Fluorination at Saturated Carbon. 2. Direct Fluorination of Steroids

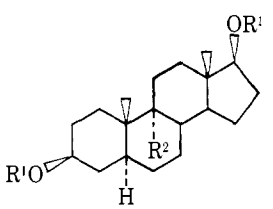
Sir:

The selective replacement of a hydrogen attached to an unactivated, quadruply linked (saturated) carbon presents an exacting challenge, first generally met by intramolecular atom transfer processes.[1] Although these reactions have notably facilitated synthesis, significant synthetic opportunities remain: among steroids, for instance, one finds (a) substitution at C-9 (corticoid synthesis), (b) substitution at C-14 (cardenolide synthesis), (c) substitution at C-17 (conversion of plant sterols into medically useful steroids).

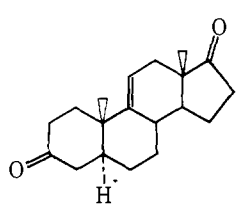
Traditional approaches to attack at saturated carbon have involved free radical reactions. Although extremely selective radical reagents exist,[2] the relatively nonpolar nature of radical transition states leads to such a rapid attenuation of the influence of *remote* polar groups that realization of the regioselectivity required by objectives (b) and (c), for instance, through a bimolecular radical process seems unlikely. For this reason, the most elegant and promising approach to the problems (a) to (c) has been through the use of reactive ligands *covalently* attached to the substrate.[3]

We have recently described a novel regioselective electrophilic fluorination reaction at saturated carbon.[4] It occurred to us that this reaction (by virtue of a highly polar transition state) should be extremely sensitive to the inductive effect of polar substituents, even those present at *remote* sites, and could thus accomplish a predictable, regioselective fluorination of steroids. We now describe the use of direct fluorination for the selective functionalization of carbons 9, 14, and 17 of the steroid nucleus.

Exposure of the trifluoroacetate (**1a**) to CF_3OF[5] in the presence of radical inhibitor (0.1 equiv of nitrobenzene) led to the formation of the 9α-fluorosteroid (**1b**), mp 142° $[\alpha]$D −22° (yield 34%), the structure of which was confirmed by degradation to the known diketone (**2**).[6] Exposure of either **1a** or the diacetate **1c** to elemental fluorine (diluted with 10–20 vol of N_2) under similar conditions afforded **1b** (34%) and **1d,**



1a, $R^1 = CF_3CO$; $R^2 = H$
1b, $R^1 = CF_3CO$; $R^2 = F$
1c, $R^1 = Ac$; $R^2 = H$
1d, $R^1 = Ac$; $R^2 = F$



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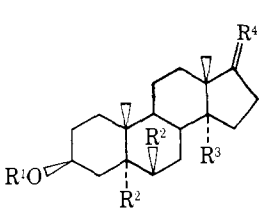
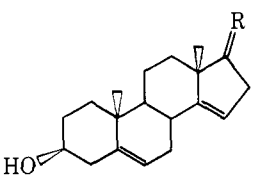
mp 138°, $[\alpha]$D −8° (yield 50%, 70% based on recovered starting material) respectively. The dibromides **3a** and **4a** upon fluorination with CF_3OF followed by reductive dehalogenation and hydrolysis afforded the 14α-fluorosteroids **3b,** mp 166°, $[\alpha]$D +2.5° (yield 42%, 47% based on recovered starting material), and **4b,** mp 202°, $[\alpha]$D 32.5° (yield 38%). The point of attachment of the fluorine was in each case established through dehydrofluorination (treatment with 2–3 equiv of BF_3 etherate at room temperature in benzene for 10 min) followed by transformation into the known Δ^{14} steroids **5**[7] and **6**.[8] The α-configuration of the fluorine is indicated by NMR and by optical rotation.[9] The configurations of the fluorine substituents assigned in this communication also follow from the mechanism of the reaction.[4]

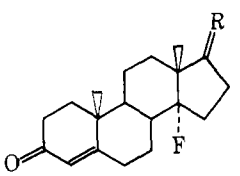


3a, $R^1 = CF_3CO$; $R^2 = Br$; $R^3 = H$; $R^4 = O$
3b, $R^1 = H$; $R^2 = \Delta^{5,6}$; $R^3 = F$; $R^4 = O$
4a, $R^1 = CF_3CO$; $R^2 = Br$; $R^3 = H$; $R^4 = \alpha H, \beta COCH_3$
4b, $R^1 = H$; $R^2 = \Delta^{5,6}$; $R^3 = F$; $R^4 = \alpha H, \beta COCH_3$
4c, $R^1 = Ac$; $R^2 = Cl$; $R^3 = H$; $R^4 = \alpha H, \beta COCH_3$

