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A NOVEL METHOD TO BUILD ACETYL AND HYDROXYACETYL SIDE-CHAINS IN 17-OXOSTEROIDS[1]

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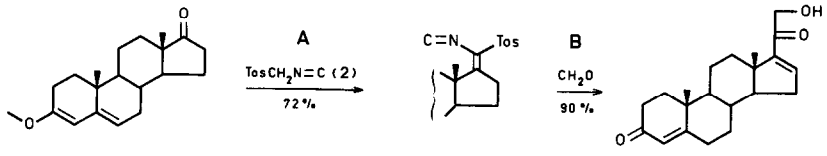
Nine examples are given of the title process.

Current interest in the construction of side-chains at C-17 in steroids reflects ongoing changes on the market of starting materials.[2] Efficient microbiological methods are now available for the production of 17-oxosteroids.[3] Therefore, practical methods are needed to convert the keto group into pharmacologically useful side-chains, among which the hydroxyacetyl group of corticosteroids takes a prominent position.[4] We report such a method.

In our method the carbonyl oxygen at C-17 is replaced by a hydroxyacetyl group under concomitant formation of a 16,17 double bond. Scheme I gives, by way of example, the synthesis of 21-hydroxypregna-4,16-diene-3,20-dione (4a) from the enolether 1a of androst-4-ene-3,17-dione (AD).[5] A high overall yield of 4a is obtained in few simple operations. The Table shows similar results obtained with other steroids.

SCHEME I



1a 3a 4a

A: 1) $TosCH_2N=C$, *t*-BuOK, THF, -35°C; 2) $POCl_3$, Et_3N.

B: 1) PTC: 40% CH_2O, 10 equiv. MeOH, $C_6H_5CH_3$/50% NaOH, TEBACl; 2) 8% H_2SO_4, THF.

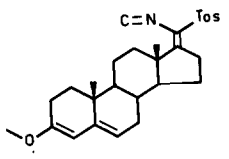
(Tos = *p*-toluenesulfonyl)

This new process involves the introduction of the 20-C=O by means of tosylmethyl isocyanide (TosMIC, 2)[6] via 3, and of 21-CH_2OH with formaldehyde via 9. Conversion A of 1 to 3 is basically a Knoevenagel-type condensation of TosMIC, a two step one-pot process described previously for simple aldehydes and ketones.[7] Conditions of the first step (see Scheme I) of this process needed crucial adjustments for two reasons: (i) to cope with the lower reactivity of the 17-oxo group of 1, (ii) to avoid elimination of sulfinic acid (TosH) from intermediate 10.[8]

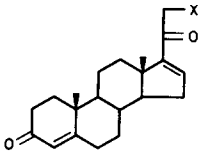
Conversion B of 3 to 4 is a specific adaptation of a new general method for the synthesis of enones (see succeeding letter).[9] Scheme II describes the series of reactions that is involved. Addition of 10 equivalents of MeOH to the phase transfer (PTC) medium of step B leads directly to the sulfur-free oxazoline 9, instead of the conjugate acid of 7.[10] This forms an essential feature of our method, which greatly facilitates the acid catalyzed hydrolysis of

TABLE. 17-(Hydroxyacetyl)-Δ^{16}-steroids (4) and 17-(Isocyanotosylmethylene)steroids (3) Prepared According to Scheme I.[a]

Compounds 3[b]	Compounds 4
Yield (%, based on 1)	Yield (%, based on 3)
Mp (°C)	Mp (°C)
Spec. rot. ($[\alpha]_D^{20}$, c = 1.00, $CHCl_3$)	Spec. rot. ($[\alpha]_D^{20}$, c = 1.00, $CHCl_3$)

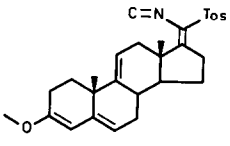


3a 72%
205° (dec)
[α] -85° (c=0.675)

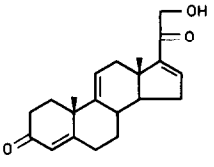


4a X=OH 92%
215-220° (dec)[c]
[α] +145°

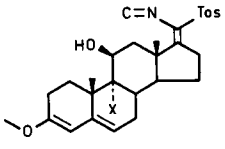
12a X=H 70%[d]
180°[e]
[α] +168°



3b 77%
172° (dec)
[α] -109°

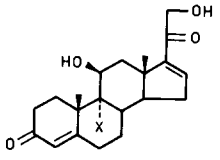


4b 93%
205-208°[f]
[α] +204°



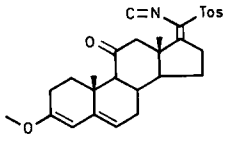
3c X=H 76%
188° (dec)
[α] -81°

3d X=F 64%
180° (dec)
[α] -87°

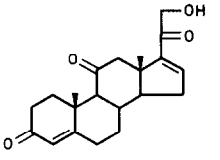


4c X=H 68%
148-153°[g]
[α] +198°

4d X=F 71%
175-186°[h]
[α] +165° (c = 0.9)

