NEW METHODS OF SPECIFIC FLUORINATION

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ABSTRACT

The application of hypofluorites (fluoroxy-compounds), especially tri-fluoromethyl hypofluorite, in the synthesis of fluorinated steroids is described. Hypofluorites are powerful but selective fluorinating agents with unusual electrophilic character. They should find considerable application not only in the synthesis of fluorinated steroids, but for preparation of fluorinated compounds of many different types.

INTRODUCTION

During the last thirty years organic fluorine compounds have become of considerable economic importance. The initial impetus in this field of Chemistry came during the last War when the 'Manhatten project' de-manded the fractionation of the isotopes of uranium hexafluoride. A whole series of perfluoro-organic compounds was synthesized to provide com-pounds resistant to uranium hexafluoride vapour. In consequence methods of catalytic perfluorination have become well developed and hosts of per-fluoro-organic compounds are known in the aliphatic, alicyclic and aromatic series.

A more recent development is the realizaton that organic molecules may have their biological properties profoundly changed when an atom of hydrogen is replaced by one of fluorine. For example, the innocent and biologically essential acetic acid is converted into an insidious and powerful poison when one hydrogen of the methyl group is replaced by fluorine as in monofluoro-acetic acid. Not all changes of this kind are similar. Indeed, in medicinal chemistry, important and beneficial drugs have been synthesized by the specific replacement of hydrogen by fluorine. Particularly striking is the situation with corticosteroid drugs. The most active and useful cortico-steroids used at present in therapy have the 9α-hydrogen and, sometimes, the 6α-hydrogen replaced by fluorine. Typical part structures are shown in formulae (I) and (II).

SPECIFIC FLUORINATION OF ORGANIC COMPOUNDS

Theoretical considerations suggest that there should be three difference modes of fluorination of organic molecules depending upon whether fluorine atoms, fluorine anions, or fluorine cations are involved. Fluorination by fluorine atoms is the way in which perfluoro-compounds are prepared. In general, fluorine atoms are too reactive to effect the specific fluorination of an organic substrate though by working at low temperature it is possible
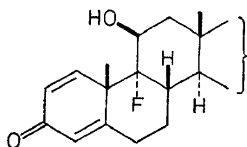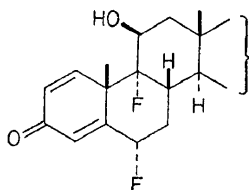
(I)   (II)

in certain cases to carry out addition reactions of fluorine to olefinic linkages.

The formation of most carbon–fluorine bonds in a specific manner has hitherto been carried out by the addition of negative (anionic) fluorine anions to carbon bearing partial or integral positive charge. Thus the enhanced biological activity of 9α-fluoro-steroids [see (I)] was discovered by J. Fried when he reacted the corresponding β-epoxide (III) with hydrogen fluoride. *Trans* diaxial opening of this epoxide to give the fluorohydrin system (I) involves the protonation of the epoxide and the incipient opening of the epoxide ring to generate positive charge at C-9. At the same time the anion of hydrofluoric acid (F$^-$ or, more correctly, HF$_2^-$) reacts at C-9 to form the desired carbon–fluorine bond. Most methods of 6-fluorination of steroids also involve similar considerations.

Other examples of reagents where the carbon–fluorine bond is formed by addition of fluoride anion or its equivalent are the decomposition of diazonium fluoroborates, the reactions of sulphur tetrafluoride and the use of Et$_2$N—CF$_2$—CFClH.

