

Steroids XL. Michael Reaction with Steroidal 3-Keto-1-enes, 3-Keto-1,4-dienes and 3-Keto-1,4,6-trienes in the Presence of Tetramethylguanidine

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New 1-nitromethyl- and 1,7-di(nitromethyl)-steroids have been prepared by condensing of unsaturated 3-ketones with nitromethane in the presence of tetramethylguanidine.

MICHAEL additions to steroidal 3-keto-1,4,6-trienes V conducted in our laboratory gave numerous new 1-substituted derivatives VI¹. These compounds may be used as intermediates for synthesis of steroids with an additional ring fused with A ring². The Michael addition to 3-keto-1-ene III led also to expected 1 α -nitromethylcompound IV in satisfactory yield whereas experiments with various solvents and bases in order to get the addition of nitromethane to 3-keto-1,4-dienes I didn't succeed. However, good results have been obtained with the aid of tetramethylguanidine (TMG), a base with extremely high pK³. The addition of nitromethane to 3-keto-1,4-dienes in the presence of TMG gave the desired nitromethyl-compounds II in good yield. The Michael reaction of 3-keto-1-ene III with the nitromethane proceeded in the presence of TMG similarly as in the presence of potassium tert. butoxide to yield IV.

3-Keto-1,4,6-trienes V reacted with nitromethane in the presence of TMG at r.t. in a different way than in the presence of tert. butoxide as the base. They afforded a more polar product which was shown to be a disubstituted enone VII. The same product VII was obtained as the component of the reaction mixture along with 1 α -monosubstituted compound VI when the trienone V was refluxed with nitromethane in the presence of tert. butoxide as catalyst.

The structures of all new compounds were confirmed by spectral and analytical data.

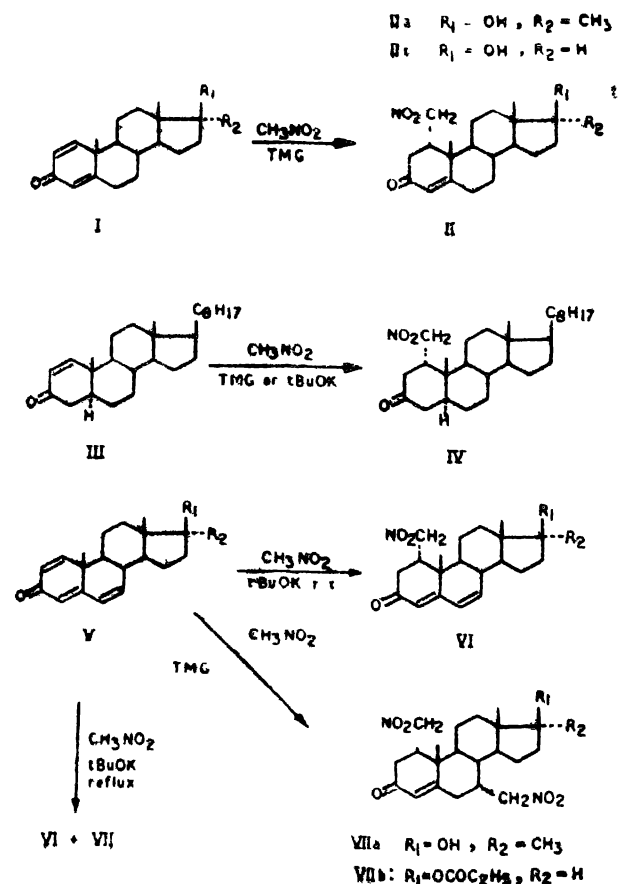
It follows from our experiments that in some cases TMG is a better catalyst of Michael reaction than the usually applied bases.

Experimental

Spectra and elemental analyses have been recorded in the Department of Physical Methods and Analysis of the Institute. M. p.s have been determined on a Boethius apparatus.

