Organic Reactions of Fluoroxy-compounds: Electrophilic Fluorination of Activated Olefins

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ALTHOUGH reactions of fluoroxy-compounds[1] with organic substrates[2] have been reported, their use as organic reagents has been neglected. We now report that alkylfluoroxy-compounds with certain olefinic linkages react smoothly and selectively to afford products bearing fluorine linked to the carbon constituting the more nucleophilic terminus of the olefinic substrate. The reaction† is applicable to complex, sensitive substrates and proceeds without complication even in the presence of a variety of functional groups. Thus keto-, alkoxy-, and acyloxy-groups all survive our reaction conditions. Hydroxyl and N-H groups may be acylated to a small extent by the traces of carbonyl difluoride present. This esterification is avoided by the addition of methanol to the mixture or by subsequent hydrolysis (aqueous sodium carbonate) during work up.

The vinyl ester (Ia) consumed one equivalent of fluoroxytrifluoromethane[3] (CF_3OF) to afford 2α-fluorocholestanone together with two by-products, m.p. 108—110°, $[\alpha]_D$ + 26° (all $[\alpha]_D$ in $CHCl_3$) and m.p. 114—115°, $[\alpha]_D$ + 6°, having the composition of adducts of the vinyl acetate (Ia) with CF_3OF and with F_2 respectively. Mild hydrolysis of either adduct afforded 2α-fluorocholestanone establishing expressions (IIa) and (IIb) respectively, for the adducts. The α-orientation of the fluorine at C-2 in these compounds (indicated by n.m.r. spectra) was confirmed by the lithium aluminium hydride reduction of each to a mixture of 2α-fluoro-5α-cholestane 3β-ol and its 3α-epimer. The same mixture of epimers was obtained from 2α-fluorocholestanone, whilst 2β-fluorocholestanone gave a different pair of fluorohydrins. Each of the four epimers gave back the appropriate fluoro-ketone on chromic acid oxidation. Although the stereochemistry of these adducts at C-3 is at present uncertain, we favour the α-orientation for the fluorinated group. The difluoro-adduct (IIb) showed ($J_{F_2F_3}$ 14 c./sec.) typical of an equatorial–axial arrangement and ($J_{F_3H_2}$ 22 c./sec.) typical of a diaxial arrangement.

The reaction of the vinyl ester (Ia) with 2-fluoroxyperfluoropropane[1] was analogous to that with CF_3OF, the major products being 2α-fluorocholestanone and an adduct (IIc) (the constitution of which was established as above), m.p. 114—115°, $[\alpha]_D$ + 22°. The difluoro-adduct (IIb) was not evident in the mixture.

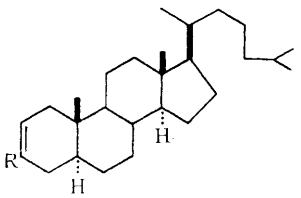
Fluoroxytrifluoromethane (CF_3OF) reacted cleanly with the vinyl ether (Ib) and the enamine (Ic) to afford in each case 2α-fluorocholestanone. The former substrate also afforded an unstable, non-ketonic product, which decomposed readily to 2α-fluorocholestanone. Although the extreme lability of this substance precluded definitive characterization, it is clearly an adduct of the general formula (II). Although there was no evidence of a similar adduct in the reaction of the enamine (Ic), such an adduct, if formed from (Ic), would be expected to undergo rapid conversion to 2α-fluorocholestanone. The ready reversion of the adducts (II) to 2α-fluorocholestanone made it possible that the initial product of the reaction of CF_3OF with (Ia) might be such an adduct. This was, however, not correct because the relative proportion of fluoro-ketone to "adduct" remained constant during the reaction and was not noticeably affected by prolonged storage. Furthermore, the adducts (IIa) and (IIb), when submitted to the reaction conditions, were recovered unchanged.

The dienol ether (IIIa) when treated with a molecular proportion of CF_3OF, afforded 4-fluorotestosterone acetate and a mixture of 6α- and 6β-fluorotestosterone acetate. The dienol acetate (IIIb) on the other hand, when treated with a slight excess of CF_3OF, reacted cleanly to give a mixture of 6α- and 6β-fluorotestosterone acetate together with the "fluorine adduct" (IV), m.p. 173—177°, which afforded 6β-fluorotestosterone on hydrolysis. The enamine (IIIc) on reaction with a slight excess of CF_3OF gave largely 4-fluorotestosterone acetate.

