Improved Conditions for Preparation and Reductive Cleavage of Steroidal Ketone Tosylhydrazones

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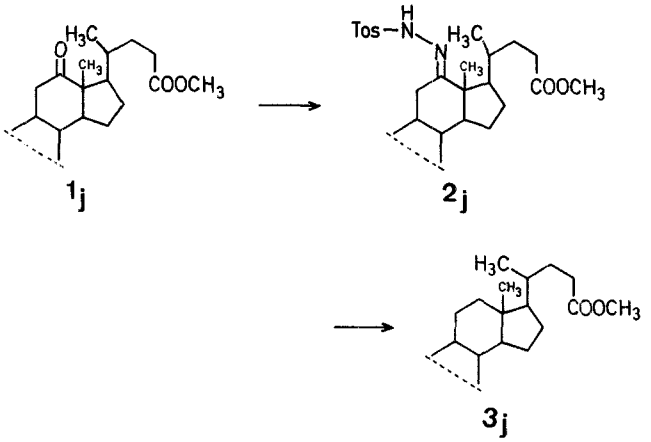
The reduction of ketones to the corresponding methylene compounds, a key transformation in organic synthesis, has been improved significantly by use of the Huang-Minlon modification of the Wolff-Kishner reduction. However, the reaction still has several drawbacks, especially when performed with ketones having other functional groups sensitive to the rather extreme conditions of temperature and alkalinity. The reaction products often are complex mixtures resulting from side reactions, from which the desired compounds are isolated with difficulty[1].

We have earlier reported a new method for the synthesis of chenodeoxycholic acid from cholic acid[2,3]. The principal reactions involved were the high-yield formation of the tosylhydrazone of methyl 3α,7α-diacetoxy-12-oxo-5β-cholanate **(2j)** and the reduction of this compound with sodium borohydride using a modification of the method of Ref.[4] to give **3j**.



The satisfactory results obtained by this modified method led us to investigate its applicability to a variety of other oxo-5α- and oxo-5β-steroids. Our previous results achieved in the

Table 1. Tosylhydrazones (**2**) prepared

1, 2	Ketone **1**	Yield[a] of **2** [%]	m.p.[b] [°C] (solvent)	Molecular Formula[c]
a	Methyl 3-oxo-5β-cholanate	98	189–191° (CH_2Cl_2)	$C_{32}H_{48}N_2O_4S$ (556.7)
b	Methyl 7α-hydroxy-3-oxo-5β-cholanate	84	173–174° (methanol)	$C_{32}H_{48}N_2O_5S$ (572.7)
c	Methyl 7α-acetoxy-3-oxo-5β-cholanate	64	98–100° (H_2O)	$C_{34}H_{50}N_2O_6S$ (614.8)
d	Methyl 12α-hydroxy-3-oxo-5β-cholanate	75	176.5–178° (H_2O)	$C_{32}H_{48}N_2O_5S$ (572.7)
e	5α-Cholestan-3-one	93	171–173° (CH_2Cl_2)	$C_{34}H_{54}N_2O_2S$ (554.8)
f	Methyl 3α-ethoxycarbonyloxy-7-oxo-5β-cholanate	76	99–101° (methanol)	$C_{34}H_{50}N_2O_7S$ (630.8)
g	3β-Acetoxy-5α-cholestan-7-one	82	235–237.5° (ether)	$C_{36}H_{56}N_2O_4S$ (612.8)
h	Methyl 12-oxo-5β-cholanate	78	138–139.5° (methanol)	$C_{32}H_{48}N_2O_4S$ (556.7)
i	Methyl 3α-acetoxy-12-oxo-5β-cholanate	93	172–174° (methanol)	$C_{34}H_{50}N_2O_6S$ (614.8)
j	Methyl 3α,7α-diacetoxy-12-oxo-5β-cholanate	82	146–147° (methanol)	$C_{36}H_{52}N_2O_8S$ (672.8)

[a] Yield of isolated, pure product.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values: C ±0.30; H ±0.27.

