



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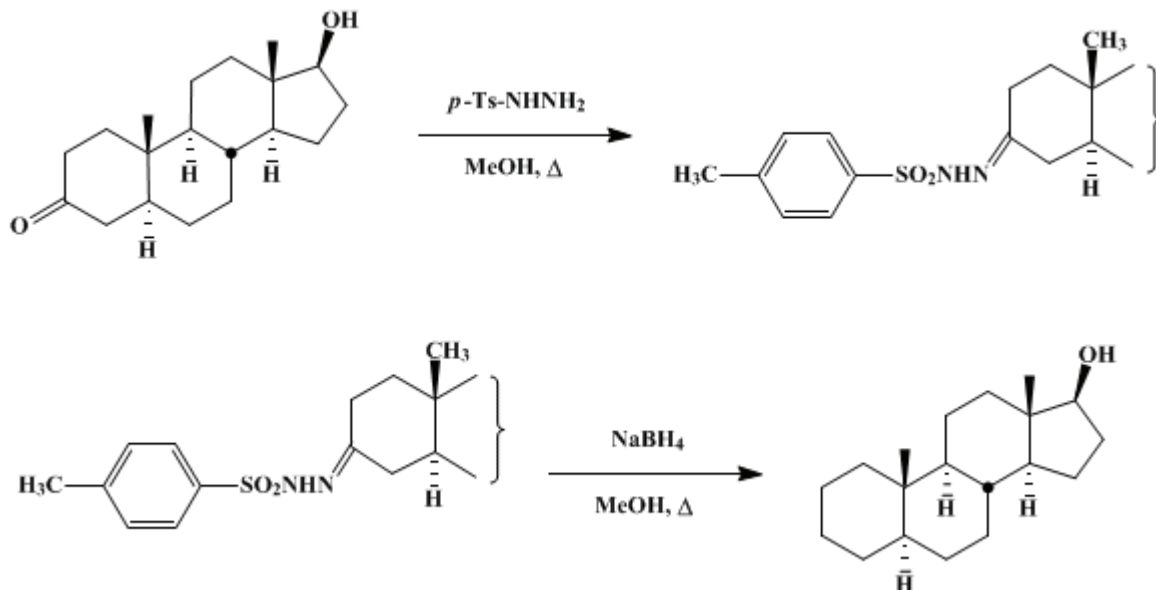
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.62 (1988); Vol. 52, p.122 (1972).

REDUCTION OF KETONES BY USE OF THE TOSYLHYDRAZONE DERIVATIVES: ANDROSTAN-17 β -OL

[Androstan-17-ol, (5 α , 17 β)-]



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1. Procedure

A 100-ml., round-bottomed flask equipped with a reflux condenser is charged with 1.00 g. (0.00345 mole) of 5 α -androstan-17 β -ol-3-one (Note 1), 0.90 g. (0.0048 mole) of tosylhydrazide (Note 2), and 70 ml. of methanol (Note 3). The mixture is heated under gentle reflux for 3 hours, then cooled to room temperature. To the solution is added 2.5 g. (0.075 mole) of sodium borohydride in small portions over one hour (Note 4) and the resulting mixture is heated under reflux for an additional 8 hours. The reaction mixture is cooled to room temperature before the solvent is removed under reduced pressure. The residue is dissolved in diethyl ether, transferred to a separatory funnel, and washed successively with water, dilute aqueous sodium carbonate, 2 *M* hydrochloric acid, and water. The ethereal solution is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue, 0.95 g. of white crystals (Note 5), is dissolved in about 20 ml. of a 7:3 (v/v) mixture of cyclohexane-ethyl acetate and applied to a column packed with 60 g. of silica gel (Merck, 0.05–0.2 mm.). The column is eluted with the 7:3 (v/v) cyclohexane-ethyl acetate mixture and a 200-ml. fraction is collected. Evaporation of this fraction under reduced pressure affords 0.70–0.73 g. (73–76%) of pure 5 α -androstan-17 β -ol. Recrystallization from aqueous methanol provides 0.64 g. of analytically pure product, m.p. 161–163°.

