New Synthesis of Steroidal Trihalogenomethylallenes, Allenic Acids, and β-Keto-esters

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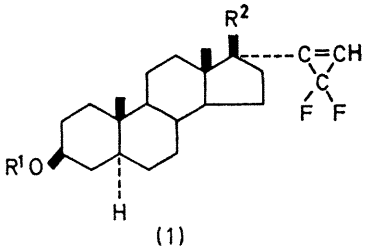
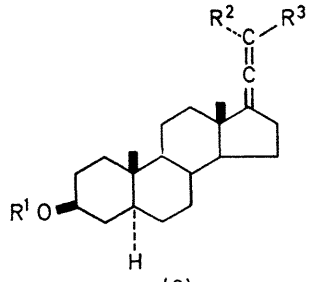
Summary Reaction of 2-chloro-1,1,2-trifluorotriethylamine with cyclopropenonyl- and difluorocyclopropenyl-methanols caused cleavage of a cyclopropane bond and formation of an allenic acid fluoride and a pair of trifluoromethylallenes, respectively.

TRIHALOGENOMETHYL allenes and α-allenic acids are not readily available.[1] We report a new method for the preparation of isomeric trifluoromethylallenes, as well as an efficient synthesis of allenic acids. A simple conversion of allenic esters into β-keto-esters is also described.



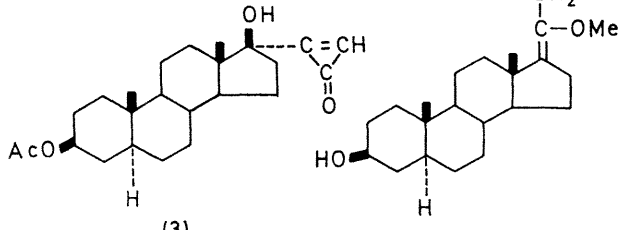
a; R^1 = Ac; R^2 = OH
b; R^1 = H; R^2 = OH
c; R^1 = Ac; R^2 = F

(1)

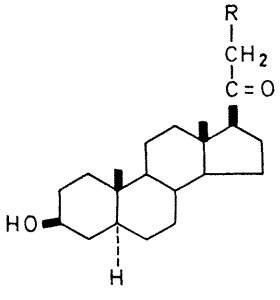


a; R^1 = Ac; R^2 = CF_3; R^3 = H
b; R^1 = Ac; R^2 = H; R^3 = CF_3
c; R^1 = Ac; R^2 = H; R^3 = COF
d; R^1 = R^2 = H; R^3 = CO_2Me
e; R^1 = R^2 = H; R^3 = CO_2H

(2)



(3) (4)

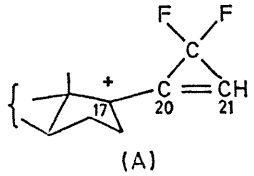


(5) a; R = CO_2Me
b; R = CO_2H
c; R = H

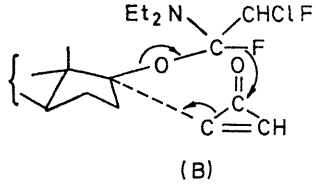
Reaction of 17α-difluorocyclopropenyl-5α-androstane-3β,17β-diol 3-acetate (1a) m.p. 165—166°, $[\alpha]_D$ − 21°,† readily obtained from (1b),[2] with 2-chloro-1,1,2-trifluorotriethylamine in dry methylene chloride[3] affords a mixture of three isomeric compounds. The first compound (6%) is the 17β-fluoro-steroid (1c) m.p. 172—174°, $[\alpha]_D$ + 14° m.s. *m/e* 410 (M^+), the formation of which could be expected from previous experience with this reagent.[3] The second compound (25%) is the trifluoromethylallene (2a) m.p. 128—129°, $[\alpha]_D$ + 7°, ν_{max} 1980 and 1740 cm^{-1}, n.m.r. 0·861 (18-H), 5·33 p.p.m. (m, 21-H). The third compound, isolated in 1% yield, is the isomeric allene (2b) m.p. 125—126°, $[\alpha]_D$ + 51°, ν_{max} 1980 and 1740 cm^{-1}, n.m.r. 0·925 (18-H), 5·44 p.p.m. (m, 21-H). The mass spectra of (2a) and (2b) exhibit a molecular ion at *m/e* 410, consistent with a trifluoro-steroid. Moreover, the strong i.r. band at 1980 cm^{-1} in both isomers confirms the presence of an allenic function. Finally, (2b) is identical with the compound obtained by treatment of 17α-trifluoropropynyl-5α-androstane-3β,17β-diol diacetate with zinc dust in diglyme.[4]

