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.

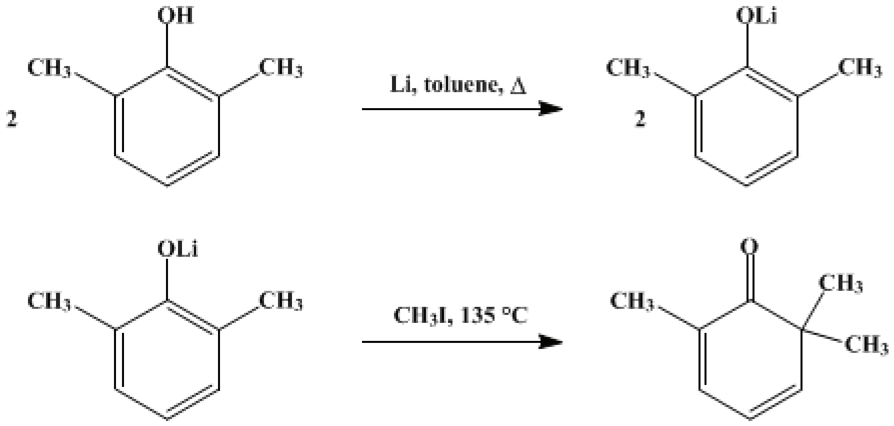
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.046.0115

Organic Syntheses, Coll. Vol. 5, p.1092 (1973); Vol. 46, p.115 (1966).

2,6,6-TRIMETHYL-2,4-CYCLOHEXADIENONE

[2,4-Cyclohexadiene-1-one, 2,6,6-trimethyl-]



Submitted by David Y. Curtin and Allan R. Stein[1].
Checked by William G. Dauben and Joel W. Rosenthal.

1. Procedure

A. *Lithium 2,6-dimethylphenoxide*. In a 300-ml. flask, equipped with a magnetic stirrer and a reflux condenser and flushed with nitrogen, are placed 150 ml. of toluene (freshly distilled from sodium), 1.40 g. (0.202 mole) of lithium metal (Note 1) and 25.0 g. (0.205 mole) of resublimed 2,6-dimethylphenol. The mixture is heated under reflux with stirring for 36 hours; a nitrogen atmosphere is maintained for the reflux period (Note 2). The condenser is replaced by a distillation head with a condenser set for distillation, and a distillation capillary is inserted in the thermometer joint. The bulk of the toluene is removed under nitrogen at reduced pressure (Note 3). The distillation head is rapidly removed, and the flask is flushed with nitrogen and closed by a stopper. The stoppered flask is transferred to a dry box flushed with nitrogen, the stopper removed, and the slurry in the flask filtered with suction through a 65-mm. sintered-glass funnel. The collected lithium salt is washed with three 75-ml. portions of hexane (freshly distilled from lithium aluminum hydride), and the white powder (Note 4) is dried at 100–150° and 0.5 mm. pressure to constant weight (3–10 hours is required). The yield of lithium 2,6-dimethylphenoxide as a fine white or light gray powder is 25.0–25.5 g. (98–100%) (Note 5) and (Note 6).

B. *2,6,6-Trimethyl-2,4-cyclohexadienone*. In a nitrogen-filled dry box, 25.0 g. of lithium 2,6-dimethylphenoxide (0.195 mole) is transferred to an oven-dried, thick-walled Pyrex® bomb tube (650 × 19 mm.). The bomb tube is stoppered with a rubber stopper fitted with a drying tube, removed from the dry box, and 75 ml. of methyl iodide (170 g., 1.20 moles) (freshly distilled from calcium hydride) is quickly pipetted into the bomb under a dry nitrogen stream. The bomb is cooled in a dry-ice bath and sealed with an oxygen torch. After warming to room temperature, the bomb is shaken to disperse the salt cake and placed in a bomb furnace which has been preheated to 135° (Note 7).

After 36 hours the furnace is allowed to cool, the bomb is removed, cooled to dry-ice temperatures, and opened carefully as there may be residual pressure. The golden brown liquid is poured into a 200-ml. flask, and the methyl iodide is removed on a rotary evaporator *Caution! (Hood)*. The residue from the flask and the bomb is washed into a 500-ml. separatory funnel with 100 ml. each of ether and 1 : 1 solution of Claisen's alkali and water (Note 8). The funnel is shaken, and the alkali layer is removed. The ether layer is extracted four additional times with 100 ml. portions of the alkali (Note 9), washed twice with 75-ml. portions of water, once with saturated aqueous salt solution, and dried by filtration through anhydrous sodium sulfate into a 200-ml. round-bottomed flask. The ether is removed on a rotary evaporator, and the 23.0 g. of yellow oil remaining is allowed to stand at room temperature for 7–

10 days to permit dimerization of the dienone (Note 10).

The 2,6-dimethylanisole is removed by vacuum distillation (nitrogen capillary bubbler) at 35–50° (0.75 mm. or less pressure). The solid dimerized product[2] in the residue is either recrystallized twice from the minimum amount of hot hexane or vacuum-distilled, b.p. 175° (25 mm.) (Note 11) followed by a single recrystallization from hexane.

The yield of purified 2,6,6-trimethyl-2,4-cyclohexadienone dimer (white needles, m.p. 119.5–121.0°) is 4.8–5.1 g. (18–19%) (Note 12), and the yield of 2,6-dimethyl anisole is 13.5–14.0 g. (51–53%).

