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.

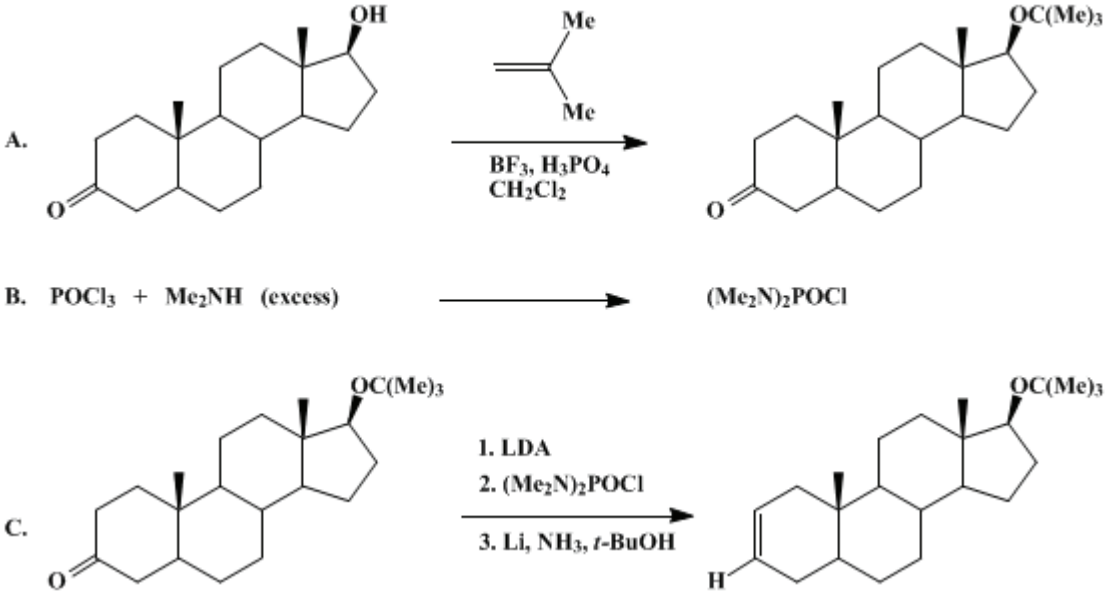
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries 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.061.0116

Organic Syntheses, Coll. Vol. 7, p.66 (1990); Vol. 61, p.116 (1983).

REDUCTIVE CLEAVAGE OF VINYL PHOSPHORODIAMIDATES: 17β-*tert*-BUTOXY-Gα-ANDROST-2-ENE



Submitted by Robert E. Ireland[1], Thomas H. O'Neil, and Glen L. Tolman.
Checked by James W. Herndon, M. F. Semmelhack, and Dieter Seebach.

1. Procedure

A. *Protection of the 17-hydroxyl group*. A solution of androstanolone ((Note 1), 4.10 g, 14 mmol) in 60 mL of dichloromethane in a 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum bearing two syringe needles (argon inlet and exit) is cooled to −20°C (refrigerated bath). Argon is allowed to pass over the surface of the mixture for 15 min and then boron trifluoride etherate ((Note 2), 0.125 mL, 0.90 mmol) is added rapidly, via syringe, followed by anhydrous phosphoric acid ((Note 3), 0.053 mL, 1.0 mmol). Isobutene (Note 4) is added as a gas through a large-bore syringe needle until approximately 100 mL has condensed. The steroid precipitates during addition of the isobutene and redissolves as the reaction proceeds. The drying tube is replaced with a stopper, the tightly sealed flask is allowed to warm to 25°C, and the mixture is stirred at this temperature for 4 hr (Note 5). The flask is cooled to 0°C, opened, and warmed to 25°C to allow excess isobutene to evaporate. The residue is poured into 2 *N* aqueous ammonium hydroxide (100 mL) and ethyl acetate (75 mL) is added. After the layers are vigorously shaken, the aqueous solution is washed with a second portion of ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue is recrystallized from hexane to give colorless crystals, mp 146–148°C, 4.10 g (86%, (Note 6)).