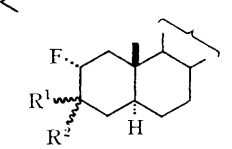
The utility of CF_3OF (and of fluoroxy-compounds in general) in the fluorination of reactive

† All reactions were carried out at −75° unless otherwise noted. The solvent of choice has been $CFCl_3$. The addition of CCl_4, $CHCl_3$, or CH_2Cl_2 to improve the solubility of the substrate has produced no complication. Although we have successfully conducted reactions with CF_3OF in acetone, ether, methanol and tetrahydrofuran, we urge caution in the use of these solvents. Acid-sensitive substrates have been protected by the inclusion of CaO, MgO, or NaF. Use of pyridine for this purpose led to the formation of a *highly explosive by-product* and is therefore discouraged.

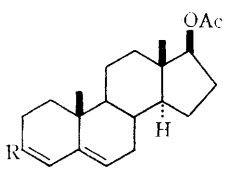
olefins is indicated by the yields, recorded in the Table. Our preliminary studies show that CF_3OF is efficiently consumed by olefins even in the presence of a large excess of compounds which react with radicals (*e.g.* oxygen, diethyl ether,



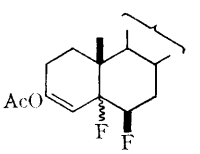
(Ia) R=OAc
(Ib) R=OMe
(Ic) R=N



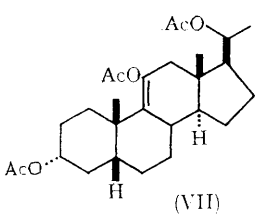
(IIa) R^1=OCF$_3$, R^2=OAc
(IIb) R^1=α-F, R^2=β-OAc
(IIc) R^1=OCF(CF$_3$)$_2$, R^2=OAc



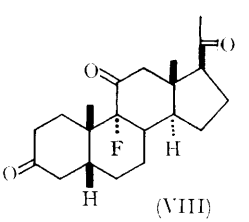
(IIIa) R=OMe
(IIIb) R=OAc
(IIIc) R=N



(IV)

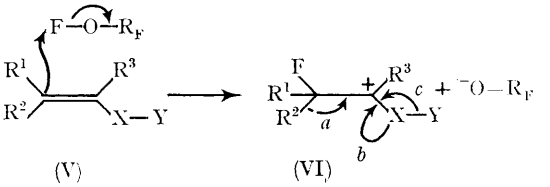


(VII)



(VIII)

acetone, tetrahydrofuran, toluene, *etc.*). This precludes any sequence demanding homolytic scission of the O-F bond prior to attack on the ethylenic linkage. Free-radical involvement at a subsequent stage of the reaction appears unlikely, as neither the number, nature, nor proportion of the products formed in the reaction of (Ia) with CF_3OF were affected by the presence of radical "scavengers" (see above). These data and the nature of the mixtures obtained are most economically accommodated by nucleophilic attack of the π electrons of the olefin (V) upon the fluorine to afford a cationic intermediate (VI). Although the cation (VI) is probably not stabilized by fluorine bridging,[4] it would certainly be intimately associated with an anion.[5] Electron transfer in the sense of *a*, *b*, and *c* must determine the ultimate fate of (VI). If the substrate is an "activated" olefin (X, a liberal donor of electrons), the intermediate (VI) would be stabilized by electron donation in the sense *b*. It would be expected to capture a nucleophile to give an adduct or suffer fragmentation (or hydrolysis) to afford a fluoroketone. This accords well with the results described above. If, on the other hand, X is a



(V) (VI)

poor donor of electrons (carbon, for instance), fragmentation (or rearrangement) in the sense *a* or *c* would be expected to prevail. The resulting product could then contain an ethylenic linkage susceptible to further attack by CF_3OF.

The formation of difluoro-adducts in the reactions of CF_3OF may be explained by the equilibrium[6] $CF_3O^- \rightleftharpoons COF_2 + F^-$. Alternately, CF_3O^- may itself be an ambifunctional nucleophile. An alternate explanation involving the decomposition[7] of CF_3OF to COF_2 and molecular fluorine is not acceptable since, in our hands, fluorine[8] reacts under our experimental conditions† with the substrates studied inefficiently and rather indiscriminately.

It is appropriate to compare the fluoroxy-reagents with perchloryl fluoride as there is a striking similarity in their reactions with *highly nucleophilic* olefins, such as (Ib) and (Ic), and (IIIa) and (IIIb). The location of fluorine in the product is the same[9] and the resulting stereochemistry is similar. Differences are apparent when less reactive substrates are considered. Simple vinyl acetates are reported to react very sluggishly with $FClO_3$ to yield mixtures of fluorinated and *chlorinated* products.[10] Such substrates react avidly with fluoroxy-compounds to afford *fluorinated* products (see above). Although unactivated olefins and deactivated olefins (such as αβ-unsaturated ketones) do not normally react with $FClO_3$, they react with CF_3OF under mild conditions.

A profitable exploitation of the great reactivity of fluoroxy-compounds lies in the conversion of (Ia) to 2α-fluorocholestanone. A more striking

example is provided by the conversion of the hindered and unreactive[11] vinyl acetate (VII) to the important fluoro-ketone (VIII) in good yield.