Hitherto only one reagent has been known where the carbon–fluorine bond is formed from the attack of a nucleophilic centre upon positively polarized fluorine (equivalent of F$^-$). This is the compound perchloryl fluoride (ClO$_3$F). Perchloryl fluoride, which has the structure

$$O=\overset{\displaystyle \overset{O}{\|}}{\underset{\displaystyle \underset{O}{\|}}{Cl}}—F$$
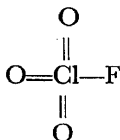
reacts readily with the anions of weak acids to give fluoro-derivatives. Thus β-dicarbonyl systems are fluorinated at the central carbon atom and phenols are fluorinated *ortho* and *para*, as expected for an electrophilic fluorinating reagent. Double bonds which are electron rich, for example vinyl ethers and enamines, are fluorinated at the β-carbon atom to give, after working up, the corresponding α-fluoroketones. Perchloryl fluoride is a valuable reagent but suffers from the disadvantages that it reacts only with strongly nucleophilic centres and that the by-product of its reaction, chloric acid, is dangerously explosive in admixture with organic compounds. A number of unfortunate explosions have occurred when using perchloryl fluoride.

We have recently discovered[1–3] a new family of electrophilic fluorinating reagents which are more powerful than perchloryl fluoride but also far more tractable. In addition, they do not cause explosions provided that organic

bases are not used as solvents or co-solvents. This family of reagents can be represented by the expression R_F—O—F where R_F is a fully fluorinated carbon radical. They can be described as hypofluorites or as fluoroxy-compounds. The simplest member of the series is trifluoromethyl hypo-fluorite (CF_3OF) which is available commercially. For this reason most of our work has been carried out with this compound, but we have in no way neglected more complicated hypofluorites.
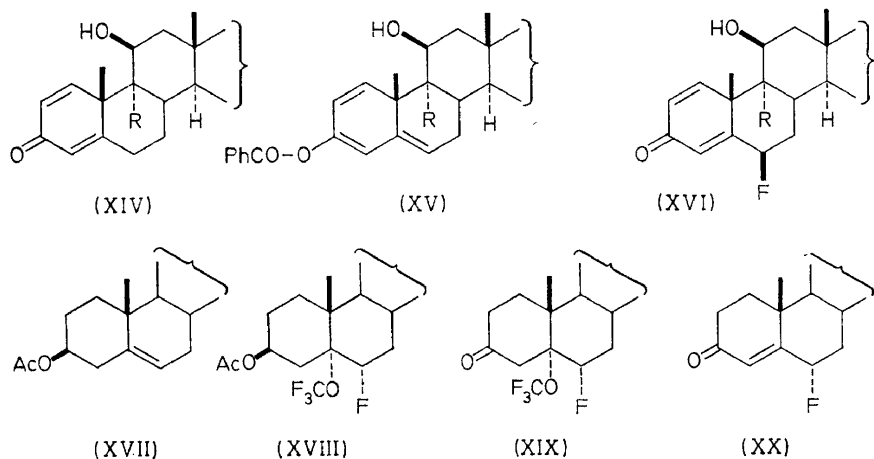
Trifluoromethyl hypofluorite reacts with electron-rich olefins like 3-methoxycholest-2-ene (III) and 3-pyrrolidylcholest-2-ene (IV) in the same way as perchloryl fluoride to furnish 2α-fluorocholestanone (V) in good yield. Reaction with 3-acetoxycholest-2-ene (VI) followed by mild alkaline hydrolysis of the product also gave a high yield of 2α-fluorocholestanone (V). A more detailed study of this reaction showed that the initial products of reaction were the fluoro-ketone (V) and two by-products: $2\alpha,3\alpha$-difluoro-


(III)   (IV)   (V)   (VI)

