New Approach to the Synthesis of α-Fluoro-oxo-steroids

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Summary The mixture of fluoroxy compounds formed when fluorine reacts with sodium trifluoroacetate, acts on steroidal enol acetates to give α-fluoroketones in good yields.

THE synthesis of α-fluoro-oxo-steroids has interested chemists for over 20 years. Although the reaction between the enamine of the oxo-steroid and perchloryl fluoride may be used,[1] the limitations of this reagent are well known. It tends to form chlorinated or oxygenated compounds and also it successfully fluorinates only particularly reactive nucleophiles[2] such as the relatively sensitive enamines, while the stable and easily prepared enol acetates usually do not react. Further, although the reagent itself is stable, explosions have been caused by the chloric acid which is a by-product.

Fluoroxytrifluoromethane, CF_3OF, may replace ClO_3F in reactions with electron-rich olefins,[3,4] but it is expensive and of limited availability, and we therefore sought a more readily available reagent. Elemental fluorine can accomplish sometimes surprisingly selective electrophilic fluorination of various steroids.[5] Hence, we first studied the reaction between fluorine and 5α-androst-3-ene-3,17β-diol diacetate (**4**), but it was impossible to isolate any α-fluoro-ketone from the resultant complicated mixture.

$$CF_3CF_2OF + \textit{trans}\text{-PhCH}{=}\text{CHPh} \rightarrow \underset{\textbf{(3)}}{\text{PhCHFCH(OCF}_2\text{CF}_3\text{Ph}\ (\text{DL-}\textit{threo})}$$

(1) **(2)**

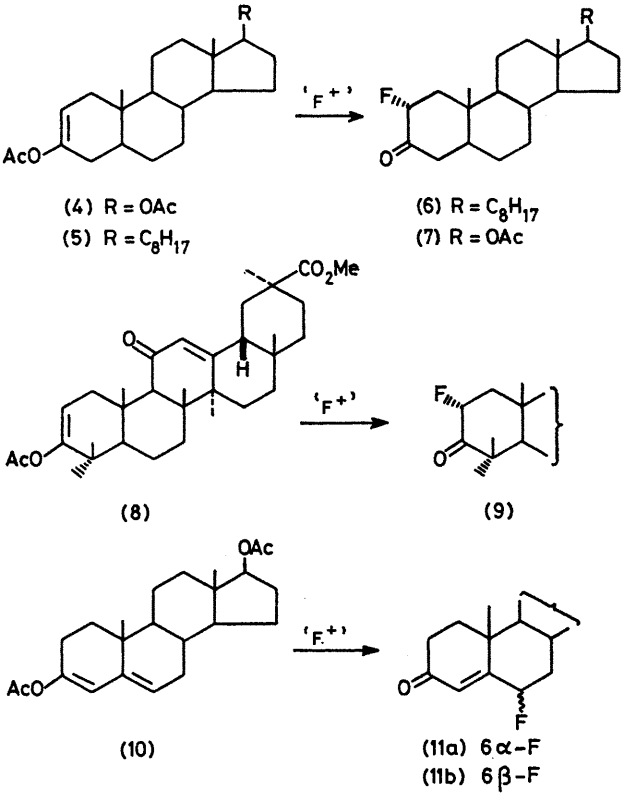
When fluorine was passed through a suspension of CF_3CO_2Na in Freon at −75 °C, an oxidative solution was obtained,† an important component of which is fluoroxypentafluoroethane (**1**).[6] We have shown the presence of (**1**) by reactions with olefins. Thus, DL-*threo*-α-fluoro-α′-pentafluoroethoxybibenzyl (**3**) (m.p. 87 °C)‡ resulted from the *cis* addition of CF_3CF_2OF to *trans*-stilbene (**2**).

A number of addition reactions of CF_3CF_2OF to olefins showed that (**1**) is responsible for no more than 50% of the oxidative power of such solutions. It was clear that other perfluoroxy compounds were also present.[6] All these compounds, like CF_3OF and (**1**), possess an electrophilic fluorine attached to an excellent leaving group of type R_fO^-.

† The oxidative power of the reaction mixture can be determined by titration of the iodine liberated from KI.

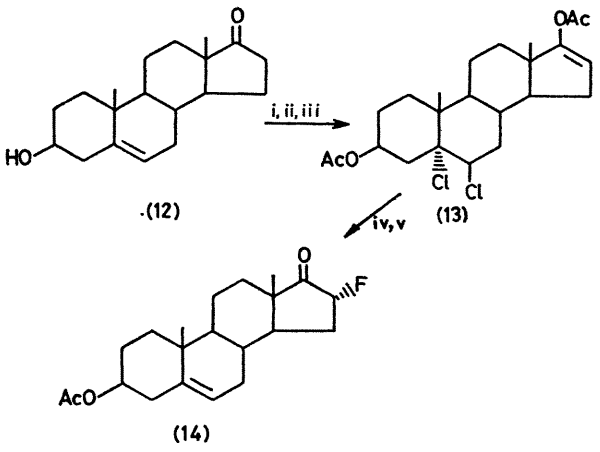
‡ A more detailed description of this reaction as well as its mechanism will appear elsewhere.

