Tetrapropylammonium perruthenate as a mild and efficient oxidant for sensitive steroidal alcohols

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Tetrapropylammonium perruthenate N-methylmorpholine N-oxide oxidation of steroidal alcohols is described. The reagent combination is mild and gave good yields of the corresponding ketones. Although the oxidation can generate ketones from 3-, 11-, 15-, 17-, and 20-hydroxy steroids, the oxidation of homoallylic alcohols proceeds in low yields. Finally, we observed that the oxidation reagents will convert 17α-hydroxy-20-keto steroids to 17-keto systems in excellent yield. (Steroids **58**:205–208, 1993)

Keywords: tetrapropylammonium perruthenate; N-methylmorpholine N-oxide; oxidation; steroidal alcohols; steroid

Introduction

Griffith and Ley[1] described the preparation and use of tetrapropylammonium perruthenate (TPAP) as a catalytic oxidant used in conjunction with N-methylmorpholine N-oxide (NMO) for the oxidation of primary and secondary alcohols to aldehydes and ketones. This reagent combination is efficient, requires a simple work-up, generates a minimum amount of inorganic residues for disposal, and most important, is tolerant of a wide variety of functional groups such as silyl ethers, ketals, double bonds, acetylenes, and esters. Although a number of examples have been given in the literature illustrating the synthetic utility of this reagent combination,[2,3] few reports on the oxidation of steroidal alcohols have appeared.[4]

We have had the opportunity to examine the scope of the TPAP/NMO oxidation of a number of steroidal alcohols and our results are presented here.

Experimental

Melting points (mp) were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 (90-MHz) spectrometer in deuteriochloroform using tetramethylsilane (TMS) as an internal standard (δ = 0.0). Infrared (IR) spectra were recorded on a Perkin-Elmer model 1600 FTIR instrument equipped with a diffuse reflectance accessory using a KBr matrix. Tetrapropylammonium perruthenate and N-methylmorpholine N-oxide were obtained from Aldrich Chemical Company. Anhydrous methylene chloride and acetonitrile were obtained from freshly opened bottles and stored over 4-Å molecular sieves.

In reactions that gave known compounds, the products were compared (NMR, IR, thin-layer chromatography (TLC), and mp) with authentic samples. Unless indicated otherwise, literature melting points are those found in the Merck Index, 10th Edition.

Generalized procedure for TPAP/NMO oxidations

A mixture of the steroid alcohol (1.0 eq), NMO, and powdered 4-Å molecular sieves (1.0 g/0.5 mmol) in the specified solvent (10 ml/0.5 mmol) was stirred under nitrogen for 20 minutes. TPAP was added and the reaction was monitored by TLC. When complete, the mixture was filtered and the filtrate was evaporated to near dryness. The residue was taken up in a minimum amount of ether/methylene chloride. This solution was passed through a short column of neutral alumina, eluting with 100% ether. Evaporation of the solvent gave the ketone.

13β-Ethyl-11-oxo-3-methoxy-17β-t-butyldimethylsilyloxygona-1,3,5(10)-triene (2)

mp = 150–151 C. NMR: δ 0.90 (s,-Si(t-Bu)), 1.03 (t, J = 3 Hz, 13β-$CH_2C\underline{H}_3$) 3.40 (br.d, 9α-H), 3.73 (s, 3-$OC\underline{H}_3$), 3.97 (br.t, 17α-H), 6.59 (d, J = 3 Hz, C-4H), 6.73 (d of d, J = 9 Hz, J′ = 3 Hz, C-2H), 7.33 (d, J = 9 Hz, C-1 H) ppm. IR (cm^{-1}) 2,980, 1,712, 1,609, 1,505. MS (m/z): M^+ = 428. Analysis calculated: C 72.84, H 9.41. Found: C 72.90, H 9.46.

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13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one **(4)**

mp = 144–146 C (lit.[5] 146–148 C), NMR: δ 0.76 (t, J = 6 Hz, 13β-$CH_2\underline{CH_3}$), 3.76 (s, $O\underline{CH_3}$) 6.56–6.86 (m, C-2 and C-4 H), 7.22 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 2,994, 1,732, 1,607, 1,502.

3-Ethylenedioxy-13β-Ethyl-11β-hydroxygon-5(10)-en-17-one 11-nitrate **(6)**

NMR: δ 0.73 (t, J = 6 Hz, 13β-$CH_2\underline{CH_3}$), 2.60 (d of d, J = 15 Hz, J′ = 2 Hz, 9α-H), 3.97 (br.s, -$O\underline{CH_2}\underline{CH_2}O$-), 5.59 (q, J = 3 Hz, 11α-H) ppm. IR (cm^{-1}) 2,924, 1,736, 1,620, 1,265.