Table 2. Spectral Data of Tosylhydrazones **2**

2	I.R. (KBr) ν [cm⁻¹]	¹H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	3220, 1640, 1595, 1328, 1167, 817	0.64 (s, 3H, CH_3-18); 0.91 (s, 3H, CH_3-19); 2.37 (s, 3H, C_6H_4—CH_3); 3.60 (s, 3H, $COOCH_3$); 7.20, 7.73 (2d, 2H each, J = 8.1 Hz, C_6H_4—CH_3)
b	3225, 1638, 1598, 1327, 1165, 815	0.65 (s, 3H, CH_3-18); 0.91 (s, 3H, CH_3-19); 2.36 (s, 3H, C_6H_4—CH_3); 3.58 (s, 3H, $COOCH_3$); 3.77 (m, 1H, 7β-H); 7.18, 7.72 (2d, 2H each, J = 9.0 Hz, C_6H_4—CH_3)
c	3220, 1638 1598, 1330, 1167, 810	0.65 (s, 3H, CH_3-18); 0.93 (s, 3H, CH_3-19); 1.99 (s, 3H, 7α-O—CO—CH_3); 2.39 (s, 3H, C_6H_4—CH_3); 3.61 (s, 3H, $COOCH_3$); 4.85 (m, 1H, 7β-H); 7.25, 7.77 (2d, 2H each, J = 8.1 Hz, C_6H_4—CH_3)
d	3200, 1638, 1595, 1323, 1165, 818	0.67 (s, 3H, CH_3-18); 0.89 (s, 3H, CH_3-19); 2.36 (s, 3H, C_6H_4—CH_3); 3.59 (s, 3H, $COOCH_3$); 3.88 (m, 1H, 12β-H); 7.19, 7.72 (2d, 2H each, J = 7.2 Hz, C_6H_4—CH_3)
e	3250, 1630, 1600, 1340, 1332, 1173, 813	0.63 (s, 3H, CH_3-18); 0.82 (s, 3H, CH_3-19); 0.85 (d, 6H, J = 5.4 Hz, CH_3-26 + CH_3-27); 2.36 (s, 3H, C_6H_4—CH_3); 7.18, 7.70 (2d, 2H each, J = 9.0 Hz, C_6H_4—CH_3)
f	3230, 1638, 1600, 1330, 1320, 1165, 807	0.60 (s, 3H, CH_3-18); 1.03 (s, 3H, CH_3-19); 1.31 (t, 3H, J = 7.2 Hz, 3α-O—CO—O—CH_2—CH_3); 2.40 (s, 3H, C_6H_4—CH_3); 3.62 (s, 3H, $COOCH_3$); 4.12 (q, 2H, J = 7.2 Hz, 3α-O—CO—O—CH_2—CH_3); 4.38 (br. m, 1H, 3β-H); 7.24, 7.72 (d, 2H each, J = 9.0 Hz, C_6H_4—CH_3)
g	3225, 1640, 1598, 1336, 1165, 807	0.58 (s, 3H, CH_3-18); 0.87 (d, 6H, J = 7.2 Hz, CH_3-26 + CH_3-27); 0.92 (s, 3H, CH_3-19); 1.95 (s, 3H, 3α-O—CO—CH_3); 2.37 (s, 3H, C_6H_4—CH_3); 4.5 (br.m, 1H, 3α-H); 7.18, 7.69 (2d, 2H each, J = 9.0 Hz, C_6H_4—CH_3)
h	3240, 1633, 1600, 1323, 1163, 808	0.66 (d, 3H, J = 6.3 Hz, CH_3-21); 0.82 (s, 3H, CH_3-18); 0.95 (s, 3H, CH_3-19); 2.37 (s, 3H, C_6H_4—CH_3); 3.61 (s, 3H, $COOCH_3$); 7.21, 7.73 (2d, 2H each, J = 8.1 Hz, C_6H_4—CH_3)
i	3250, 1630, 1598, 1323, 1163, 807	0.69 (d, 3H, J = 6.3 Hz, CH_3-21); 0.81 (s, 3H, CH_3-18); 0.98 (s, 3H, CH_3-19); 2.00 (s, 3H, 3α-O—CO—CH_3); 2.37 (s, 3H, C_6H_4—CH_3); 3.63 (s, 3H, $COOCH_3$); 4.57 (br. m, 1H, 3β-H); 7.24, 7.75 (2d, 2H each, J = 7.2 Hz, C_6H_4—CH_3)
j	3180, 1623, 1583, 1324, 1150, 812	0.64 (d, 3H, J = 5.4 Hz, CH_3-21); 0.81 (s, 3H, CH_3-18); 0.96 (s, 3H, CH_3-19); 2.00, 2.01 (2s, 3H each, 3α, 7α-di-O—CO—CH_3); 2.42 (s, 3H, C_6H_4—CH_3); 3.64 (s, 3H, $COOCH_3$); 4.5 (br.m, 1H, 3β-H); 4.9 (m, 1H, 7β-H); 7.32, 7.76 (2d, 2H each, J = 8.1 Hz, C_6H_4—CH_3)

preparation of 12-oxosteroid tosylhydrazones[5] by literature methods[6,7] (heating the ketones and *p*-toluenesulfonic hydrazide in methanol or ethanol in the presence or absence of a catalytic amount of concentrated hydrochloric or sulfuric acid) were unsatisfactory: the products were contaminated with the corresponding azine or the reaction was incomplete even after 24 h. However, with a change of solvent to acetic acid, the reaction proceeds smoothly to completion even at room temperature, and affords the desired tosylhydrazones in good isolated yields (64–98%; see Table 1).