General procedure for Michael addition in the presence of TMG

A mixture of steroid (1 g), nitromethane (1.5 ml) and TMG (3.5 ml) was left at r.t. for 10 days. 40% Acetic acid (50 ml) was then added and the mixture was extracted with chloroform (3 x 50 ml). The organic layer was washed with water, NaHCO₃ aq. soln. and dried over anhydrous Mg(SO₄)₂. The solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel (elution with 2-10% acetone-benzene) and crystallized from acetone-hexane or methanol.



General procedure for Michael reaction under reflux condition

To the soln. of a steroid (200 mg) in 20 ml of tert. butanol, 1 ml of potassium tert. butoxide soln. (40 mg of potassium in 1 ml of tert. butanol) and 1 ml of nitromethane were added. The mixture was refluxed for 6 h, then acidified with 40% acetic acid and worked up as above.

1 α -Nitromethyl-17 α -methylandro-4-en-17 β -ol-3-one (IIa) Analysis :

For C₂₁H₃₁NO₄-Calc. : 69.77% C, 8.65% H, 3.88% N ;
found : 69.75% C, 8.63% H, 3.87% N.

M.p. : 80-82° ; MS(m/e) : 361, 344, 331, 328, 326, 304, 270, 201, 173, 161, 147, 121 ; PMR (CDCl₃, δ , ppm) : 5.78(1H, s), 4.33(2H, m), 1.42(3H, s), 1.20(3H, s), 0.90(3H, s) ; UV(C₂H₅OH, nm) : 244 ; IR(Nujol, cm⁻¹) : 3450, 1670, 1555 ; Yield: 70%.

1 α -Nitromethylandro-4-en-17 β -ol-3-one (IIb) Analysis :

For C₂₀H₂₉NO₄-Calc. : 69.48% C, 8.41% H, 4.03% N ;
found : 69.13% C, 8.31% H, 4.00% N.

M.p. 142-144° ; PMR (CDCl₃, δ , ppm) : 5.85(1H, s), 4.40(2H, m), 3.75(1H, t), 1.45(3H, s), 0.88(3H, s) ; UV (C₂H₅OH, nm) : 244 ; IR (Nujol, cm⁻¹) : 3400, 1670, 1555 ; Yield: 65%.

1 α -Nitromethyl-5 α -cholestan-3-one (IV) Analysis :

For C₂₈H₄₇NO₃-Calc. : 75.16% C, 10.63% H, 3.14% N ;
found : 75.05% C, 10.43% H, 3.16% N.

M.p. 111-112° ; PMR(CDCl₃, δ , ppm) : 4.40(2H, t) and signals of methyl group protons ; IR(Nujol, cm⁻¹) : 1710, 1560 ; Yield : 56%.

1 α , 7 ξ -Dinitromethyl-17 α -methylandro-4-en-17 β -ol-3-one (VIIa)

An oil ; MS (m/e) : 420, 403, 387, 385, 374, 331, 279, 149, 121 ; PMR (CDCl₃, δ , ppm) : 5.95(1H, s), 4.45(4H, m), 1.48(3H, s), 1.27(3H, s), 0.97(3H, s) ; UV (C₂H₅OH, nm) : 240 ; IR (Nujol, cm⁻¹) : 3450, 1670, 1555 ; Yield : 48%.

1 α , 7 ξ -Dinitromethyl-andro-4-en-17 β -propionoxy-3-one (VIIb) Analysis :

For C₂₄H₃₄N₂O₇-Calc. : 62.32% C, 7.41% H, 6.06% N ;
Found: 62.19% C, 7.25% H, 5.86% N.

M.p. 252-253° ; MS(m/e) : 462, 445, 432, 4.5, 331 ; PMR (CDCl₃, δ , ppm) : 5.85(1H, s), 4.40(5H, m), 1.52(3H, s), 0.95(3H, s) ; UV (C₂H₅OH, nm) : 240 ; IR (Nujol, cm⁻¹) : 1720, 1670, 1555 ; Yield : 42%.

References

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