



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.

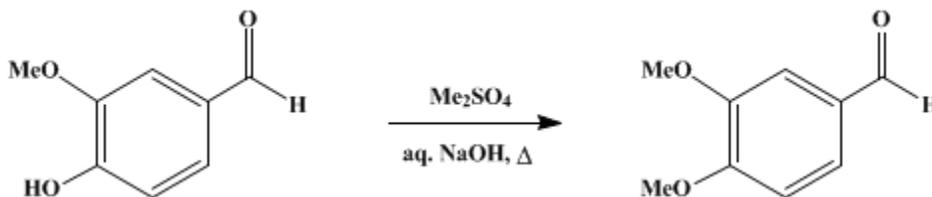
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

Organic Syntheses, Coll. Vol. 2, p.619 (1943); Vol. 13, p.102 (1933).

VERATRALDEHYDE



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1. Procedure

In a 3-l. three-necked flask a mixture of 182 g. (1.2 moles) of [vanillin](#) ([Note 1](#)) and 450 cc. of boiling water is heated on a steam bath. A solution of [sodium hydroxide](#) is prepared by dissolving 150 g. of u.s.p. [sodium hydroxide](#) in 200–300 cc. of water and diluting to 750 cc. A 360-cc. portion of this solution is heated to about 100° and added in one lot to the hot mixture of [vanillin](#) and water ([Note 2](#)). The flask is now fitted with a reflux condenser, mechanical stirrer, and 250-cc. separatory funnel.

Heating is continued on a steam bath, and 189 g. (142 cc.) of [methyl sulfate](#) ([Note 3](#)) is added through the separatory funnel just rapidly enough to maintain the gentle ebullition which starts after the addition of the first 10–15 cc. ([Note 4](#)). After the addition of all the [methyl sulfate](#), which requires about one hour, the reaction mixture is heated for forty-five minutes longer and an additional portion of 39 g. (30 cc.) of [methyl sulfate](#) is added at the same rate as the first portion. At the end of this addition the reaction mixture should show an acid reaction to litmus ([Note 5](#)). After ten minutes' heating the reaction mixture is rendered slightly alkaline by the addition of about 60 cc. of the [sodium hydroxide](#) solution (prepared above), and another 39-g. portion of [methyl sulfate](#) is added. The alternate addition of [sodium hydroxide](#) solution and of [methyl sulfate](#) (39-g. portions) is repeated twice more, so that a total of 345 g. (2.7 moles) of [methyl sulfate](#) is added. The reaction mixture is then made strongly alkaline by the addition of 150 cc. of the [sodium hydroxide](#) solution and is heated for twenty minutes after the last addition of [methyl sulfate](#). The reaction mixture is cooled rapidly to 25° ([Note 6](#)) with continued stirring, and the [veratraldehyde](#) is extracted with three 300-cc. portions of [ether](#).

The combined [ether](#) extracts are dried over anhydrous [magnesium sulfate](#), and the [ether](#) is distilled. There remains a slightly yellow oil which soon solidifies. The yield is 164–173 g. (82–87 per cent of the theoretical amount) of [veratraldehyde](#) melting at 43–44.5°. This product is sufficiently pure for many purposes, but it can be purified further with slight loss by distillation under diminished pressure. From 164 g. of the above product there is obtained 156 g. of pure [veratraldehyde](#), boiling at 153°/8 mm. and melting at 46° ([Note 7](#)). Since this aldehyde is easily oxidized in the air it should be stored in a tightly corked or sealed container.

2. Notes

1. A good grade of [vanillin](#) (m.p. 81–82°) should be used.
2. The reactants are mixed while hot in order to avoid precipitation of the [sodium salt of vanillin](#).
3. A practical grade of [methyl sulfate](#) gives satisfactory results. [Methyl sulfate](#) is very toxic; the vapor must not be inhaled or the liquid spilled. [Ammonia](#) is a specific antidote. The preparation is preferably carried out under a good hood.
4. The yield is usually lowered if this ebullition does not occur.
5. In order to obtain a good yield the reaction mixture must be allowed to become acid at several times. For this reason the last 156 g. of [methyl sulfate](#) is added in four small portions, and the reaction mixture is allowed to become acid after each portion is added. It is convenient to test the reaction of the solution by lowering through the condenser tube a glass tube with a piece of litmus paper attached at the end.
6. If the reaction mixture is cooled too slowly or below 25°, the [veratraldehyde](#) may solidify at this

stage. If this occurs it is advisable to remelt the product before extracting with ether.