TABLE

Substrate	Product	Yield[a]
(IIa)	2α-Fluorocholestanone	60%
(IIb)	2α-Fluorocholestanone	70%
(IIc)	2α-Fluorocholestanone	45%[b]
(IIIb)	6α- and 6β-Fluorotestosterone acetate	74%[c]
(IIIb)	6α-Fluorotestosterone acetate	50%[d]
(IIIc)	4-Fluorotestosterone acetate	35%

[a] Although all mixtures were processed hydrolytically to convert adducts into the corresponding fluoroketones, no other attempts were made to maximize yields. The yields reported should therefore be considered as minimal. Unless otherwise indicated, the yields refer to isolated products with appropriate physical constants.

[b] The major by-product was cholestanone arising from the spontaneous hydrolysis of starting material.

[c] Estimated by v.p.c.; major by-product, testosterone acetate (16%).

[d] After hydrolysis with NaOH, equilibration with HCl, and re-acetylation.

The marked and selective reactivity of fluoroxy-compounds towards olefinic linkages is most closely approximated in reactions of the halogens, Br_2 or Cl_2. This analogy is strengthened by the apparent cationic nature of the reaction intermediates.

It is therefore possible to consider fluoroxy-compounds as "pseudohalogen" derivatives of fluorine. If this analogy is apt, the applications of fluoroxy-compounds to organic synthesis are numerous, particularly since these substances appear to combine the tractability of the rather unreactive perchloryl fluoride with the reactivity of elemental fluorine.

All new compounds had the correct analytical values. Infrared, n.m.r. (Drs. L. Phillips and P. G. Sammes and Mr. M. D. Yudis) and mass (Dr. E. S. Waight and Mr. P. Boshoff) spectra were in each case consistent with the assigned structures.

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[1] We use the nomenclature introduced by J. H. Prager and P. G. Thompson, *J. Amer. Chem. Soc.*, 1965, **87**, 230.

[2] (a) J. A. C. Allison and G. H. Cady, *J. Amer. Chem. Soc.*, 1959, **81**, 1089; (b) R. S. Porter and G. H. Cady, *J. Amer. Chem. Soc.*, 1957, **79**, 5625; (c) S. M. Williamson and G. H. Cady, *Inorg. Chem.*, 1962, **1**, 673; (d) P. D. Schuman, E. C. Stump, G. Westmoreland, and W. S. Durrell, presented at 152nd National Meeting of the American Chemical Society, New York, September, 1966, Abstract K25.

[3] K. G. Kellogg and G. H. Cady, *J. Amer. Chem. Soc.*, 1948, **70**, 3986.

[4] G. A. Olah, C. A. Cupas, and M. B. Comisarow, *J. Amer. Chem. Soc.*, 1966, **88**, 362; P. E. Peterson and R. J. Bopp, *J. Amer. Chem. Soc.*, 1967, **89**, 1283; G. A. Olah and J. M. Bollinger, *J. Amer. Chem. Soc.*, 1967, **89**, 4744.

[5] R. F. Merritt, *J. Amer. Chem. Soc.*, 1967, **89**, 609, and *J. Org. Chem.*, 1966, **31**, 3871.

[6] M. E. Redwood and C. J. Willis, *Canad. J. Chem.*, 1965, **43**, 1893; C. T. Ratcliffe and J. M. Shrieve, *Chem. Comm.*, 1966, 674; F. Seel, R. Budenz, and W. Gambler, *Angew. Chem. Internat. Edn.*, 1967, **6**, 256.

[7] R. S. Porter and G. H. Cady, *J. Amer. Chem. Soc.*, 1957, **79**, 5628.

[8] R. F. Merritt and T. E. Stevens, *J. Amer. Chem. Soc.*, 1966, **88**, 1822; R. F. Merritt, *J. Org. Chem.*, 1966, **31**, 3871; R. F. Merritt, *J. Amer. Chem. Soc.*, 1967, **89**, 609.

[9] S. Nakanishi, K. Marita, and E. V. Jensen, *J. Amer. Chem. Soc.*, 1959, **81**, 5259; B. M. Bloom, U. V. Bogert, and R. Pinson, *Chem. and Ind.*, 1959, 1317; R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, 1958, **23**, 1406; see also J. W. Chamberlin in "Steroid Reactions, an Outline for Organic Chemists", ed. Carl Djerassi, Holden-Day, San Francisco, 1963, pp. 164—167.

[10] S. Nakanishi and E. V. Jensen, *J. Org. Chem.*, 1962, **27**, 702; see also Y. Osawa and M. Neeman, *J. Org. Chem.*, 1967, **32**, 3055.

[11] Netherlands Patent 6,510,255 (*cf. Chem. Abs.*, 1966, **65**, 776c).