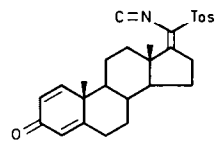


3e 71%
ca 220° (dec)
[α] -86.5°

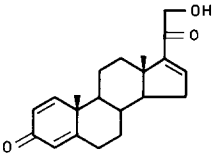


4e 73%
213-218°[i]
[α] +235°

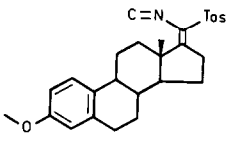
TABLE (continued)



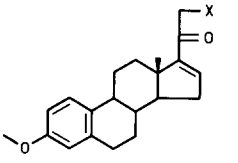
3f 59%
181-183° (dec)
[α] +181°



4f 83%
162-174°
[α] +92.5°



3g 72%
82-86° (dec)
[α] +46°



4g X=OH 92%
144-146°
[α] +81°

12g X=H 97%[d]
187°
$[\alpha]^{22}$ +122°

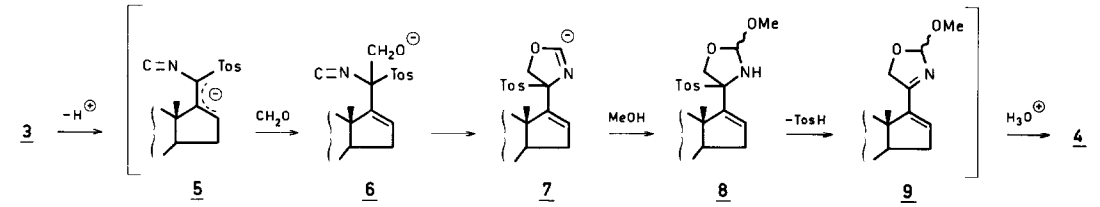
a) Satisfactory IR, ^{1}H NMR, and elemental analyses or MS data were obtained for all new compounds.
b) Compounds 3 were assigned the C-17,20 E-structure by analogy with lit. 7.
c) Lit.[12] mp 227-232°.
d) Compds. 12 were obtained by alkylation of 3 with MeI at C-20 to give 11, followed by hydrolysis, analogous to the succeeding paper (Scheme II, and lit. 9).
e) Lit.[13] mp 186-188°; $[\alpha]^{21}$ +154° (EtOH).
f) Lit.[12] mp 204-209° and 215-218°; [α] +194°.
g) Lit.[12] mp 154-156°; [α] +200° (c = 0.47).
h) Lit.[14] no physical data were reported.
i) Lit.[12] mp 223-228°; $[\alpha]^{24}$ +236°.

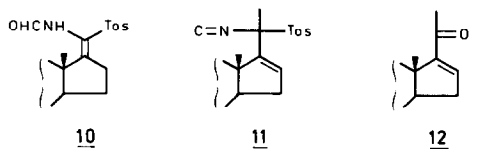
9 to the hydroxyacetyl group of the final product 4. Obviously, the enolether protection of the A-ring is removed simultaneously.

Protection of the 3-oxo group in AD (above, and footnote 5) is necessary for the conversion of 1a to 3a. The same protection was used for steroids 1b-e with identical A-rings. The lower reactivity of the 3-oxo group of androsta-1,4-diene-3,17-dione (ADD) makes it possible to prepare 3f without protection.[11] The results of the Table further show that no protection is needed of a β-OH or an oxo group at C-11 to prepare 3c-e.

The Table also includes two examples of the introduction of a 17-acetyl group by methylation of 3 with MeI through 11 to give 12 (cf. reference 7).

SCHEME II





Acknowledgement

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5. Unprotected AD reacts with TosMIC and base preferentially at the 3 position. When, however, protection is removed from the A ring of 3a ($AcOH/H_2O$), reaction B remains possible.
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7. A.M. van Leusen, F.J. Schaart and D. van Leusen, Recl. Trav. Chim. Pays-Bas 98, 258 (1979); cf A.M. van Leusen and J. Wildeman, ibid. 101, 202 (1982).
8. Such elimination is known to lead to nitriles, including 17-C≡N steroids: (a) J.R. Bull and A. Tuinman, Tetrahedron, 31, 2151 (1975); (b) O.H. Oldenziel, D. van Leusen and A.M. van Leusen, J. Org. Chem. 42, 3114 (1977); (c) A.M. van Leusen and P.G. Oomkes, Synth. Comm. 10, 399 (1980); (d) U. Schöllkopf and R. Schröder, Angew. Chem. Int. Ed. Eng. 12, 407 (1973).
9. A.M. van Leusen and J. Moskal, succeeding paper.
10. As a matter of fact, protonated 7 (contaminated with some oxazole) was obtained when MeOH was left out of the PTC medium. It was hydrolyzed directly to 4, however, in much lower yield.
11. It should be mentioned that a reaction of TosMIC was reported with the 1,2-double bond of 17β-hydroxy-17α-methylandrosta-1,4-diene-3-one to give a pyrrole: W. Kroszczynski, Rosz. Chem. 49, 813 (1975), (Chem. Abstr. 83, 114724h (1975)); cf ref. 6.
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