The dienone monomer may be regenerated from its dimer as desired by heating the dimer above 170° for several minutes in a test tube and quenching, or by distillation at 25 mm. (Note 11) through a short condenser into a dry ice-acetone cooled receiver. The monomer may be stored for several days at dry-ice temperatures without appreciable dimerization.

2. Notes

1. The lithium should be added in the form of very small pieces. The pieces are most conveniently prepared as follows. Trim the oxide layer off a small block of lithium metal under mineral oil, grip it with tweezers and rinse the mineral oil off in a beaker of dry ether. Hold the block in the ether vapors momentarily to dry, and then plunge it into a tared beaker of mineral oil for weighing. Cut the block into strips with a sharp knife, remove the pieces one by one, and squeeze them into long flat ribbons with pliers which are frequently dipped into the mineral oil. Cut the ribbons into short sections over another beaker of dry ether, swirl and transfer the pieces to a third beaker of ether to wash off the last traces of mineral oil before adding the lithium to the reaction flask.
2. A positive pressure of nitrogen is maintained by attachment of a mercury bubbler on the top of the reflux condenser.
3. If heating is desired to speed the toluene removal, a steam or an oil bath is used to prevent charring of the salt.
4. If the salt is lumpy, it is best to grind it into a fine powder in an agate mortar before washing it with the hexane. The fine powder is more easily washed and reacts more readily in the alkylation reaction.
5. The lithium phenoxide may be prepared in larger quantities and may be stored for some time sealed under nitrogen and protected from light by wrapping the flask with aluminum foil. Traces of water lead to a gummy salt, while traces of oxygen cause a purple coloration. Quite badly discolored salt has been used successfully in the alkylation procedure, but yields tend to be reduced by tar formation.
6. Titration of a portion of the salt with 0.1*N* hydrochloric acid to methyl orange end-point shows the salt to be 97–103% lithium 2,6-dimethylphenoxide.
7. The temperature used is not crucial, but the best yield is obtained in the 120–180° range. At higher temperatures considerable tar forms, while at lower temperatures dienone yields are sacrificed.[3]
8. Claisen's alkali is a solution of 350 g. of potassium hydroxide in 250 ml. of water made up to 1 liter with methanol.
9. About 4.5 g. or 18% of the starting 2,6-dimethylphenol may be recovered from the combined alkaline extracts by acidification with concentrated hydrochloric acid and extraction of the liberated phenol with ether.
10. The Diels-Alder dimerization of 2,6,6-trimethyl-2,4-cyclohexadienone to 1,4,6,6,9,9-hexamethyl-$\Delta^{3,11}$-tricyclo-[6.2.2.0 ^{2,7}]-dodecane-5,10-dione[2] facilitates its separation from the major alkylation product, 2,6-dimethylanisole.
11. In the distillation of the dienone it is necessary to maintain a pot temperature of 175–200° to reverse the dimerization (Note 10).
12. An additional 0.5–1.0 g. of the dienone dimer may be obtained by allowing the 2,6-dimethylanisole fraction to stand for several days and then redistilling it.

3. Discussion

This preparation of 2,6,6-trimethyl-2,4-cyclohexadienone is based upon the published procedure of the submitters,[2] and it is the only preparation of the 2-substituted-2,4-cyclohexadienones. The simpler

6,6-dimethyl-2,4-cyclohexadienone is more conveniently prepared by the method of Alder.[4]

4. Merits of the Preparation

The use of lithium in toluene for the preparation of alkali metal phenoxides appears to be the most convenient and least expensive procedure. The procedure also has the merit of giving the salt as a finely divided powder.

The alkylation procedure can be used to prepare a wide variety of 2-substituted-2,4-cyclohexadienones,[2,3,5,6] which are useful starting materials. The compounds can serve either as dienes or dienophiles[7] in the Diels-Alder reaction and can be opened photochemically to yield substituted $\Delta^{3,5}$-hexadienoic acids.[8]

References and Notes

1. Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois.
2. T. L. Brown, D. Y. Curtin, and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 4339 (1958)
3. R. R. Fraser, doctoral dissertation, University of Illinois, Urbana, Illinois, 1958, p. 76.
4. K. Alder, F. H. Flock, and H. L. Lessenich, *Ber.*, **90**, 1709 (1957).
5. A. R. Stein, unpublished results.
6. D. Y. Curtin and D. H. Dybvig, *J. Am. Chem. Soc.*, **84**, 225 (1962); D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 6016 (1958); D. Y. Curtin, R. J. Crawford and M. Wilhelm, *J. Am. Chem. Soc.*, **80**, 1391 (1958); N. Kornblum and R. Seltzer *J. Am. Chem. Soc.*, **83**, 3668 (1961).
7. D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **81**, 662 (1959).
8. D. H. R. Barton and G. Quinkert, *J. Chem. Soc.*, **1** (1960).

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

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

Methyl iodide (74-88-4)

lithium (7439-93-2)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

2,6-dimethylphenol (576-26-1)

2,6,6-Trimethyl-2,4-cyclohexadienone,
2,4-Cyclohexadiene-1-one, 2,6,6-trimethyl- (13487-30-4)

lithium 2,6-dimethylphenoxide

2,6-dimethylanisole,
2,6-dimethyl anisole (1004-66-6)

lithium phenoxide

tricyclo-[6.2.2.0 ^{2,7}]-dodecane-5,10-dione

6,6-dimethyl-2,4-cyclohexadienone

methyl orange (547-58-0)