(VII)   (VIII)   (IX)   (X)
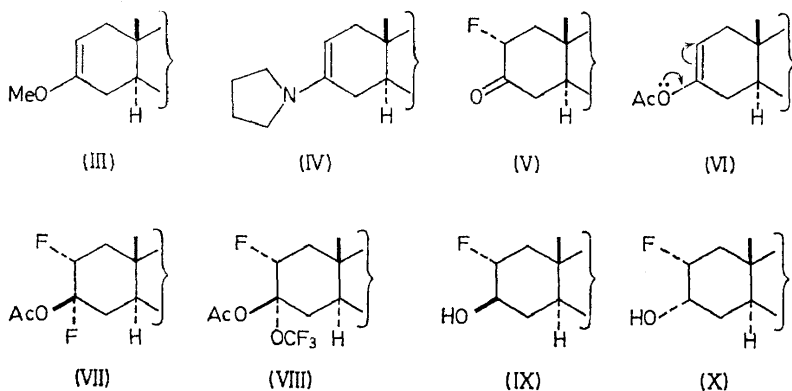
cholestanol acetate (VII) and $2\alpha,3(?)\alpha$-trifluoromethoxycholestanol acetate (VIII). Both of these compounds gave 2α-fluorocholestanone (V) on mild alkaline hydrolysis. More detailed evidence for their structures is as follows. Reduction of 2α-fluorocholestanone, the difluoride (VII) and the adduct (VIII) with lithium aluminium hydride afforded in each case a mixture of 2α-fluorocholestan-3β-ol (IX) and 2α-fluorocholestan-3α-ol (X). Since lithium aluminium hydride cannot cause inversion of configuration during reduction this proves that both the difluoride (VII) and the adduct (VIII) have the 2α-fluoro-configuration. The n.m.r. spectrum of the difluoride (VII) showed diaxial hydrogen (2β)-fluorine (3α) coupling as well as equatorial fluorine (2α)-axial fluorine (3α) coupling. The configuration of the difluoride (VII) is thus established. The configuration of the adduct (VIII) at C-3 is less certain, but is strongly implied by later work on the addition reactions of trifluoromethyl hypofluorite.

The 2α-fluoro-ketone (V) is not formed by decomposition of the difluoride (VII) or of the adduct (VIII) since these compounds are stable under the reaction conditions. Also the proportions of the fluoro-ketone (V), the difluoride (VII) and the adduct (VIII) are independent of the percentage reaction of the enol-acetate (VI) or of the duration of the reaction.

The reaction of trifluoromethyl hypofluorite with the enol-acetate (VI) proceeds smoothly in the presence of oxygen and in solvents such as diethyl ether, acetone, tetrahydrofuran and toluene which normally react readily with radicals. We consider that this evidence excludes a free radical homolytic mechanism. A polarization of the reagent in the sense CF_3—O—F when combined with normal polarization of the enol acetate (VI) (see arrows) predicts the position of fluorination in this and all other compounds studied. The derived oxonium ion from the enol-acetate (VI), as shown in (XI), can then suffer three different fates. Attack of anion upon the acyl-carbonyl, as in the chlorination or bromination of enol-acetates, affords the 2α-fluoro-ketone (V). Additon of OCF_3^- anion gives the adduct (VIII).

(XI)   (XII)   (XIII)

Decomposition of this anion to COF_2 and F^- followed by addition of the latter then affords the difluoride (VII). The mechanism thus explains all the observed facts.

Some potentially useful applications of trifluoromethyl hypofluorite can now be given. The enol-acetate (XII), which is readily available from the 'bile acid' route to corticosteroids, reacts smoothly with the reagent to furnish, after mild alkaline hydrolysis and chromic acid oxidation, the fluoro-ketone (XIII) from which, in principle, 9α-fluoro-corticoids [as (I)] will be easily prepared.

Similarly, the dienone system of corticoids of part structure (XIV, R = H or F) is easily converted into the trienol benzoate system (XV, R = H or F). Reaction of compounds of the latter type with trifluoromethyl hypofluorite gives in good yield 6β-fluoroketones (XVI, R = H or F). Epimerization at the six position then provides, in principle, a very convenient route to 6α-fluoro-corticoids.

We must now consider the reactions of trifluoromethyl hypofluorite with unactivated ethylenic linkages. In general, ordinary ethylenic linkages react rapidly but give complex mixtures of products. From the reaction with pregnenolene acetate [part structure (XVII)] a modest yield of an adduct (XVIII) was obtained. The constitution and stereochemistry of this adduct were determined by n.m.r. spectroscopy and by the following chemical sequence. The adduct was hydrolysed by base to the corresponding alcohol which by chromic acid oxidation gave the ketone (XIX). Treatment of the latter with alkali afforded the known 6α-fluoroprogesterone (XX).

