Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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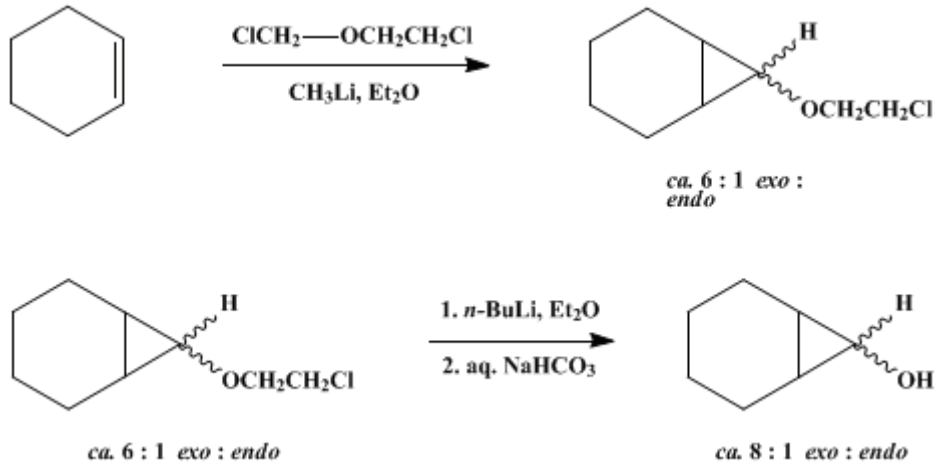
exo/endo-7-NORCARANOL



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1. Procedure

A. *exo/endo-7-(2-Chloroethoxy)bicyclo[4.1.0]heptane*. A 2-l., three-necked, round-bottomed flask is equipped with a sealed stirrer, a pressure-equalizing dropping funnel, and a condenser fitted with a nitrogen-inlet tube (Note 1). The flask is flushed with dry nitrogen, and to it are added 500 ml. of cyclohexene (Note 2) and 49.0 g. (0.300 mole) of dichloromethyl 2-chloroethyl ether (Note 3). To the stirred solution at room temperature is added dropwise 430 ml. (0.47 mole) of a 1.1*N* ethereal solution of methyllithium (Note 4) at a rate adequate to maintain gentle reflux of the ether; the addition requires *ca.* 4 hours (Note 5). The reaction mixture is poured into 1.5 l. of ice water, the aqueous layer is separated, and the organic layer is extracted with four 300-ml. portions of water and dried over anhydrous sodium sulfate. The solvents are removed by distillation through a 10-cm. Vigreux column (Note 6), and the residue is distilled under reduced pressure to yield 21–29 g. (40–56%) of *exo/endo*-7-(2-chloroethoxy)bicyclo[4.1.0]heptane, b.p. 98–101° (10 mm.). This material is sufficiently pure for the next step (Note 7).

B. *exo/endo-7-Norcaranol*. A 500-ml. three-necked flask equipped with a magnetic stirrer, a pressure-equalizing dropping funnel, and a condenser fitted with a nitrogen-inlet tube (Note 1) is flushed with nitrogen, and a solution of 20.0 g. (0.115 mole) of *exo/endo*-7-(2-chloroethoxy)bicyclo [4.1.0]heptane in 150 ml. of dry ether is added. To this solution is added dropwise at room temperature 280 ml. (0.45 mole) of a 1.6*N* solution of *n*-butyllithium in hexane over a 30- to 45-minute period (Note 5). The mixture is poured into 800 ml. of ice-cold, saturated, aqueous sodium bicarbonate, and the aqueous phase is separated and extracted with four 150-ml. portions of ether. The organic solutions are combined and dried over anhydrous sodium sulfate, and the solvents are removed by distillation through a 10-cm. Vigreux column at a maximum bath temperature of 65°. The residue is distilled under reduced pressure to yield 11.6–12.3 g. (90–95%) of *exo/endo*-7-norcaranol, b.p. 80–85° (10 mm.) (Note 8) and (Note 9).

2. Notes

1. The nitrogen-inlet system described by Johnson and Schneider[2] is satisfactory.
2. The cyclohexene was dried over potassium hydroxide pellets and distilled from sodium before use.
3. The checkers prepared this ether in the following manner. 2-Ethoxy-1,3-dioxolane was prepared in 82% yield from ethylene glycol and ethyl orthoformate and treated with acetyl chloride to give 2-chloroethyl formate by the procedures of Baganz and Domaschke;[3] the overall yield was 56–60%. The

