



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.

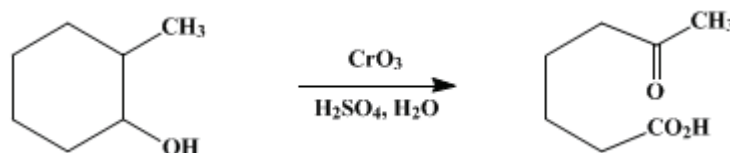
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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δ -ACETYL-*n*-VALERIC ACID

[Heptanoic acid, 6-oxo-]



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1. Procedure

A solution of 368 g. of 96% **sulfuric acid** in 664 ml. of water is cooled to room temperature and placed in a 3-l. three-necked flask provided with a mechanical stirrer, a thermometer, and a dropping funnel. To this acid solution is added 114 g. (1 mole) of **2-methylcyclohexanol** (Note 1). A mixture of 220 g. (2.2 moles) of **chromic oxide** (Note 2) in 368 g. of 96% **sulfuric acid** and 664 ml. of water is added from the dropping funnel to the **2-methylcyclohexanol** suspension at such a rate that the temperature of the mixture remains at $30 \pm 2^\circ$ (Note 3). Good agitation and an ice bath are necessary to control the temperature in this range. The mixture is stirred at $30 \pm 2^\circ$ for 1 hour and then at room temperature until all the **chromic oxide** is consumed (Note 4). The **sulfuric acid** solution is extracted with **ether** until the returns from the **ether** extractions fall to an insignificant amount. Approximately 10 extractions with 200-ml. portions of **ether** are required (Note 5). The **ether** extracts are combined, and the **ether** is removed by distillation on the steam bath. The resulting crude **δ -acetyl-*n*-valeric acid** is a yellow liquid with a sharp odor and amounts to about 130 g. The crude acid is purified by distillation through a 30-in. Vigreux column, using a variable take-off, a reflux ratio of 3:1, and a pressure of 1 mm. A fore-run of approximately 30 g. of material distilling up to $122^\circ/1$ mm. is obtained. The main fraction which distils at 122 – $123^\circ/1$ mm. is pure **δ -acetyl-*n*-valeric acid** and amounts to 66–79 g. (46–55%). The pure acid is a colorless crystalline hygroscopic solid which melts (sealed capillary) at 34 – 35° and is miscible with water in all proportions. The literature records the melting point of **δ -acetyl-*n*-valeric acid** as ranging from 31° to 42° .^{2,3,4}

2. Notes

1. Eastman Kodak Company practical grade **2-methylcyclohexanol** was used in this preparation.
2. Technical grade **chromic oxide** (99.5% CrO_3) in flake form was used.
3. An alcohol-Dry Ice bath is very convenient for this purpose; with this bath only about 45 minutes is needed for the addition of the **chromic oxide** solution. A water-ice bath can be used, but a longer time will be required for the addition of the **chromic oxide** solution.
4. The **chromic oxide** content of the mixture at any time may be determined by titrating a test portion against standard **ferrous ammonium sulfate** solution. If the mixture is allowed to stand overnight at room temperature without stirring, it will be free from **chromic oxide**. A convenient procedure is to perform the oxidation in the afternoon and the extraction the next day.
5. A liquid-liquid continuous extractor is convenient for extracting the crude acid from the aqueous solution. With such apparatus, it is possible to extract all the crude **δ -acetyl-*n*-valeric acid** from the aqueous acid in 6–8 hours.
6. The fore-run and the still residue contain some **δ -acetyl-*n*-valeric acid**. These fractions may be combined and redistilled to yield an additional 5–10% of **δ -acetyl-*n*-valeric acid**, but the low cost of the starting materials and the ease of preparing the crude **δ -acetyl-*n*-valeric acid** scarcely justify the labor unless a considerable number of batches are being prepared.

3. Discussion

δ -Acetyl-*n*-valeric acid has been prepared by the oxidation of 1-methylcyclohexene with potassium permanganate;⁵ by the oxidation of 2-methylcyclohexanone with chromic oxide and sulfuric acid,^{6,7} with neutral potassium permanganate,⁸ and by air in the presence of adipic acid and manganese nitrate;⁹ by the reaction of methylzinc iodide on the ethyl ester of adipic acid chloride, followed by saponification of the ester so obtained;¹⁰ by the saponification of the ethyl ester of diacetylvaleric acid;² by the hydrolysis of ethyl α -acetyl- δ -cyanovaleate with boiling 20% hydrochloric acid;³ by the permanganate oxidation of 1-methyl-1,2-cyclopentanediol;¹¹ and by the alkaline cleavage of 2-acetylcyclopentanone.¹²

References and Notes

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 4. Blaise and Kohler, *Compt. rend.*, **148**, 490 (1909).
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 6. Wallach, *Ann.*, **359**, 300 (1908).
 7. Ruzicka, Seidel, Schinz, and Pfeiffer, *Helv. Chim. Acta*, **31**, 422 (1948).
 8. Acheson, *J. Chem. Soc.*, **1956**, 4232.
 9. Badische Anilin- und Soda-Fabrik, Ger. pat. 812,073 [*C. A.*, **47**, 2769 (1953)].
 10. Blaise and Koehler, *Bull. soc. chim.*, [4] **7**, 222 (1910).
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Appendix

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

ethyl ester of adipic acid chloride

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

Adipic acid (124-04-9)

potassium permanganate (7722-64-7)

ferrous ammonium sulfate (10045-89-3)

2-methylcyclohexanone (583-60-8)

Heptanoic acid, 6-oxo-,
 δ -ACETYL-*n*-VALERIC ACID (3128-07-2)

2-methylcyclohexanol (583-59-5)

chromic oxide (1308-38-9)

1-methylcyclohexene

manganese nitrate (10377-66-9)

methylzinc iodide

ethyl α -acetyl- δ -cyanovalerate

1-methyl-1,2-cyclopentanediol

2-acetylcyclopentanone (1670-46-8)

ethyl ester of diacetylvaleric acid