7. **Veratraldehyde** of sufficient purity for most synthetic purposes may be prepared rapidly and conveniently by the method of Barger and Silberschmidt, *J. Chem. Soc.* **133**, 2924 (1928). In a 1-l. three-necked, round-bottomed flask (or a wide-mouthed bottle), fitted with a mechanical stirrer, a reflux condenser, and two separatory funnels, 152 g. (1 mole) of **vanillin** is melted by warming on a steam bath. With vigorous stirring, a solution of 92 g. (1.5 moles) of 90 per cent **potassium hydroxide** in 150 cc. of water is run in at the rate of two or three drops a second; twenty seconds after this is started, the addition of 160 g. (120 cc., 1.25 moles) of **methyl sulfate** is begun at about the same rate. (Just before use, the **methyl sulfate** is washed with an equal volume of ice-water, followed by one-third its volume of cold, saturated **sodium bicarbonate** solution.) The external heating is stopped after a few minutes, and the mixture continues to reflux from the heat of reaction. A turbidity soon develops, and separation into two layers occurs after about one-half of the **methyl sulfate** has been added. The addition of both reagents should be completed in about twenty minutes.

The color of the reaction mixture, which is purplish brown at the beginning, changes abruptly to yellow towards the end. A temporary greenish yellow during the earlier part of the reaction indicates that the solution has become acid, and this condition should be corrected by increasing the rate of addition of the alkali. The final yellow color is permanent, and at the end the reaction mixture is alkaline to litmus.

The reaction mixture is transferred at once to a large beaker covered with a watch glass and allowed to cool without disturbance, preferably overnight. The hard, crystalline mass of **veratraldehyde** is removed, ground in a mortar with 300 cc. of ice-water, filtered with suction, and dried in a vacuum desiccator. The yield is 152–158 g. (92–95 per cent of the theoretical amount) of a product melting at 42.5–43.5°. This material gives a 90 per cent yield of the oxime (m.p. 89–90°) and an overall yield of 68–70 per cent of **veratronic nitrile** (m.p. 65–66°)—compare p. 622, below. The nitrile thus produced is satisfactory for the preparation of **aminoveratrole** (p. 44). (John R. Johnson and H. B. Stevenson, private communication.)

3. Discussion

Veratraldehyde has been prepared by treatment of **veratrole** with **hydrogen cyanide** in the presence of **aluminum chloride**;¹ by condensing **veratrole** with **formylpiperidine** and hydrolyzing the product;² and by methylating **vanillin** with **methyl iodide**,³ **methyl sulfate**,⁴ **methyl *p*-toluenesulfonate**,⁵ or **trimethylphenylammonium hydroxide**.⁶

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 2*, 55
- *Org. Syn. Coll. Vol. 2*, 622
- *Org. Syn. Coll. Vol. 4*, 735

References and Notes

1. Gattermann, *Ann.* **357**, 367 (1907).
 2. Akabori and Senoh, *Bull. Chem. Soc. Japan* **14**, 166 (1939) [*C. A.* **33**, 6270 (1939)].
 3. Tiemann, *Ber.* **8**, 1135 (1875); **11**, 663 (1878); Juliusberg, *ibid.* **40**, 119 (1907).
 4. v. Kostanecki and Tambor, *ibid.* **39**, 4022 (1906).
 5. Kanevska, *Arch. Pharm.* **271**, 462 (1933).
 6. Rodionow, *Bull. soc. chim. (4)* **45**, 116 (1929).
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Appendix

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

oxime

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

hydrogen cyanide (74-90-8)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

Veratronic nitrile (2024-83-1)

aminoveratrole

magnesium sulfate (7487-88-9)

Veratraldehyde (120-14-9)

vanillin (121-33-5)

veratrole (91-16-7)

formylpiperidine (2591-86-8)

trimethylphenylammonium hydroxide (1899-02-1)

sodium salt of vanillin

Methyl p-toluenesulfonate (80-48-8)