Synthesis of Steroidal Allenyl Ketones

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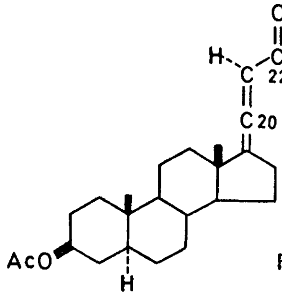
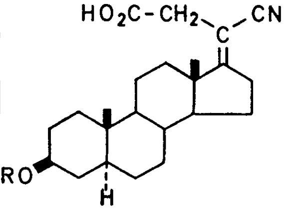
Summary Alkylation of the allenic acid fluoride (**1**) is a regiospecific reaction which depends on the nature of the alkylating agent; whereas treatment of (**1**) with lithium dimethylcopper affords the 20-vinylic methylated 22-keto-steroid (**3**), reaction with dimethylcadmium provides a mixture of isomeric allenyl methyl ketones (**5a**) and (**5b**).

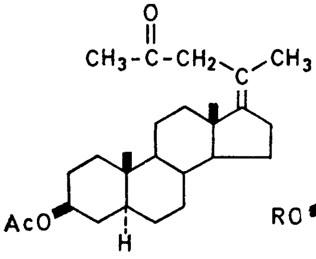
Few convenient methods for the preparation of allenic ketones are available.[1] We report a novel efficient synthesis of allenyl ketones from the readily accessible allenyl acid fluoride (**1**).[2]



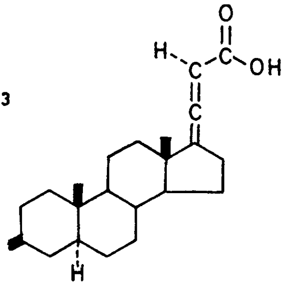
(1)



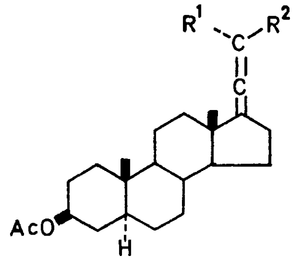
(2) a ; R = Ac
b ; R = H



(3)



(4) a ; R = Ac
b ; R = H



(5) a ; R¹ = Ac ; R² = H
b ; R¹ = H ; R² = Ac

Cyanide ion, like methoxide,[2] adds as in the Michael reaction to the central carbon atom of the allenyl moiety of (**1**). Thus, treatment of (**1**) with potassium cyanide in aqueous ethanol under reflux causes simultaneous alkylation at C-20 and hydrolysis of the acid fluoride, yielding the steroidal $\Delta^{17(20)}$-20-cyano-22-acids (**2a**) (55%) m.p. 196—197° $[\alpha]_D \pm 0°$, λ_{max} 223—224 nm (log ϵ 4·10), ν_{max} 2225, 1740, and 1725 cm^{-1}, δ 0·846 p.p.m. (18-H), *m/e* 413 (M^+)† and (**2b**) (30%) m.p. 228—229°, *m/e* 731 (M^+), separated by preparative t.l.c.

We investigated the behaviour of the allenyl acid fluoride moiety of (**1**) toward organometallic reagents, to determine if alkylation would occur as in the Michael reaction at C-20 or by substitution of the fluorine at C-22.

Treatment of (**1**) with 1·5 equiv. of lithium dimethylcopper in ether solution at 0° for 4 h leads to simultaneous alkylation at C-20 and C-22, providing the methyl ketone (**3**) (60% yield) m.p. 138°, $[\alpha]_D$ − 52°, ν_{max} 1730 and 1710 cm^{-1}, δ 0·83 (18H, 19-H), 1·6 (20-Me), 2·0 (3-OAc), 2·13 (22-Ac), 3·26 p.p.m. (21-CH_2), *m/e* 400 (M^+), together with a small amount (10%) of the 3-acetoxyallenic acid (**4a**) m.p. 179—180°, identified by base hydrolysis to the known 3-alcohol derivative (**4b**).[2] Similar results are obtained, in lower yields, when the reaction is performed with 0·5 equiv. of lithium dimethylcopper. Dimethylcadmium is found to be more selective than the dialkylcopper reagent. When the allenyl acid fluoride (**1**) is allowed to react with 1 equiv. of dimethylcadmium at reflux temperature in benzene solution for 0·5 h, a mixture of three substances is obtained. The major compound (51% yield) is the allenyl methyl ketone (**5a**) m.p. 127—130°, $[\alpha]_D$ − 19°, λ_{max} 232, 316—320 nm (log ϵ 4·27, 2·08), ν_{max} 1950, 1735, and 1680 cm^{-1}, δ 0·83 (19-H), 0·92 (18-H), 1·99 (22-Ac), 2·16 (3-OAc), 5·69 p.p.m. (t, *J* 4 Hz, 21-H), *m/e* 384 (M^+). It is accompanied by its geometric isomer (**5b**) (10%) m.p. 175—177°, $[\alpha]_D$ + 49°, λ_{max} 232, 316—320 nm (log ϵ 4·17, 2·06), ν_{max} 1940, 1735, and 1670 cm^{-1}, δ 0·83 (19-H), 0·98 (18-H), 1·99 (22-Ac), 2·15 (3-OAc), 5·71 p.p.m. (m, 21-H), *m/e* 384 (M^+). The last substance (3% yield) is identical with the C-20 methylated keto-derivative (**3**) (see above).

The stereospecificity during the alkylation reactions of (**1**) at C-20 is of interest, since in all experiments performed so far,[2] only one $\Delta^{17(20)}$-geometric isomer has been identified.

The configuration of the double bond indicated in (**2**) and (**3**) is supported by the 18-methyl signal in their n.m.r. spectrum.

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† The mass spectra were measured on an Atlas CH-4 mass spectrometer, equipped with an EFO-4B ion source. Satisfactory analyses have been obtained for all compounds described.

[1] Th. F. Rutledge, "Acetylenes and Allenes", Reinhold, New York, 1969.

[2] P. Crabbé, H. Carpio, and E. Velarde, *Chem. Comm.*, 1971, 1028.