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(XIV)　　　　　　　　(XV)　　　　　　　　(XVI)

(XVII)　　　　(XVIII)　　　　(XIX)　　　　(XX)

Similarly 17β-acetoxyandrost-4-ene [part structure (XXI)] gave a complex mixture of products on treatment with trifluoromethyl hypofluorite. However, the corresponding 3β-acetoxy-derivative (XXII) reacts very cleanly with trifluoromethyl hypofluorite to afford a major product (XXIII) and a minor product, probably (XXIV). The constitution and stereochemistry of the adduct (XXIII) were established by n.m.r. spectroscopy and by the following sequence of chemical reactions. The adduct was hydrolysed by base to the diol (XXV) which, by chromic acid oxidation, gave the diketone (XXVI). Treatment of the latter with base gave the known 4-fluorodiketone (XXVII).

(XXI)　　　(XXII)　　　(XXIII)　　　(XXIV)

(XXV)　　　(XXVI)　　　(XXVII)　　　(XXVIII)

(XXIX)　　　(XXX)　　　(XXXI)　　　(XXXII)

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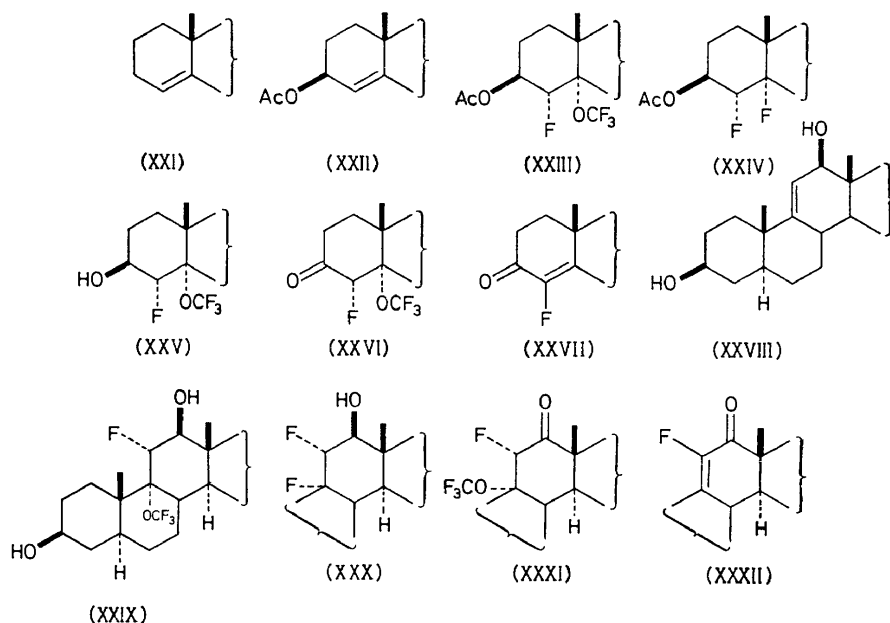
In analogous experiments a steroid of part-structure (XXVIII) similarly afforded, as major product, an adduct (XXIX) and, as minor product, a difluoride (XXX). The constitution and stereochemistry of the adduct was established by n.m.r. spectroscopy and by the following chemical sequence. The diol (XXIX) was oxidized by chromic acid to the diketone (XXXI). Base induced elimination from the latter afforded the α-fluoro-α,β-unsaturated ketone (XXXII). In a similar sequence of reactions the difluoride (XXX) gave the corresponding difluoro-diketone and thence the same unsaturated ketone (XXXII).