Glycolic acid methyl ester (3-ethylenedioxy-13β-ethyl-17β-hydroxygon-5(10)-ene-11β)methyl-ether **(8)**

mp = 111–113 C; NMR: δ 0.90 (t, J = 6 Hz, 13β-$CH_2\underline{CH_3}$), 3.33–3.57 (m, 11β-CH_2O-), 3.77 (s, -$O\underline{CH_2}\underline{CH_2}O$-), 3.97 (s, -$CO_2CH_3$), 4.08 (s, $O\underline{CH_2}$, CO_2CH_3) ppm. IR (cm^{-1}) 1,752, 1,725, 1,427, 1,372. MS (m/z): M^+ = 432. Analysis calculated: C 69.42, H 8.39. Found: C 69.32, H 8.39.

3β,17β-Diacetoxyandrost-5-en-15-one **(10)**

mp = 185–189 C. NMR: δ 0.88 (s, 18-CH_3), 1.03 (s, 19-CH_3), 2.00 (s, 3H), 2.07 (s, 3H), 4.6 (br.s, 3α-H), 5.0 (t, J = 8.7 Hz, 17α-H), 5.41 (br.d, J = 5.4 Hz, C-6H) ppm. IR (cm^{-1}) 2,943, 1,734.

Androst-4-ene-3,17-dione **(12)** *from Androst-4-ene-3ξ,17β-diol* **(11)**

mp = 170–171 C (lit. 173–174 C). NMR: δ 0.90 (s, 18-CH_3), 1.20 (s, 19-CH_3), 5.77 (br.s, C-4H) ppm. IR (cm^{-1}) 2,915, 1,730, 1,668, 1,621.

Progesterone **(14)** *from Pregn-4-ene-3,20-diol* **(13)**

mp = 129–130 C (lit. 127–131 C). NMR: δ 0.80 (s, 18-CH_3), 1.20 (s, 19-CH_3), 2.15 (s, 20-CH_3), 5.80 (br.s, C-4 H) ppm. IR (cm^{-1}) 2,915, 1,699, 1,664, 1,614.

Androst-4-ene-3,11,17-trione **(16)**

mp = 222–224 C (lit. 220–221 C). NMR: δ 0.87 (s, 18-CH_3), 1.43 (s, 19-CH_3), 5.75 (br.s, C-4 H) ppm. IR (cm^{-1}) 2,980, 1,740, 1,702, 1,669, 1,608.

Androst-4-ene-3,17-dione **(12)** *from 17α-hydroxyprogesterone* **(18)**

mp = 169–170 C. NMR: δ 0.90 (s, 18-CH_3), 1.20 (s, 19-CH_3), 5.77 (br.s, C-4 H) ppm. IR (cm^{-1}) 2,912, 1,732, 1,670, 1,620.

3β-Acetoxyandrost-5-en-17-one **(20)**

mp = 167–169 C (lit.[6] 169–170 C). NMR: δ 0.90 (s, 18-CH_3), 1.05 (s, 19-CH_3), 2.05 (s, 3-OAc), 4.67 (br.m, 3α-H), 5.48 (br.d, J = 6 Hz, C-6H) ppm. IR (cm^{-1}) 2,949, 1,738, 1,242.

Pregn-5-ene-3,20-dione **(22)**

mp = 138–142 C (lit.[7] 139–148 C). NMR: δ 0.67 (s, 18-CH_3), 1.17 (s, 19-CH_3), 2.13 (s, 20-CH_3), 5.40 (m, C-6 H) ppm. IR (cm^{-1}) 2,936, 2,884, 1,712, 1,428.

Pregn-4-ene-3,6,20-trione **(23)**

mp = 192–193 C (lit.[8] 193–194 C). NMR: δ 0.67 (s, 18-CH_3), 1.17 (s, 19-CH_3), 2.13 (s, 20-CH_3), 6.20 (s, C-4 H) ppm. MS (m/z): M^+ = 328. IR (cm^{-1}) 2,960, 2,872, 1,690, 1,677, 1,600, 1,355.

Estrone from estradiol

All traces of moisture must be excluded from the phase transfer catalyzed acetylation conditions described below. Failure to do so results in low yield and/or no reaction.

