Generalised Electrophilic Fluorination by Fluoroxy-compounds

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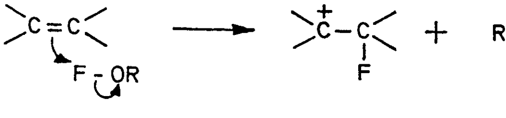
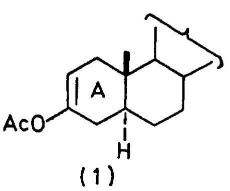
Summary Several different types of fluoroxy-compounds have been shown to behave in solution as electrophilic fluorinating agents; of the reagents studied bis(fluoroxy)-difluoromethane shows promise on the grounds of economy and efficiency.

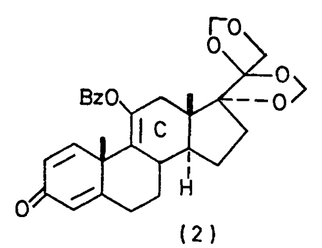
IN our initial publications[1] on the use of fluoroxytrifluoromethane ($CF_3{\cdot}OF$) as an electrophilic fluorinating agent we hypothesized that fluoroxy-compounds as a class might be disposed to undergo *nucleophilic attack at fluorine* in the sense of Scheme 1. If so, these compounds would comprise a large class of useful fluorinating agents. This contention was reinforced by our observation that 2-fluoroxyperfluoropropane reacted with 3-acetoxy-5α-cholest-2-ene (**1**) in a manner analogous to that observed for $CF_3{\cdot}OF$.[1] We now report further evidence which substantiates our initial hypothesis.



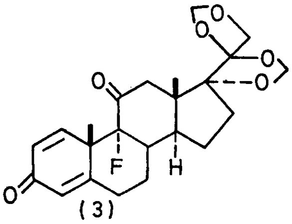
SCHEME 1



(1)



(2)



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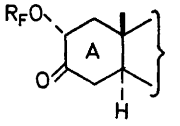
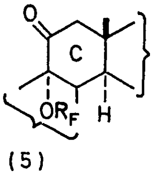


(4)

(R_F=perfluoroalkyl or SF_5)



(5)

(R_F=perfluoroalkyl or SF_5)

The fluoroxy-reagents we have chosen to study are those which might be expected to react by a mechanism different from that we have observed for $CF_3{\cdot}OF$ and/or which might be expected to possess certain advantages compared with $CF_3{\cdot}OF$. Thus the observation that 2-fluoroxy-2-trifluoromethylperfluoropropane undergoes a one-electron reduction on reaction with iodide ion, in contrast to the two-electron reduction which characterizes a variety of secondary and primary fluoroxy-compounds,[2] suggested that perhaps tertiary fluoroxy-compounds might be disposed to free radical reactions. Similarly, fluoroxy-sulphur pentafluoride $SF_5{\cdot}OF$[3]) has been suggested by Williamson to add to olefins in the absence of diluent *via* a free-radical mechanism,[4] Finally, bis(fluoroxy)difluoromethane [$CF_2(OF)_2$, easily available through fluorination of CO_2 in the presence of CsF[5]] was of interest both by virtue of the unusual nature of the geminal fluoroxy-groups and because each of the 'electrophilic' fluorines is, in principle, available for use.

TABLE 1

Fluoroxy-reagent	Mol. equiv.	Product	Yield[a] (%)
$(CF_3)_3C{-}OF^b$	2^d	2α-Fluorocholestanone[e]	40
$(CF_3)_2(C_2F_5)C{-}OF^c$	4	2α-Fluorocholestanone[f,g]	45
$SF_5{\cdot}OF$	1	2α-Fluorocholestanone	60
$CF_2(OF)_2$	0·5	2α-Fluorocholestanone[e]	65
$CF_3{\cdot}OF$	1	2α-Fluorocholestanone	62

[a] No attempt was made to optimize the yields by hydrolysis of intermediate addition products. Yields refer to isolated, crystallised product. [b] Prepared by fluorination of $(CF_3)_3C{-}OK$ at 78°. [c] Prepared by fluorination of $(CF_3)_2(C_2F_5)C{-}OCs$ at −78°. [d] Fluoroxy-reagent not all consumed. [e] Addition product observed but not fully characterized. [f] Addition product observed and fully characterized. [g] Considerable starting material remained ('stoicheiometry' of this reaction highly variable).