In an analogous series of reactions trifluoromethyl hypofluorite was reacted with the diacetate of (XXVIII) to give, as major product, an adduct and, as minor product, a difluoride. Acetylation of the diols (XXIX)
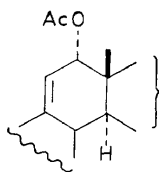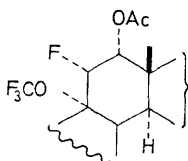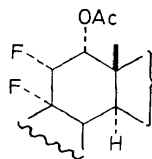
(XXXIII)   (XXXIV)   (XXXV)
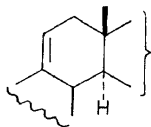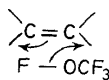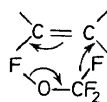
(XXXVI)   (XXXVII)   (XXXVIII)

and (XXX) furnished the same two diacetates, as were obtained directly from the diacetate of (XXVIII). Similarly the diacetate (XXXIII) afforded an adduct (XXXIV) and a difluoride (XXXV).

The olefin (XXXVI) without allylic substitution gave a complex mixture of products with trifluoromethyl hypofluorite, just as did the olefin (XXI) (see above). It is clear, therefore, that allylic substitution has a profound effect upon the smoothness of reaction of an olefinic linkage. This may, perhaps, be explained by the stabilization of the intermediate fluoronium

ion in the sense: R—Ö—C—C—C⊕
                              |
   F
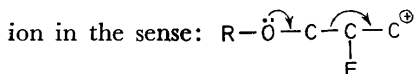
A comparable stabilization does not, of course, exist in an unsubstituted olefin.

Noteworthy, in all these cases, is the *cis*-addition of the reagent and the lack of influence of the nature of the allylic groups upon the course of the reaction. Clearly the acetate groups are not forming acetoxonium ions or the reaction would follow a different course when OAc was replaced by

OH. We believe that *cis*-addition of electrophilic reagents may be the rule rather than the exception when there is not an intermediate cyclic ion.

A further mechanism for the formation of these adducts and difluorides must also be considered. This mechanism can be represented by the expressions (XXXVII) and (XXXVIII) where cyclic polarized transition states are implied. Such a mechanism would explain the *cis*-addition and the direction of polarization of the transition state. It would also explain how methanol added to the solvent in large (molecular) excess does not interfere in the formation, of adduct and of difluoride. The latter observation can, however, be explained if an 'intimate' ion pair is involved. Strong evidence for the existence of an 'intimate' ion pair is provided by the fact that, whilst the fluorocarbonium ion cannot be captured by an external nucleophile (methanol), it can be trapped by an internal nucleophile. Thus the 9(11)-olefin (XXXIX) reacts with trifluoromethyl hypofluorite to furnish the phenol (XL) in modest yield as well as several other products. This phenol must arise from a rearrangement of the intermediate fluorocarbonium ion (XLI; see arrows). The C-19 methyl group thus acts as an internal nucleophile in the neutralization of the positive charge at C-9.
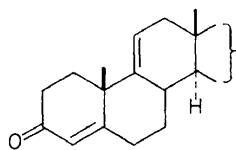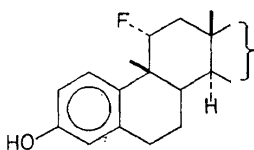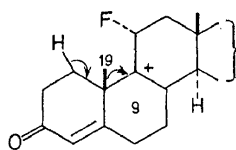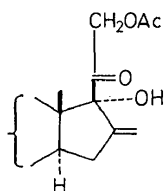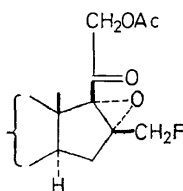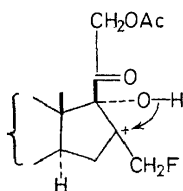

(XXXIX)   (XL)   (XLI)


(XLII)   (XLIII)   (XLIV)

A more striking example is the following. Reaction of trifluoromethyl hypofluorite with the olefin (XLII) affords, as sole product, the oxide (XLIII). In this case it is the 17α-hydroxyl group which captures internally (XLIV; see arrow) the fluorocarbonium ion at C-16.

The application of hypofluorites, and of trifluoromethyl hypofluorite in particular, as fluorinating agents is certainly general. The following examples will serve to illustrate further the scope of these new reagents.