B. *Preparation and reductive cleavage of the vinyl phosphorodiamidate*. A dry, 250-mL flask equipped with magnetic stirrer, syringe port (Note 7), and argon outlet is flushed three times with argon. To the flask are added 40 mL of dry tetrahydrofuran (THF) and 1.17 mL (8.4 mmol) of dry diisopropylamine (Note 8). The flask is cooled in an acetone–dry-ice bath while 7.4 mmol of butyllithium in hexane (Note 9) is added dropwise with stirring. After the addition is complete, the solution is allowed to warm for 15 min. The flask is then cooled in an ice–water bath. To this solution is added 1.61 g (4.6 mmol) of 17β-*tert*-butoxy-5α-androstan-3-one in 30 mL of 2:1 THF/DMPU (Note 8) solution. The reaction mixture is stirred with ice cooling for 15 min. *N,N,N′,N′*-Tetramethyldiamidophosphorochloridate, 5.83 mL (0.038 mol) (Note 10), is added dropwise with stirring. After 15 min, the bath is removed; the flask is allowed to warm to 25°C and is stirred for an

additional 2 hr. The excess reagent is hydrolyzed by slow addition of 30 mL of saturated aqueous sodium bicarbonate solution and stirring for 30 min. After three extractions with 100-mL portions of diethyl ether, the combined organic layers are washed twice with 100 mL of water and 100 mL of saturated sodium chloride solution. The solution is dried over anhydrous magnesium sulfate and the ether is removed under reduced pressure on a rotary evaporator to afford 2.9–3.0 g of a crude yellow solid (Note 11). The crude phosphorodiamidate is dissolved in 40 mL of dry THF and added to a dry, three-necked, 250-mL flask equipped with overhead stirrer, cold finger condenser (acetone–dry ice), argon bubbler, and acetone–dry-ice bath. Dry ammonia is distilled into the flask until the phosphorodiamidate begins to precipitate. The bath is removed and the solution is allowed to warm to reflux. Dry *tert*-butyl alcohol (1.75 mL, (Note 12)) is added in one portion. To the clear solution is added 1.5 cm of 1/8-in., cleaned lithium wire in 0.3-cm portions. The blue color is maintained (by the addition of lithium wire if necessary) with stirring for 4 hr and then allowing the stirred solution to warm to room temperature overnight. Sodium benzoate is added in 25-mg portions until the blue color is discharged. Ammonium chloride (0.50 g) is added in one portion, the condenser removed, and the ammonia allowed to evaporate. The residue is taken up in 100 mL of diethyl ether and 100 mL of water. The layers are separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are washed with 100 mL of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. The ether is removed under reduced pressure on a rotary evaporator. The crude olefin is filtered through 15 g of silica gel (Note 13) using benzene–ethyl acetate (2:1) as eluant, to give an off-white solid that is recrystallized from a minimum amount of absolute ethanol to give, after drying, 1.0 g (67%) (Note 14) of 17β-*tert*-butoxy-5α-androst-2-ene, mp 114–117° C (Note 15).