Although a 5,6-dibromide liberated bromine when exposed to F_2, treatment of the dichloride **4c** with elemental fluorine afforded the 14α-fluorosteroid which was, without isolation, transformed into **6** (overall yield from **4c** 45%). The fluorosteroids **3b** and **4b** upon oxidation afforded 14α-fluoroandrost-4-ene-3,17-dione (**7**), mp 217°, $[\alpha]$D +181°, and 14α-fluoroprogesterone (**8**), mp 175°, $[\alpha]$D +204°, respectively, the first representatives of a new class of fluorinated steroid hormones.

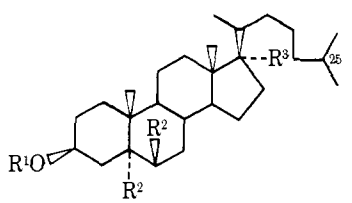


5, R = O
6, R = αH, $\beta COCH_3$



7, R = O
8, R = αH, $\beta COCH_3$

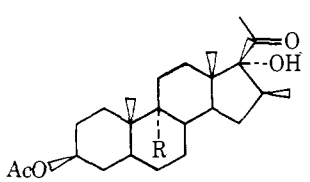
While cholestanol trifluoroacetate (**9a**) with elemental fluorine afforded the desired 17α-fluorocholestanol trifluoroacetate (**9b**),[10] mp 130°, $[\alpha]$D +20.2°, the yield (25%) was diminished through formation of fluorinated by-products. As



9a, $R^1 = CF_3CO$; $R^2 = R^3 = H$
9b, $R^1 = CF_3CO$; $R^2 = H$; $R^3 = F$;
9c, $R^1 = Ac$; $R^2 = Cl$; $R^3 = H$;
9d, $R^1 = H$; $R^2 = \Delta^{5,6}$ $R^3 = F$

spectral evidence indicated that fluorines of the by-products were present in the nucleus, we turned to a substrate with additional electron withdrawing groups in an attempt to "force" fluorination exclusively toward carbon 17α—or the side chain. Exposure of the dichloride **9c** to F_2 followed by reductive dechlorination afforded the desired 17α-fluorocholesterol **9d,** mp 149°, $[\alpha]$D −30.6° (yield 40%), together with 17α,25-difluorocholesterol,[11] mp 159°, $[\alpha]$D −34.0° (yield 20%).

The selective direct fluorination of steroids which we described is tolerant of sensitive functional groups, for instance, the corticoid side chain. This is nicely illustrated by the fluorination of the substrate **10a** into the corresponding 9α-fluorinated derivative **10b,** mp 150°, $[\alpha]$D +12.8° (yield 50%).



10a, R = H
10b, R = F

From the foregoing, it is apparent that treatment of a complex, substituted hydrocarbon substrate with either elemental fluorine or a fluoroxy reagent (with radical inhibitor) comprises an effective, predictable, and regioselective process for substitution at saturated carbon.[12]

References and Notes

(1) K. Heusler and J. Kalvoda in "Organic Reactions in Steroid Chemistry", Vol. II, J. Fried and J. Edwards, Ed., Van Nostrand–Reinhold, New York, N.Y., 1972, p 237; R. H. Hesse, *Adv. Free-Radical Chem.*, **3**, 83 (1969).

(2) R. Breslow, R. Corcoran, J. A. Dale, S. Liu, and P. Kalicky, *J. Am. Chem. Soc.*, **96**, 1973 (1974); R. Breslow, J. A. Dale, P. Kalicky, S. Liu, and W. N. Washburn, *ibid.*, **94**, 3276 (1972).

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(4) D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and H. T. Toh, *J. Am. Chem. Soc.*, preceding paper in this issue.

(5) Fluorinations were carried out as in ref 4, solvents used were mixtures of $CFCl_3$ and $CHCl_3$ or CH_2Cl_2. All reactions were carried out under aerobic conditions in the presence of excess sodium trifluoroacetate and/or anhydrous sodium fluoride to prevent HF catalyzed elimination of HF.

(6) C. W. Shoppee, *J. Chem. Soc.*, 1134 (1946).

(7) F. Frappier, M. Pais, and F. X. Jarreau, *Bull. Soc. Chim. Fr.*, 610 (1972).