3-Acetoxyestra-1,3,5(10)-trien-17β-ol **(24)**

Powdered sodium hydroxide (110 mg, 2.75 mmol) and tetrabutylammonium hydrogen sulfate (4.0 mg, 1 mol%) were added to a well-stirred, dry dioxane (4.0 ml) solution of estradiol (300 mg, 1.1. mmol) in a 15-ml tube under nitrogen. The mixture was stirred for 20 minutes before an acetylchloride in dioxane (1.0 M) solution (1.4 ml) was added slowly. During the course of the addition, the mixture became increasingly turbid and the yellow color of the phenolate anion was quenched near the end of the addition. The solids were centrifuged out and the supernatant was transferred to a round-bottomed flask. The solids were leached with additional dioxane and centrifuged twice. Evaporation of the combined dioxane supernatant gave 337 mg (98%) of 3-acetate **(24)**. NMR: δ 0.78 (s, 18-CH_3), 2.27 (s, 3-OAc), 3.72 (t, J = 6 Hz, 17α-H), 6.75–7.0 (m, C-2 and C-4 H), 7.3 (d, J = 9 Hz, C-1H) ppm.

3-Acetoxyestra-1,3,5(10)-trien-17-one **(25)**

mp = 126–128 C (lit. 125–127 C). NMR: δ 0.90 (s, 18-CH_3), 2.27 (s, 3-OAc), 6.75–7.0 (m, C-2 and C-4H), 7.30 (d, J = 9 Hz, C-1H) ppm.

3-Hydroxyestra-1,3,5(10)-trien-17-one

A methanol solution (5 ml) of 3-acetate **(25)** was treated with aqueous sodium hydroxide (0.5 N, 1.3 equivalent). The mixture was stirred for 15 minutes. The yellow color of the phenolate anion was quenched with the addition of dilute HCl. After extractive work-up and evaporation of the ethyl acetate, recrystallization of the residue from acetone gave estrone, mp = 253–255 C (lit. 254–256 C).

Results and discussion

Our initial experience with the TPAP/NMO oxidation was in the conversion of 13β-ethyl-11α-hydroxy-3-methoxy-17β-*t*-butyldimethylsilyloxygona-1,3,5(10)-triene **(1)** (Figure 1) to 13β-ethyl-11-oxo-3-methoxy-17β-*t*-butyldimethylsilyloxygona-1,3,5(10)-triene **(2)**, a system analogous to 11-keto estrogens, which are susceptible to facile epimerization at C-9.[9] Under a variety of standard oxidation conditions,[10–14] we obtained unacceptable yields of ketone **(2)** and significant degradation of the starting alcohol **(1)**. Furthermore, ketone **(2)** that was obtained by these methods was shown to be a C-9 epimeric mixture. Finally, TPAP/NMO oxidation of **(1)** afforded ketone **(2)** in 62.5% yield with no epimerization at C-9.

In most instances, the oxidations were complete within 1 hour and gave the corresponding ketone in better than 90% yield. It has been observed that potassium ruthenate (Ru^{VI}) can selectively oxidize benzylic