2. Notes

1. Androstanolone was obtained from Aldrich Chemical Company, Inc., and used without purification. The recheckers used material from Fluka Chemical Corp.
2. Boron trifluoride etherate was distilled before use.
3. Anhydrous phosphoric acid was prepared by slow addition of 5 g of 15% phosphoric acid to 2 g of phosphorus pentoxide.[2]
4. Isobutene, reagent grade, was obtained from Phillips Company.
5. The flask was stoppered with a greased 24/40 ground-glass stopper held in place by rubber bands stretched over appropriately placed wire hooks. The pressure at 25°C was slightly more than 1 atm.
6. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.74 (s, 3 H), 1.02 (s, 3 H), 1.13 (s, 9 H), 3.36 (m, 1 H); IR ($CHCl_3$) cm^{-1}: 1715 (C=0), 1255, 1205.
7. All solutions were added via glass syringes under rigorously anhydrous conditions.
8. Diisopropylamine and tetrahydro-1,3-dimethyl-2-(1H)-pyrimidinone (dimethyl propylene urea, DMPU) (Fluka Chemical Corp.) were distilled from calcium hydride. The original procedure used a THF–hexamethylphosphoric amide (HMPA) mixture. Because of the suspected carcinogenicity of HMPA, *Organic Syntheses* is recommending its replacement with DMPU whenever possible.
9. Butyllithium in hexane was obtained from Alfa Products. Morton Thiokol, Inc. or Foote Mineral Company. The checkers titrated the solution before[3] use.
10. *N,N,N′,N′*-Tetramethyldiamidophosphorochloridate was obtained by the recheckers from Fluka Chemical Corp. If desired, it may be prepared as follows. In a dry, 2-L, three-necked flask equipped with overhead stirrer, thermometer, argon outlet, and pressure-equalizing addition funnel is placed 400 mL of diethyl ether (Note 7). The flask is cooled in an isopropyl alcohol–dry-ice bath while 100 g (2.2 mol) of anhydrous dimethylamine is added in one portion. A solution of 85 g (0.56 mol) of phosphoryl chloride in 200 mL of diethyl ether is added at a rate to maintain the temperature at −35 ± 5°C. The addition time is approximately 1.5 hr. After the addition is complete, the bath is removed, and stirring is continued for 4 hr. The thick white slurry is filtered through a coarse frit and the filter cake is washed with 4000 mL of diethyl ether. The combined filtrates are concentrated under aspirator pressure on a rotary evaporator. Fractional distillation of the concentrate through a 10-cm Vigreux column gives 71–80 g (74–84%) of the *N,N,N′,N′*-tetramethyldiamidophosphorochloridate, bp 58.5–59°C (0.6 mm) *d* 1.126; IR (neat) cm^{-1}: 1470, 1450, 1290, 1230, 980; ^{1}H NMR (neat) δ: 2.69 (d $J_{P\text{-}H}$ = 13).
11. Spectral data are as follows: IR (CCl_4) cm^{-1}: 1660, 1350, 1215; ^{1}H NMR ($CDCl_3$) δ: 0.69 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 1.11 (s, 9 H, CH_3), 2.60 (d, 3 H, $J_{P\text{-}H}$ = 10, *N*-CH_3), 3.28 (m, 1 H, OC*H*), 5.12 (m, 1 H, C=C*H*).

12. *tert*-Butyl alcohol was dried by distillation from calcium hydride.
13. Silica gel 60 (particle size 0.063–0.200 μm) is available from E. Merck, A. G.
14. In the original procedure employing HMPA, the yield was 1.1–1.2 g (71–78%).
15. Spectral data are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.63 (s, 3 H, C*H*$_3$), 0.67 (s, 3 H, C*H*$_3$), 1.02 (s, 9 H, C*H*$_3$), 3.28 (m, 1 H, OC*H*), 5.43 (m, 2 H, vinyl H); IR ($CHCl_3$): The product was characterized by cleavage of the *tert*-butyl ether (CF_3CO_2H, CH_2Cl_2, 0°C) to give 17β-hydroxy-5α-androst-2-ene, mp 161–162°C, lit.[4] mp 163–165°C.

3. Discussion

The reduction of a carbonyl group to an olefin has been accomplished by the Shapiro modification[5] of the Bamford–Stevens reaction and by the hydride reduction of the corresponding enol ether,[6] enol acetate,[7] or enamine.[8] The nickel reduction of the thioketal has also been used successfully.[9]

The lithium/amine reduction of *N,N,N′,N′*-tetramethylphosphorodiamidates is a general method for the cleavage of the C-O bond.[10] In addition to the reductive deoxygenation of carbonyl compounds to generate olefins, the phosphorodiamidates of alcohols are reduced in high yield to give alkanes. Alcohols in which the hydroxyl group is greatly hindered could be unreactive toward *N,N,N′,N′*-tetramethyldiaminophosphorochloridate. In such cases, treatment of the alcohols with butyllithium and *N,N*-dimethylphosphoramidic dichloride in 1,2-dimethoxyethane and *N,N,N′,N′*-tetramethylethylenediamine followed by addition of dimethylamine gave rise to *N,N,N′,N′*-tetramethylphosphorodiamidates in good yields.[11] Combined in a two-step process (e.g., RCOR' → RCHOHR' → RCH$_2$R'), the method allows the reductive removal of a carbonyl functionality. This two-step process compares favorably with the analogous Wolff–Kishner reduction. Additionally, reduction of the enol phosphorodiamidate by dialkyl cuprate reagents generates a substituted olefin.[12]