We thus studied the use of this oxidative solution, *in toto*, in reactions with activated olefins such as steroidal enol acetates. Thus, a cooled solution of cholestanone enol acetate (**5**) (0·5 mol equiv.) in a little methylene chloride was added at −75 °C to the above mentioned oxidative solution. After stirring for 1 min at this temperature, the mixture was poured on to thiosulphate solution and the organic layer worked up in the usual way. Purification by t.l.c. or h.p.l.c. gave 2α-fluorocholestanone (**6**) (45% yield; m.p. 172 °C;[7] ν_{max} 1730 cm^{-1}; δ ($CDCl_3$) 5·0 (1H, d,q-like, 2-H_{ax}, J_{FH} 48, J_1 12, and J_2 7 Hz).



Similarly, the reaction of (**4**) with the oxidative solution, in contrast to its reaction with elemental fluorine, gave (**7**) in 50% yield (m.p. 196 °C);[8] ν_{max} 1750 cm^{-1}, δ ($CDCl_3$) 4.96 (1H, d,q-like, 2-H_{ax}, J_{FH} 48, J_1 13, and J_2 7 Hz).

While the double bond in the steroids (**4**) and (**5**) is mainly localized between C(2) and C(3), this is wholly the case with the enol acetate of methyl 3-oxoglycyrrhetate (**8**), from which the 2α-fluoro-derivative (**9**) was obtained in 85% yield (m.p. 265 °C);[9] ν_{max} 1735(sh), 1725, and 1655 cm^{-1}; δ 5·71 (1H, s, 12-H) and 5·24 (1H, d,q-like, 2-H_{ax}, J_{FH} 48, J_1 6, and J_2 12 Hz); $[\alpha]_D^{25}$ −163·3° ($CHCl_3$, *c* 1·0).



i, Ac_2O–Pyridine; ii, Cl_2; iii, isopropenyl acetate; iv, 'F+'; v, Zn–AcOH–EtOH.

This method is also applicable to the preparation of the medicinally important 6- or 16-fluoro steroids. Reaction of the mixture of fluoroxy-compounds with the dienol acetate (**10**) gave a mixture of 6α- and 6β-fluorotestosterone acetate which was resolved by t.l.c. (**11a**): m.p. 175 °C, yield 27%;[10] ν_{max} 1745 and 1695 cm^{-1}; δ 6·1 (1H, br. s, 4-H), 5·1 (1H, dm, 6-H_{ax}, J_{FH} 48 Hz), 1·19 (3H, s, 19-H_3) and 0·84 (3H, s, 18-H_3); (**11b**): m.p. 114 °C, yield 43%;[10] ν_{max} 1740 and 1690 cm^{-1}; δ 5·9 (1H, d, 4-H, *J* 4·5 Hz), 5·03 (1H, dm, 6-H_{eq}, J_{FH} 48 Hz), 1·3 (3H, d, 19-H_3), *J* 1·7 Hz), and 0·85 (3H, s, 18-H_3). 3β-Hydroxyandrost-5-en-17-one (**12**) was also studied. It was acetylated, the double bond was protected by chlorination, and the corresponding enol acetate (**13**) was obtained. This product was treated with the oxidative solution and after dechlorination the 16α-fluoroketone (**14**) (m.p. 205 °C)[11] was obtained in 85% yield based on (**13**), ν_{max} 1760 and 1725 cm^{-1}; δ 5·0 (1H, dm, 16β-H, J_{HF} 48 Hz), 1·05 (3H, s, 19-H_3), and 0·92 (3H, s, 18-H_3).

Formally, this reaction is effectively a fluorination of activated olefins with elemental fluorine. This represents a major advantage over the previously used reagents.§

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§ **I.r., n.m.r.** (^1H and ^{19}F), and mass spectra were in all cases consistent with the assigned structures.

[1] C. Djerassi and J. W. Chamberline, 'Steroid Reactions,' Holden Day, San Francisco, 1963, p. 155.
[2] See for instance: Y. Osawa and N. Neeman, *J. Org. Chem.*, 1967, **32**, 3055; W. A. Sheppard, *Tetrahedron Letters*, 1969, 83.
[3] D. H. R. Barton, L. S. Godhino, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804.
[4] For an excellent review of the chemistry of CF_3OF see R. H. Hesse, *Israel J. Chem.*, 1978, **17**, 60.
[5] D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and S. Rozen, *J. Amer. Chem. Soc.*, 1976, **98**, 3036.
[6] CF_3CF_2OF, along with some other fluoroxy compounds, was synthesized over 10 years ago (J. H. Prager and P. G. Thompson, *J. Amer. Chem. Soc.*, 1965, **87**, 230; P. G. Thompson and J. H. Prager, *ibid.*, 1967, **89**, 2263). However, because of the difficulties of its original synthesis, the tedious procedure and the low yields in which it had been made, it has never previously been employed in organic synthesis.
[7] S. Nakanishi, K. Morita, and E. V. Jensen, *J. Amer. Chem. Soc.*, 1959, **81**, 5259.
[8] This compound had also been synthesized by one of the authors (S.R.) during his work with D. H. R. Barton, R. H. Hesse, and M. M. Pechet in the Research Institute for Medicine and Chemistry, Cambridge, Mass. He is very grateful for the opportunity to work in their laboratories. See also ref. 7.
[9] S. Rozen, I. Shahak, and E. D. Bergmann, *J. Org. Chem.*, 1975, **40**, 2966.
[10] C. Chavis and M. Mousseron-Canet, *Bull. Soc. chim. France*, 1971, 632.
[11] S. Nakanishi and E. V. Jensen, *J. Org. Chem.*, 1962, **27**, 702.