In the sugar series vinyl ethers such as 3,4,6-tri-*O*-acetyl-D-glucal (XLV) are readily prepared and should be easily fluorinated at C-2. Reaction of the glucal (XLV) with trifluoromethyl hypofluorite affords[4] the adduct (XLVI) (26 per cent), the corresponding difluoride (XLVII) (34 per cent),

the stereoisomeric adduct (XLVIII) (5·5 per cent) and its corresponding difluoride (XLIX) (7·6 per cent). It is of interest that, in all cases, the products are formed by *cis*-addition. A further point to note is that the ratio of difluoride to adduct is much higher for the addition reactions of the vinyl ether (XLV) than it is for the addition reactions of allylic derivatives as summarized above. This can be understood readily in terms of the
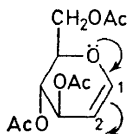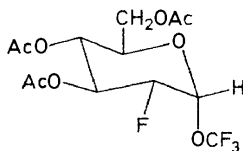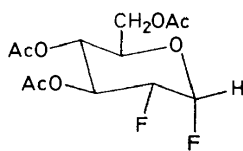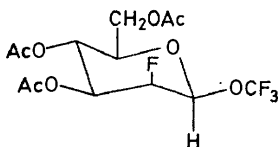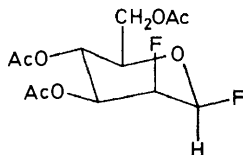

(XLV)   (XLVI)   (XLVII)

(XLVIII)   (XLIX)

stability of the fluorocarbonium ion intermediate. In the glucal case the intermediate ion is an oxonium ion and therefore stabilized relative to the intermediate ions in addition to the olefinic linkage. The longer life for the intermediate oxonium ion gives time for the decomposition of the trifluoromethoxide ion to fluoride ion and COF_2 and thus a greater proportion of difluoride is to be expected.

Another striking example of this phenomenon is provided by the reaction of diphenylacetylene with trifluoromethyl hypofluorite. The major product of reaction is a nicely crystalline compound $Ph—CF_2—CF(OCF_3)—Ph$. We consider that the reagent first adds to the acetylenic linkage to furnish $Ph—CF=C(OCF_3)—Ph$. This then reacts more rapidly than diphenylacetylene with the reagent to furnish $Ph—CF_2—C^{\oplus}(OCF_3)—Ph$. This ion is stabilised as a benzyl cation and as an oxonium ion. It has, therefore, a sufficient life-time so that all the counter-ion decomposes to fluoride anion and COF_2. Thus the almost exclusive product of reaction is $Ph—CF_2—CF(OCF_3)—Ph$. The intermediate olefin is considered to be more nucleophilic than diphenylacetylene and thus its presence in the reaction mixture cannot be detected.

We have also studied[5] the addition of trifluoromethyl hypofluorite to *cis* and *trans*-stilbene. Both olefins react stereospecifically to give adduct and difluoride and the evidence indicates exclusive *cis*-addition with *trans*-stilbene and almost exclusive *cis*-addition with the *cis*-isomer.

We have already[2] reported on the use of trifluoromethyl hypofluorite as an electrophilic fluorination agent for aromatic compounds. In suitable cases the reagent effects in one step a process which otherwise requires an inconvenient multistep sequence (the Schiemann reaction).

References

[1] D. H. R. Barton, L. S. Godinho, R. H. Hesse and M. M. Pechet. *Chem. Comm.* 804 (1968).
[2] D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo and M. M. Pechet. *Chem. Comm.* 806 (1968).
[3] D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia and M. M. Pechet. *Chem. Comm.* 227 (1969).
[4] J. Adamson, A. B. Foster, L. D. Hall and R. H. Hesse, *Chem. Comm.* 309 (1969).
[5] D. H. R. Barton, R. H. Hesse, S. N. Loo, L. Ogunkoya and M. M. Pechet, in preparation.