The phosphorodiamidate group can also serve as a protecting group for the hydroxyl function, since it is stable to CH_3Li, $LiAlH_4$, KOH, and 0.2 *N* aqueous HCl, but is quantitatively cleaved by butyllithium–TMEDA (tetramethylethylenediamine).[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 126

References and Notes

1. The Chemical Laboratories of the California Institute of Technology, Pasadena, CA 91125. Contribution No, 5718. This work was made possible in part by a grant from the National Institutes of Health. Present address: Department of Chemistry, University of Virginia, Charlottesville, VA.
2. Beyeman, H. C.; Heiswolf, G. J. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 203.
3. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem*. **1976**, *41*, 1879.
4. Fetizon, M.; Jurion, M.; Nguyen Trong, A. *Org. Prep. Proced, Int*. **1974**, *6*, 31–35.
5. Shapiro, R. H. *Org. React*. **1976**, *23*, 450 and references cited therein.
6. Larson, G. L.; Hernandez, E.; Alonzo, C.; Nieves, I. *Tetrahedron Lett*. **1975**, 4005; Pino, P.; Lorenzi, G. P. *J. Org. Chem*. **1966**, *31*, 329.
7. Cagliot, L.; Caielli, G.; Maina, G.; Salva, A. *Gazz. Chim. Ital*. **1962**, *92*, 309.
8. Lewis, J. W.; Lynch, P. P. *Proc. Chem. Soc. (London)* **1963**, 19; Coulter, J. M.; Lewis, J. W.; Lynch, P. P. *Tetrahedron* **1968**, *24*, 4489.
9. Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron* **1969**, *25*, 2826; Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem*. **1963**, *28*, 1443.
10. Ireland, R. E.; Muchmore, D. C.; Hengarten, U. *J. Am. Chem. Soc*. **1972**, *94*, 5098; Ireland, R. E.; Pfister, G. *Tetrahedron Lett*. **1969**, 2145.
11. Liu, H.-J.; Lee, S. P.; Chan, W. H. *Can. J. Chem*. **1977**, *55*, 3797.
12. Blaszczak, L.; Winkler, J.; O'Kuhn, S. *Tetrahedron Lett*. **1976**, 4405.

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

silica gel

VINYL PHOSPHORODIAMIDATES

17β-tert-BUTOXY-Gα-ANDROST-2-ENE

ethanol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nickel (7440-02-0)

phosphoric acid (7664-38-2)

sodium benzoate (532-32-1)

ammonium hydroxide (1336-21-6)

dimethylamine (124-40-3)

dichloromethane (75-09-2)

Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

isobutene (9003-27-4)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

tert-butyl alcohol (75-65-0)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

diisopropylamine (108-18-9)

tetramethylethylenediamine (20485-44-3)

phosphoryl chloride (10025-87-3)

N,N,N',N'-Tetramethyldiamidophosphorochloridate (1605-65-8)

androstanolone (521-18-6)

vinyl phosphorodiamidate

phosphorodiamidate

tetrahydro-1,3-dimethyl-2-(1H)-pyrimidinone (7226-23-5)

dimethyl propylene urea (7226-23-5)

17β-hydroxy-5α-androst-2-ene

N,N,N',N'-tetramethyldiaminophosphorochloridate

phosphorus pentoxide (1314-56-3)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

17β-tert-Butoxy-5α-androstan-3-one (87004-41-9)

17β-tert-Butoxy-5α-androst-2-ene (87004-43-1)

N,N-dimethylphosphoramidic dichloride (677-43-0)