Organic Syntheses

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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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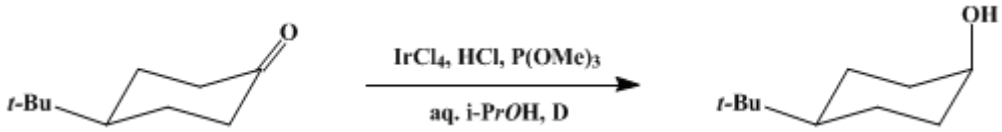
cis-4-*tert*-BUTYLCYCLOHEXANOL

[Cyclohexanol, 4-(1,1-dimethylethyl)-, *cis*-]



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1. Procedure

To a solution of 4.0 g. (0.012 mole) of iridium tetrachloride (Note 1) in 4.5 ml. of concentrated hydrochloric acid is added 180 ml. of water followed by 52 g. (50 ml., 0.42 mole) of trimethyl phosphite (Note 2). This solution then is added to a solution of 30.8 g. (0.200 mole) of 4-*tert*-butylcyclohexanone (Note 3) in 635 ml. of 2-propanol contained in a 2-l. flask equipped with a reflux condenser. The solution is heated at reflux for 48 hours (Note 4), at which time the 2-propanol is removed with a rotary evaporator. The remaining solution is diluted with 250 ml. of water and extracted with four 150-ml. portions of diethyl ether. The combined ether extracts are washed with two 100-ml. portions of water, which are combined with the aqueous residue (Note 5), dried over magnesium sulfate or potassium carbonate, and concentrated on a rotary evaporator, yielding 29–31 g. (93–99%) of *cis*-4-*tert*-butylcyclohexanol as a white solid. Analysis of the crude product by GC shows it contains 95.8–96.2% *cis*-alcohol and 4.2–3.8% of the *trans* isomer with essentially no ketone remaining (Note 6). Recrystallization from 40% aqueous ethanol affords greater than 99% pure *cis*-alcohol, m.p. 82–83.5° after sublimation (Note 7).

2. Notes

1. Iridium tetrachloride was originally obtained from Platinum Chemicals, Inc., Box 565, Asbury Park, New Jersey 07712, or from Alfa Products, Thiokol/Ventron Division, P.O. Box 299, 152 Andover St., Danvers, Massachusetts 01923. More recently, the procedure has been repeated successfully with material obtained from Pfaltz and Bauer, Inc., a subsidiary of Aceto Chemical Co., Inc., 375 Fairfield Ave., Stamford, Connecticut 06902.
2. The order of mixing the catalyst components is required for good results, and the sequence described should be followed. Particular care should be taken *not* to add the trimethyl phosphite before the water, as the reaction between it and concentrated hydrochloric acid is extremely violent.
3. 4-*tert*-Butylcyclohexanone was obtained from Dow Chemical Company or Aldrich Chemical Co. Inc.
4. The reaction solution is often dark-colored at the beginning but lightens as reflux continues. The reflux time may be varied with the amount of ketone to be reduced. The completeness of the reaction may be followed by removing small aliquots, working up these samples as described in the text, and analyzing the product mixture by GC (see (Note 6)).
5. The iridium catalyst used in this preparation may be regenerated by reducing the volume of the aqueous residue to about 200 ml. at diminished pressure. This solution is then used instead of the iridium tetrachloride and water called for in the procedure.
6. The product was analyzed by GC using a 9-ft. 20% Carbowax 20M on 45/60 Chromosorb W column at 150°. The order of increasing retention times is: ketone, *cis*-alcohol, *trans*-alcohol.
7. Recrystallization is best accomplished by dissolving the crude product in hot ethanol (approx. 35 ml. per 10 g.) followed by adding water (approx. 25 ml. per 10g.) and allowing the solution to cool slowly to 0°. The fluffy white needles are filtered using a sintered-glass funnel and dried over P_2O_5 at atmospheric pressure. Recooling the filtrate affords a second crop of product, for an overall yield of 75–87%.

3. Discussion

4-*tert*-Butylcyclohexanol has been prepared from *p*-*tert*-butylphenol by reduction under a variety of conditions.[3,4] Eliel and Ro[5] obtained *cis*-rich 4-*tert*-butylcyclohexanol by the reduction of 4-*tert*-butylcyclohexanone with hydrogen on platinum oxide in glacial acetic acid containing some hydrogen chloride; Sommerville and Theimer have similarly reduced *p*-*tert*-butylphenol with 5% rhodium on carbon.[6,7] They have also prepared *cis*-rich alcohol by fractional distillation of the *cis*-*trans* mixture over an equilibrating catalyst, such as aluminum isopropoxide in the presence of 4-*tert*-butylcyclohexanone.[6] Eliel and Nasipuri[8] have also obtained 4-*tert*-butylcyclohexanol containing 80–92% of the *cis* isomer by the reduction of 4-*tert*-butylcyclohexanone with isobornyloxyaluminum dichloride.

The present[9] procedure employs a readily available starting material and produces essentially pure *cis* isomer in good yield. In view of the fact that the catalyst may be reused several times with little loss in stereoselectivity, the expense of the iridium tetrachloride is not a serious impediment.

The method is useful in the preparation of other axial alcohols. Henbest[9] has reported the reductions of 3-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and cholestanone to the axial alcohols by this procedure, although for the preparation of cholestan-3α-ol the procedure of Edward[10] is preferred by the checkers. Recently[11] 2,4,4-trimethylcyclohexanone has been reduced to the pure axial alcohol by this method in 90% yield.

Since this preparation was submitted, a number of reductions of 4-*tert*-butylcyclohexanone to the *cis* alcohol, with 93–100% selectivity, using various bulky, complex metal hydrides have been described: lithium tri-*sec*-butylborohydride (L-Selectride),[12,13] lithium trisiamylborohydride,[13,14,15] lithium tri-*trans*-2-methylcyclopentylborohydride,[14] lithium dimesitylborohydride,[16] lithium 2,6-di-*tert*-butylphenoxyneopentoxyaluminumhydride;[17] high (94–99%) selectivity is also attained by catalytic hydrogenation with various rhodium catalysts.[18,19] Hydrogenation over rhodium-on-carbon[18] (94% *cis*) followed by purification with liquid chromatography appears to be an attractive method, one which avoids the need for special reagents.

References and Notes

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

cis-rich 4-tert-butylcyclohexanol

lithium trisiamylborohydride

rhodium-on-carbon

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride,
hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

platinum oxide

carbon (7782-42-5)

2-propanol (67-63-0)

aluminum isopropoxide

magnesium sulfate (7487-88-9)

Cholestanone (566-88-1)

trimethyl phosphite (121-45-9)

iridium tetrachloride (10025-97-5)

iridium (7439-88-5)

rhodium (7440-16-6)

isobornyloxyaluminum dichloride

3,3,5-trimethylcyclohexanone (873-94-9)

cholestan-3α-ol

2,4,4-trimethylcyclohexanone

lithium dimesitylborohydride

4-tert-Butylcyclohexanone (98-53-3)

4-tert-Butylcyclohexanol (98-52-2)

p-tert-butylphenol (98-54-4)

cis-4-tert-Butylcyclohexanol,
Cyclohexanol, 4-(1,1-dimethylethyl)-, cis- (937-05-3)

3-tert-butylcyclohexanone (936-99-2)

lithium tri-sec-butylborohydride

lithium tri-trans-2-methylcyclopentylborohydride

lithium 2,6-di-tert-butylphenoxyneopentoxyaluminumhydride