The reduction of tosylhydrazones with sodium borohydride to give the corresponding methylene compounds has been carried out in boiling neutral solvents such as methanol,

Table 3. Methylene Compounds (3) prepared by Reduction of Tosylhydrazones (2)

Product[a]		Yield[b] [%]	m.p. [°C][c] found	reported
3a	Methyl 5β-cholanate	62	84–86° (acetone)	83–84°[d]
3b	Methyl 7α-hydroxy-5β-cholanate	87	77–79° (acetone)	78–79°[9]
3c	Methyl 7α-acetoxy-5β-cholanate	56	93–95.5° (methanol/H_2O)	95–96°[11]
3d	Methyl 12α-hydroxy-5β-cholanate	53	118–119.5° (methanol/H_2O)	119–120°[9]
3e	5α-Cholestane	58	77–79° (acetone)	78–80°[d]
3f	Methyl 3α-ethoxycarbonyloxy-5β-cholanate	48	137–139° (methanol/H_2O)	139–140.5°[d]
3g	3β-Acetoxy-5α-cholestane	76	107–108.5° (methanol/ether)	106–107°[d]
3h	Methyl 5β-cholanate	60	83.5–85 (acetone)	83–84°[d]
3i	Methyl 3α-acetoxy-5β-cholanate	59	133–135° (methanol)	133–134°[9]
3j	Methyl 3α,7α-diacetoxy-5β-cholanate	60	133–133.5° (methanol/H_2O)	130–132°[9]

[a] The physical and spectral data of all products **3** were in good agreement with those of authentic samples.
[b] Yield of isolated, pure product.
[c] Unocrrected.
[d] Authentic sample.

dioxan, or tetrahydrofuran[8]. When this method was applied to the reduction of tosylhydrazono-3-acetoxy-5β-cholanic esters, all three functional groups in the molecule were transformed: the tosylhydrazone moiety was reduced to a methylene group, the C–24 methoxycarbonyl group was reduced to a primary alcohol group, and the 3-acetoxy group was cleaved to a hydroxy group[3]. We have now found that compounds of this type **(2)** can be selectively reduced at the tosylhydrazone moiety to give satisfactory yields of the corresponding methylene compounds **(3)** without significant side reactions by using sodium borohydride in acetic acid [probably $NaBH(OAc)_3$[4]] at room temperature (Table 3).

Thus, the two-step procedure described here represents a mild and simple method for the selective deoxygenation of ketones **(1)** having alkoxycarbonyl groups and possibly also acyloxy groups without concomitant reduction of these latter groups.

Melting points were determined on an electrical hot stage and are uncorrected. T.L.C. was carried out with Merck precoated silica gel $60F_{254}$. ^{1}H-N.M.R. spectra were obtained on a Hitachi R-22 (90 MHz) spectrometer.

All starting materials **1** were dried by azeotropic removal of water (using dichloromethane or benzene) before use. Compounds **1a–f, h, i, j** were prepared from lithocholic, deoxycholic, chenodeoxycholic, or cholic acids or cholesterol by known methods[9]. Compound **1g** was obtained by the procedure of Ref.[10].

Tosylhydrazones (2) of Oxosteroids (1); General Procedure:
p-Toluenesulfonic hydrazide (745 mg, 4 mmol) is added to a stirred solution of the oxosteroid **1** (2 mmol) in acetic acid (20 ml). The mixture is allowed to stand at room temperature for 12 h and is then diluted with water (30 ml). The precipitated solid product **(2a, e, g, h)** is isolated by suction, washed with water, and recrystallized from the solvent given in Table 1. Oily products **(2b, c, d, f, i, j)** are extracted from the mixture with dichloromethane (2 × 25 ml). The organic extract is washed with 5% sodium hydrogen carbonate solution (30 ml) and then with water to neutrality, and is dried with Drierite®. The solvent is evaporated and the residual oil brought to crystallization by treatment with the solvent given in Table 1. The product is isolated by suction and recrystallized from the same solvent.

Reduction of Tosylhydrazones (2) to the Corresponding Methylene Compounds (3); General Procedure: To a stirred solution of the tosylhydrazone **(2**; 0.6 mmol) in acetic acid (10 ml) is added sodium borohydride (pellets; 227 mg, 6 mmol) at such a rate that the temperature of the mixture does not exceed 60 °C. Stirring is continued at room temperature for 3 h, the flask is then immersed in an ice bath, and ice chips (~ 20 g) are gradually stirred into the mixture. Solid products **(3a, g–j)** are isolated by suction, washed with water, and recrystallized from the solvent given in Table 3. Oily products **(3b, f)** are extracted from the mixture with dichloromethane (2 × 15 ml). The organic extract is washed with 5% sodium hydrogen carbonate solution (20 ml) and then with water to neutrality, and is dried with Drierite®. The solvent is evaporated and the remaining product recrystallized from methanol. In the case of compounds **3c, d, e**, the dichloromethane extract is column-chromatographed on alumina using benzene as eluent, and recrystallized from the solvent given in Table 3.

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