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.

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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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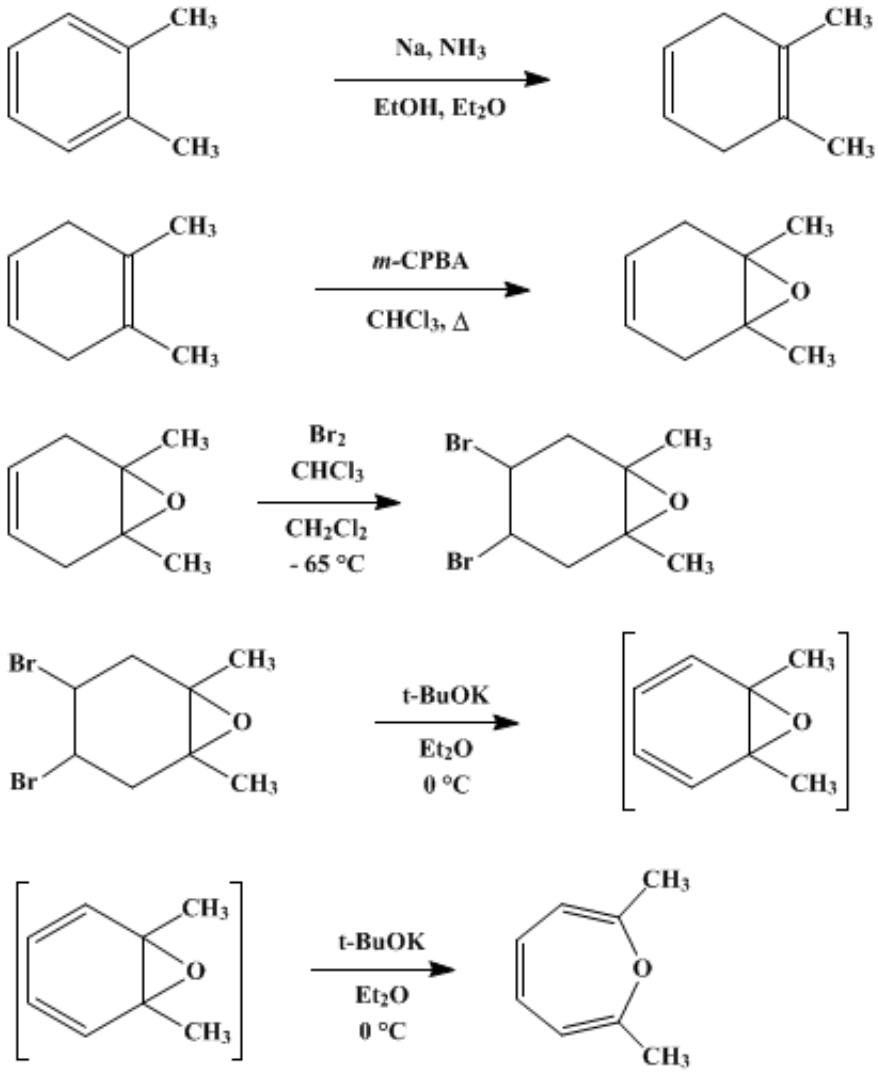
2,7-DIMETHYLOXEPIN

[Oxepin, 2,7-dimethyl-]



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Checked by Jon Malmin and Ronald Breslow.

1. Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973,

A. *1,2-Dimethyl-1,4-cyclohexadiene*. *Caution! This step should be conducted in a hood to avoid exposure to ammonia fumes.* A 5-l. three-necked flask, cooled in a dry ice-isopropyl alcohol bath, is fitted with an efficient stirrer and a dry ice condenser. The flask is charged with approximately 2.5 l. of liquid ammonia, the stirrer is started, and 450 g. of anhydrous diethyl ether, 460 g. (10 moles) of absolute ethanol, and 318.5 g. (3.0 moles) of *o*-xylene (Note 1) are added slowly in that order (Note 2). Then 207 g. (9.0 g. atoms) of sodium is added in small pieces over a 5-hour period (Note 3). The ammonia is allowed to evaporate overnight. The flask is now equipped with a reflux condenser, and approximately 800 ml. of ice water is slowly added with stirring to dissolve the salts (Note 4). The two layers which form are separated and the upper organic layer is washed three times with 800-ml. portions of water and dried over anhydrous magnesium sulfate. The liquid is separated from the drying agent and is distilled through a 20-cm. Vigreux column. The fraction boiling at 70–72° (48 mm.) is collected and weighs 250–300 g. (77–92%). The 1,2-dimethyl-1,4-cyclohexadiene is sufficiently pure for the epoxidation reaction (Note 5).

B. *1,2-Dimethyl-1,2-epoxycyclohex-4-ene*. A 2-l. three-necked flask equipped with an efficient stirrer, a reflux condenser, and a dropping funnel is charged with 41 g. (0.38 mole) of 1,2-dimethyl-1,4-cyclohexadine. Over a period of 2 hours 80 g. (0.46 mole of 85% assay) of *m*-chloroperbenzoic acid (Note 6) dissolved in 1 l. of chloroform is added with vigorous stirring. The mixture is heated to reflux on a steam bath for 3 hours and kept overnight. The contents of the flask are cooled in an ice bath and the precipitated *m*-chlorobenzoic acid is removed by filtration. The organic layer is washed with 25 ml. of 20% sodium bisulfite solution, three 100-ml. portions of 10% sodium bicarbonate solution (Note 7), and 100 ml. of saturated sodium chloride solution, in that order. The organic layer is dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure, and distilled through a 30-cm. glass bead-packed column (Note 8) to afford 32.3–36.8 g. (68–78%) of the epoxide, b.p. 55–57° (15 mm.); n^{20}D 1.4642–1.4650 (Note 9).