Formic acid hydrolysis of the difluoromethylene grouping of (1a) leads to the cyclopropenone-carbinol (3) (80% yield) m.p. 187—189°, $[\alpha]_D$ − 42°. Treatment of (3) with 2-chloro-1,1,2-trifluorotriethylamine in dry methylene chloride gives the allenic acid fluoride (2c) in 80% yield m.p. 175°, $[\alpha]_D$ − 36°, λ_{max} 226 nm (log ε 4·23), ν_{max} 1960, 1810, and 1730 cm^{-1}, n.m.r. 0·93 (18-H), 5·51 p.p.m. (t., *J* 4 Hz, 21-H).

Worth emphasizing is the fact that whereas the fluoramine reaction on (1a) gives the 17β-fluorosteroid (1c) and a modest yield of a mixture of isomeric allenes (2a) and (2b), in which the α-isomer (2a) predominates, treatment of (3) with the same reagent affords in high yield the sole product (2c), in which the configuration of the substituent at C-21 is opposite to that of (2a), as evidenced by the chemical shift of the 18-methyl protons.[4] These results seem to indicate that different reaction mechanisms are operative. Formation of the trifluoromethylallenes (2a) and (2b) can be formulated as arising from attack of fluoride ion on the cationic intermediate (A), either at C-17 to give (1c), or at



(A)



(B)

C-22 with concurrent fragmentation of the freely rotating cyclopropene ring, providing a mixture of isomeric allenes (2a) and (2b). The acid fluoride (2c) presumably results from attack of fluoride ion at the cyclopropenone carbonyl of (3), followed by ring fragmentation and concerted elimination of the 17-oxygen as represented schematically in (B).

† The mass spectra were measured on an Atlas CH-4 mass spectrometer, equipped with an EFO-4B ion source, the ionizing energy was maintained at 70 ev. Satisfactory analyses have been obtained for all compounds described.

When (2c) is allowed to react with sodium methoxide in methanol for 2 h at room temperature, it is converted into the methyl ester (2d) m.p. 89—90°, $[\alpha]_D$ − 81°, λ_{max} 222 nm (log ϵ 4·21). Further treatment of the allenic ester (2d) with sodium methoxide for 16 h affords compound (4) (95% yield), devoid of u.v. absorption above 220 nm, m.p. 117—118°, $[\alpha]_D$ + 24°, resulting from a Michael-type addition[5] of methoxide to the allenic ester group. The free allenic acid (2e) m.p. 144—145°, $[\alpha]_D$ − 29°, was obtained by hydrolysis of (2d) with sodium hydroxide in acetone solution (85% yield).

Hydrochloric acid hydrolysis of the 17,20-enol ether (4) provides the β-keto-ester (5a) in 97% yield m.p. 143—145°, $[\alpha]_D$ + 104°, thus making the above sequence a novel and efficient synthetic approach to β-keto-esters. Potassium carbonate hydrolysis of (5a) gives the corresponding free acid (5b) (60%), and treatment with 2% methanolic potassium hydroxide at reflux temperature cleaves the β-keto-ester grouping to yield 95% of 3β-hydroxy-5α-pregnan-20-one (5c), shown to be identical with an authentic sample.

Similar results obtained with 3α-difluorocyclopropenyl-steroids will be reported later.

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