The reactions of the vinyl acetate (**1**) with representative tertiary fluoroxy-reagents, with SF_5OF and with $CF_2(OF)_2$, are summarized in Table 1, and a comparison of these reagents with $CF_3{\cdot}OF$, illustrated by the conversion of the enol benzoate[6] (**2**) into the important fluoro-steroid (**3**), is summarized in Table 2. The conditions for the reactions summarized in Table 1 and 2 are as described earlier[1] [freon ($CFCl_3$)–CH_2Cl_2 as solvent].

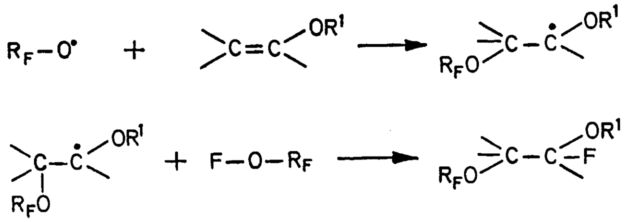
It is apparent from these data that the major transformation of the substrates in each case results from polar 'electrophilic' fluorination rather than free-radical addition or substitution. It is also apparent that both fluoroxy-groups of $CF_2(OF)_2$ are available for electrophilic fluorination. It has been suggested in authenticated free-radical

TABLE 2

Fluoroxy-reagent	Mol. equiv.	Yield[a] of (**3**) (%)
$(CF_3)_2(C_2F_5)C–OF$	Large excess	Traces
$CF_3·OF$	1	52
$SF_5·OF$	1	49
$CF_2(OF)_2$	0·5	51

[a] The crude fluorination mixture was subjected to an alkaline hydrolytic work-up.

reactions of fluoroxy-compounds that the chain carrying species is the perfluoro-alkoxy (sulphuroxyl) radical rather than fluorine atoms.[4,7] The free-radical reaction of fluoroxy-compounds with vinyl esters would, therefore, be expressed by Scheme 2 (*cf.* with ref. 4 or reactions of CF_3I[8])

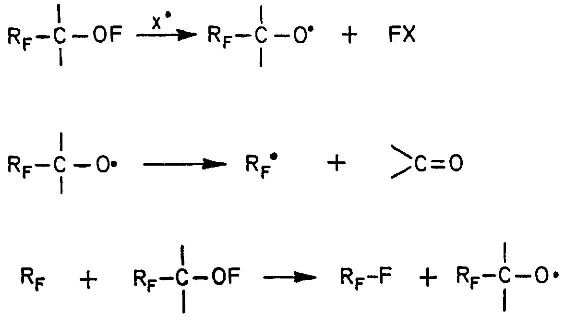


(R_F = perfluoro)

SCHEME 2

and would be expected to lead, in the case of substrates (**1**) and (**2**), to α-perfluoro-alkoxy (sulphuroxyl) ketones such as (**4**) or (**5**). This prediction is clearly of variance with the observations summarized in Table 1 and 2. It is probable, however, that the tertiary fluoroxy-reagents are susceptible to homolysis. Thus the inefficient and erratic conversion of substrates (**1**) and (**2**) into fluoro-ketones by $(CF_3)_2(C_2F_5)$-C–OF is presumably a consequence of a radical initiated homolytic self decomposition of the fluoroxy-reagent (Scheme 3). Such a decomposition would be expected of all fluoroxy-compounds bearing carbon–carbon bonds,[2] but *need not involve the* substrate.

We attribute the variation of our results (polar fluorination) from those reported by Williamson[4] (radical addition of R–O) to two factors which apparently serve to change the reaction mechanism by which the fluoroxy-reagent attacks the carbon–carbon double bond; the nature of the substrates and the effect of solvent. As most of those olefins studied by Williamson[4] were highly substituted with electron withdrawing groups, one would have expected the relative rate of *electrophilic* fluorination to be retarded with respect to free-radical addition. The effect of carrying out the reaction in the presence of a solvent is undoubtedly two-fold: first, simple dilution which reduces the rate of chain propagating and transfer reactions with respect to termination reactions, and second, the tendency of the solvent itself to intercept chain-carrying intermediates in transfer and termination reactions which do not involve the substrate.



(X = radical)

SCHEME 3

We conclude that under appropriate conditions (reactions conducted at low temp. in the presence of solvent and in the absence of free radical initiators) the attribute of electrophilic fluorination (Scheme 1) is characteristic of fluoroxy-compounds in general. This leads to the attractive possibility that, confronted with a particular substrate, one might choose a specific fluoroxy-reagent on the basis of its advantageous attributes. The differences among fluoroxy-reagents will be discussed and the reactions of a number with various substrates will be described later. It is clear, however, that bis(fluoroxy)difluoromethane is a potentially cheap and economic reagent and in these aspects superior to fluoroxytrifluoromethane.

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