C. *4,5-Dibromo-1,2-dimethyl-1,2-epoxycyclohexane*. Into a 1-l. three-necked flask fitted with an efficient stirrer, an alcohol thermometer, a dropping funnel, and a drying tube are placed 32 g. (0.26 mole) of the epoxide and 500 ml. of an anhydrous chloroform-methylene chloride mixture (1:1). The solution is cooled to –65° and 34 g. (0.21 mole) of bromine in 50 ml. of the same solvent is added dropwise while maintaining the temperature below –60° (Note 10). When the addition is complete, the reaction mixture is stirred for 30 minutes and the solvent is removed at room temperature under reduced pressure. The resulting oil (or solid) is recrystallized from a minimum amount of *n*-hexane to give 47–51 g. (80–86%) of lustrous white needles, m.p. 82–83°.

D. *2,7-Dimethyloxepin*. In a 1-l. three-necked flask fitted as above, except that the dropping funnel is replaced by a 125-ml. Erlenmeyer flask connected to the reaction flask by means of Gooch tubing, is placed a solution of 42.1 g. (0.15 mole) of the purified dibromoepoxide in 500 ml. of anhydrous ether. The solution is cooled to 0° and 33.2 g. (0.30 mole) of potassium *t*-butoxide (Note 11) is added portionwise through the Gooch tubing over a period of 1 hour while maintaining the temperature below 5°. The resulting mixture is stirred for 30 minutes and filtered. The ether is removed under reduced pressure, and the residual liquid is distilled to give 9.7–12.2 g. (52–67%) of 2,7-dimethyloxepin as an orange oil, b.p. 49–50° (15 mm). n^{27}D 1.5010 (Note 12).

2. Notes

1. Eastman Organic Chemicals, white label grade, was used without further purification.
2. It is advisable to precool these reagents before their addition to minimize excessive boiling of the liquid ammonia.
3. Only five or six pieces of sodium should be added at one time in order to avoid an almost uncontrollable exothermic reaction. The solution turns blue and then white as the sodium is consumed. When the solution turns white, another portion of sodium may be added. The last 50 g. of sodium may be added without waiting between portions because the reaction is much slower at this point.
4. Because dissolution of the salts is a highly exothermic process, the water should be added slowly. A

stream of nitrogen may be passed through the reaction during the addition of the water to ensure that no fire is started by bits of sodium that may be adhering to the upper walls of the flask.
5. The product is readily analyzed by vapor phase chromatography. Since the only impurity is *o*-xylene (conversions range from 80% to 100%), the percentage of reduction product was calculated from the gas chromatogram and this value was used to determine the amount of *m*-chloroperbenzoic acid to be used in the epoxidation.
6. *m*-Chloroperbenzoic acid was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin.
7. The separatory funnel must be vented frequently because of the large volume of carbon dioxide liberated at this point.
8. It appears necessary to effectively remove the residual *o*-xylene during this distillation in order that it not interfere (by liberation of hydrogen bromide) with the subsequent bromination of the epoxide. The checkers used a spinning-band column for this distillation.
9. The submitters worked at four times this scale with similar yields and purity.
10. Best yields are obtained if the bromination mixture is never allowed to become orange in color. If a calculated amount of bromine is added to the epoxide, the yields of dibromide are greatly diminished.
11. Potassium *t*-butoxide may be obtained from MSA Research Corporation, Callery, Pennsylvania.
12. 2,7-Dimethyloxepin is stable for long periods when stored under nitrogen at 0–5°.

3. Discussion

The procedure described is patterned after the method suggested by Vogel, Schubart, and Böll,[2] and it illustrates a general method of preparing oxepins. Furthermore, the first step represents an example of the Birch reduction of an aromatic hydrocarbon.[3] The second step is illustrative of the selective epoxidation of a diene system.[3]

Oxepins themselves are interesting examples of cyclic conjugated molecules with $4n$ π-electrons.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 200

References and Notes

1. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.
2. E. Vogel, R. Schubart and W. A. Böll, *Angew. Chem. Intern. Ed. Engl.*, **3**, 510 (1964).
3. W. Hückel and U. Wörffel, *Ber.*, **88**, 338 (1955).

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

1,2-dimethyl-1,4-cyclohexadine

ethanol (64-17-5)

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

chloroform-methylene chloride (76-01-7)

n-hexane (110-54-3)

2,7-Dimethyloxepin,
Oxepin, 2,7-dimethyl- (1487-99-6)

1,2-Dimethyl-1,4-cyclohexadiene (17351-28-9)

m-Chloroperbenzoic acid (937-14-4)

o-Xylene (95-47-6)

potassium t-butoxide (865-47-4)

m-chlorobenzoic acid (535-80-8)

1,2-Dimethyl-1,2-epoxycyclohex-4-ene (57338-10-0)

4,5-Dibromo-1,2-dimethyl-1,2-epoxycyclohexane