2. Notes

1. 5 α -Androstan-17 β -ol-3-one was supplied by Aldrich Chemical Co., Inc.
2. Tosylhydrazide was supplied by Aldrich Chemical Co., Inc. Alternately, it may be prepared by a procedure described in *Org. Synth., Coll. Vol. 5, 1055 (1973)*.
3. Tetrahydrofuran serves equally well as a solvent. However, the quantity of sodium borohydride should be reduced to 1.0 g. and the isolation procedure modified in the following way. After the solution has been refluxed for 8 hours, the reaction mixture is cooled and the excess sodium borohydride is decomposed by the slow addition of dilute hydrochloric acid. The resulting mixture is extracted with ether and the ethereal solution is washed as described.

4. Because of the ready decomposition of [sodium borohydride](#) in [methanol](#), the solution is maintained at room temperature during the addition of the metal hydride.
5. The crude product is contaminated with a small amount of a more polar substance which is subsequently removed by chromatography.

3. Discussion

The preparation of [5 \$\alpha\$ -androstan-17 \$\beta\$ -ol](#) from [5 \$\alpha\$ -androstan-17 \$\beta\$ -ol-3-one](#) may be realized by classical methods such as the Wolff-Kishner or Clemmensen reduction.

This procedure illustrates a general method for the reduction of aldehyde and ketone functions to methylene groups under very mild conditions. Since strong acids and bases are not employed, this procedure is of particular importance for the reduction of ketones possessing an adjacent chiral center.^{2,3} Moreover, the use of deuterated metal hydrides permits the preparation of labeled compounds.⁴

The reduction of the preformed tosylhydrazones with [sodium borohydride](#) may be effected in aprotic solvents, such as [tetrahydrofuran](#) or [dioxane](#).⁵ The use of [lithium aluminium hydride](#) in nonhydroxylic solvents permits the reduction of aromatic aldehydes and ketones.

References and Notes

1. Istituto di Chimica Organica, Universita di Roma, Rome, Italy.
2. The reduction of the tosylhydrazone of (+)(S)-4-methyl-3-hexanone affords [\(+\)\(S\)-3-methylhexane](#), optical purity 85%; L. Lardicci and C. Botteghi, private communication.
3. A. N. De Belder and R. Weigel, *Chem. Ind. (London)*, 1689 (1964).
4. E. J. Corey and S. K. Gros, *J. Am. Chem. Soc.*, **89**, 4561 (1967); M. Fischer, Z. Pelah, D. H. Williams, and C. Djerassi, *Chem. Ber.*, **98**, 3236 (1965).
5. L. Caglioti, *Tetrahedron*, **22**, 487 (1966); L. Caglioti and P. Grasselli, *Chim. Ind. (Milan)*, **46**, 1492 (1964); S. Cacchi, L. Caglioti, and G. Paolucci, *Bull. Chem. Soc. Jpn.*, **47**, 2323 (1974).

Appendix

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

tosylhydrazone of (+)(S)-4-methyl-3-hexanone

[hydrochloric acid](#) (7647-01-0)

[ethyl acetate](#) (141-78-6)

[methanol](#) (67-56-1)

[ether](#),
[diethyl ether](#) (60-29-7)

[sodium carbonate](#) (497-19-8)

[sodium sulfate](#) (7757-82-6)

[cyclohexane](#) (110-82-7)

dioxane (123-91-1)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

sodium borohydride (16940-66-2)

tosylhydrazide

ANDROSTAN-17 β -OL

Androstan-17-ol, (5 α , 17 β)-,
5 α -androstan-17 β -ol (1225-43-0)

5 α -androstan-17 β -ol-3-one

(+)(S)-3-methylhexane