formate was converted to dichloromethyl 2-chloroethyl ether with phosphorus pentachloride by the procedure of Gross, Rieche, and Höft,[4] and the product was distilled through a 10-cm. column containing glass helices; b.p. 107–111° (110 mm.); yield 85%.
4. The methyllithium must be prepared from methyl iodide because the presence of the iodide anion is essential. The submitters prepared methyl lithium in the following manner. Methyliodide (425.7 g., 3.00 moles) was added with stirring to 48 g. (7.0 g. atoms) of lithium in 2.5 l. of ether under nitrogen at a rate adequate to maintain gentle reflux of the ether. After 24 hours the solution of methyllithium was decanted into a storage vessel filled with nitrogen. The concentration was estimated in the usual way by hydrolysis of an aliquot and titration with 0.1*N* hydrochloric acid.
5. The addition of the organolithium solution is continued until a positive Gilman test[5] is obtained.
6. Isopropyl 2-chloroethyl ether, b.p. 118–121°, is formed in variable amounts as a by-product.
7. The *exo/endo* ratio is ~6:1; the *exo* and *endo* isomers show characteristic triplets in their n.m.r. spectra at δ 2.9 and 3.1 p.p.m., respectively.
8. The *exo/endo* ratio is ~8:1; the *exo* and *endo* isomers show characteristic triplets in their n.m.r. spectra at δ 3.0 and 3.25 p.p.m., respectively.
9. In some runs, *exo*-7-norcaranol, m.p. 57–58°, crystallized in the condenser or in the receiver.

3. Discussion

This method for the preparation of *exo/endo*-7-norcaranol is an adaptation of that described by Schöllkopf, Paust, Al-Azrak, and Schumacher.[6] The method has been used by the submitters for the preparation of the following cyclopropanols: *exo/endo*-6-hydroxybiclo[3.1.0]hexane, *exo/endo*-8-hydroxybicyclo[5.1.0] octane, *exo/endo*-9-hydroxybicyclo[6.1.0]nonane, 2,2-dimethylcyclopropanol, 2,2,3,3-tetramethylcyclopropanol, *trans*-2,3-dimethylcyclopropanol, *cis*-2,3-dimethyl-*cis/trans*-cyclopropanol, *cis/trans*-2,2,3-trimethylcyclopropanol, and *cis/trans*-2-phenylcyclopropanol.

The principal disadvantage of this procedure is that the olefin must be used in at least three- to fourfold excess in order to obtain reasonable yields. In case of rare olefins, or of olefins containing groups such as the carbonyl group which add organolithium compounds, other methods[7,8] might be more advantageous. The method is also limited to the preparation of secondary cyclopropanols.

The most satisfactory procedure for obtaining cyclopropanol itself is that of Cottle[7,9] which is also recommended for the synthesis of 1-arylcyclopropanols.[7] 1-Alkylcyclopropanols are best prepared via the corresponding acetates which are obtained by the method of Freeman[10] that involves thermolysis of a 3-acetoxy-1-pyrazolin. According to DePuy,[7] cyclopropyl acetates are best cleaved to cyclopropanols by methyllithium. However, the preparation of cyclopropyl acetates is somewhat laborious. It usually involves reactions of an olefin with ethyl diazotate—in this step the olefin must be used in excess, too—followed by a Baeyer-Villiger rearrangement of the corresponding methyl cyclopropyl ketone.[7]

The cyclopropanols, the study of whose chemistry is still in its early stages,[7,8] show promise as useful synthetic intermediates. The chemistry of their derivatives should aid in the understanding of the nature of nucleophilic substitution on three-membered rings.[7,8,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 346

References and Notes

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

exo/endo-6-hydroxybiclo[3.1.0]hexane

hydrochloric acid (7647-01-0)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

ethylene glycol (107-21-1)

Methyl iodide,
Methyliodide (74-88-4)

Ethyl orthoformate

lithium (7439-93-2)

n-butyllithium (109-72-8)

hexane (110-54-3)

Methyllithium,
methyl lithium (917-54-4)

dichloromethyl 2-chloroethyl ether (13830-34-7)

2-Ethoxy-1,3-dioxolane

2-chloroethyl formate

Isopropyl 2-chloroethyl ether

2,2-dimethylcyclopropanol

2,2,3,3-tetramethylcyclopropanol

cyclopropanol (16545-68-9)

3-acetoxy-1-pyrazolin

exo/endo-7-Norcaranol,
exo-7-norcaranol (13830-44-9)

exo/endo-7-(2-Chloroethoxy)bicyclo[4.1.0]heptane

exo/endo-8-hydroxybicyclo[5.1.0] octane

exo/endo-9-hydroxybicyclo[6.1.0]nonane

trans-2,3-dimethylcyclopropanol

cis-2,3-dimethyl-cis/trans-cyclopropanol

cis/trans-2,2,3-trimethylcyclopropanol

cis/trans-2-phenylcyclopropanol