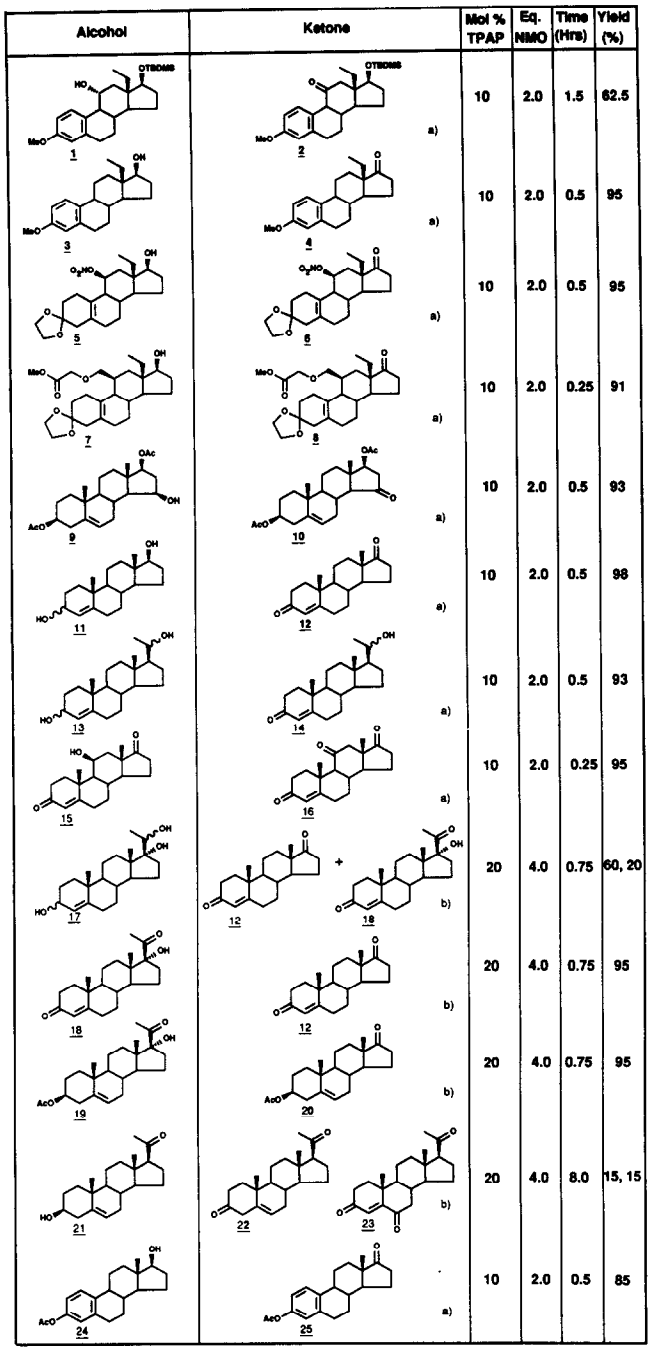

Figure 1 Oxidation of steroidal alcohols with TPAP reagent. a, solvent 100% CH_2Cl_2; b, solvent 10% CH_3CN/CH_2Cl_2.

and allylic alcohols in the presence of aliphatic alcohols.[15] Although it appeared that allylic alcohols were oxidized slightly faster than saturated alcohols, we observed no selectivity. For systems containing sensitive functional groups such as ketals, esters, silyl ethers, double bonds, and chiral centers, these groups were unaffected.

Next, we investigated if we could obtain a 17α-hydroxy-20-ketone from a 17α,20ξ-dihydroxy system. As a model compound we used pregn-4-ene-3ξ, 17α, 20ξ-triol **(17)**, available from lithium aluminum hydride (LAH) reduction of 17α-hydroxyprogesterone. Oxidation of triol **(17)** with TPAP/NMO gave a mixture of two products. Surprisingly, the major product (60%) was determined to be androstenedione **(12)**. The other product was 17α-hydroxyprogesterone **(18)** (20%).

To determine if the 17, 20-diol was being oxidatively cleaved to the 17-ketone or first being oxidized to the 20-ketone and then undergoing subsequent oxidative cleavage, we attempted direct oxidation of 17α-hydroxyprogesterone **(18)** with TPAP/NMO. Within 30 minutes the reaction was complete and we obtained androstenedione **(12)** in 95% yield. Similarly, oxidation of 17α-hydroxypregnenolone 3-acetate **(19)** gave dehydroepiandrosterone 3-acetate **(20)** in 95% yield. These results suggest that 17,20-diol systems are first oxidized to the 20-ketone, which undergoes subsequent oxidative cleavage to afford a 17-ketone.

It has been noted that oxidations of homoallylic alcohols with ruthenium complexes are often inefficient or fail completely.[4] This was the case when we attempted to oxidize pregnenolone **(21)** to pregn-5-ene-3,20-dione **(22)** with TPAP/NMO. Even with extended reaction times (overnight) and the use of more of the reagent, the reaction failed to go to completion. However, we were able to isolate pregn-5-ene-3,20-dione **(22)** and 6-ketoprogesterone **(23)** each in about 15% yield. The remaining material was starting alcohol **(21)**.

The production of 6-ketoprogesterone **(23)** in the above reaction is similar to results reported by Moreno et al.[4] in their investigation on TPAP/NMO oxidation of steroidal homoallylic alcohols. Although they also observed incomplete reaction using standard TPAP/NMO conditions, they were able to improve the yields significantly by conducting the reaction under sonochemical conditions. They offer no explanation for this phenomenon.

Attempts to oxidize estradiol to estrone were not successful, for the reaction gave a complex mixture of products. However, a convenient solution to this problem was realized by first converting estradiol to 3-acetate **(24)** via phase transfer catalyzed (PTC) acetylation.[16] Subsequent TPAP/NMO oxidation of **24**, followed by mild base hydrolysis of **25** gave estrone in 83% yield from **24**.

Based on the excellent results of this study, the TPAP/NMO oxidation has proved to be extremely useful. The efficacy, the ease of work-up, and its tolerance of sensitive functionality should make this oxidation procedure an attractive alternative to older methods. Of the methods available for the conversion of 17α-hydroxy-20-keto steroids to 17-keto systems,[17] the TPAP/NMO oxidation proves to be one of the most efficient for the two systems studied.

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