix

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

ligroin

o-benzoyloxyacetophenone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

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

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

glycerol (56-81-5)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

benzamide (55-21-0)

pyridine (110-86-1)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

sodium benzoate (532-32-1)

hydriodic acid (10034-85-2)

ferric chloride (7705-08-0)

ethyl benzoate (93-89-0)

sodium phenoxide

ethyl phenylpropiolate (2216-94-6)

2-hydroxyacetophenone (582-24-1)

Flavone (525-82-6)

3-bromoflavanone

flavylium chloride

3-benzoyl-4-hydroxycoumarin

β -morpholino-2-chlorochalcone

4-morpholinoflavylium chloride

o-Hydroxyacetophenone (118-93-4)

o-Benzoyloxyacetophenone (4010-33-7)

o-Hydroxydibenzoylmethane (1469-94-9)

ethyl o-ethoxybenzoate

potassium salt of o-hydroxydibenzoylmethane

2'-acetoxy- α,β -dibromochalcone

2'-hydroxychalcone