(8) W. Fritsch, V. Stacke, W. Haede, K. Radscheit, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **721**, 168 (1969).

(9) The 14α-fluoro-17-keto compounds **3b** and **7** differed from the 14α-H parents by $\Delta M_D \sim -20°$. The 14α-fluoro-17β-acetyl compounds **4b** and **8** differ from the 14α-H parents by $\Delta M_D \sim +30°$. In the case of analogous 14-hydroxylated compounds the 14β-series has $\Delta M_D \sim -180$ to $-200°$ (S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. L. Osborn, A. Weintraub, L. M. Reineke, and R. C. Meeks, *J. Am. Chem. Soc.*, **80**, 3382 (1958), and F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, **82**, 3209 (1960)) while ΔM_D for 14α-hydroxylation is -40 to $-60°$ for the ketone and $\sim+40°$ for the 17β-acetyl side chain (Eppstein et al., *ibid.*). Again on the basis of substituent effects on the $19CH_3$ resonances and the approximately equal effects of OH and F, one would expect the CH_3 resonance of a 14β-fluoro-17β-acetyl isomer of **4b** or **8** to occur at $\sim\delta$ 0.9 ppm while that of a 14α-epimer should occur at $\sim$0.73 ppm. The observed value for **4b** and **8** is 0.77 ppm (N. S. Bhacca and D. H. Williams "Applications of NMR spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964). Under conditions which readily epimerize 14β,17β-acetyl compounds the 14α-fluoro-17β-acetyl compounds described here were stable. This supports the configurations assigned.

(10) The location and configuration of the fluorine in compounds **9b** and **9d** follow clearly from NMR spectral data. We have observed the 9α-fluorine to resonate at 179–180 and the 14α-fluorine to resonate at 160–162. In each case the resonance appears as a broad multiplet. In the case of **9d** and **9b** the fluorine resonance occurs at 170 and is in each case a quartet, J = 31 Hz, indicative of equivalent coupling to three hydrogens (16α, 16β, and 20). This pattern is inconsistent with fluorine in any position save 17.

(11) The compound clearly bears a 17α-fluorine (^{19}F NMR: 170 ppm, quartet, J = 31 Hz). The second fluorine which resonates at 135.5 ppm ($W/2$ = 45 Hz) is clearly tertiary and is not located at C_5, 9, or 14. The ^{1}H resonance of the hydrogens at C-26 and C-27 has been shifted downfield by 0.48 ppm with respect to cholesterol and these hydrogens resonate as a doublet (J = 20 Hz), parameters consistent with the presence of a 25-fluorine substituent.

(12) All new compounds had the correct composition established by microanalysis. Optical rotations were measured in $CHCl_3$ on ca. 1% solution, ^{1}H NMR spectra were measured in $CDCl_3$ and reported as shifts downfield from internal Me_4Si (δ). ^{19}F NMR spectra were measured in $CHCl_3$ and reported as shifts upfield from internal $CFCl_3$ (ϕ^*). Complete ^{13}C NMR spectra were obtained for representatives 9α-, 14α-, and 17α-fluorinated steroids. In each case the spectra supported the assigned structures and stereochemistry. We thank Drs. L. Phillips and R. B. Jones (Imperial College, London), for these measurements which (with interpretation) will be published by them elsewhere.

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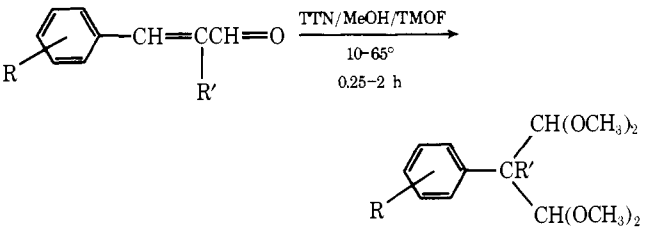
Novel Oxidative Rearrangements with Thallium(III) Nitrate (TTN) in Trimethyl Orthoformate (TMOF)[1]

Sir:

Thallium(III) nitrate (TTN), since its introduction several years ago as a conveniently prepared, highly specific, and often unique oxidant,[2] has been used to effect a wide variety of organic transformations.[3-12] The commonly employed solvents for these reactions have been dilute nitric acid, acidic methanol, or aqueous glyme containing perchloric acid. There have been reports, however, of disappointing failures with these reagent/solvent combinations. For example, α,β-unsaturated aldehydes, ketones, and esters react very slowly to give complex mixtures of products; *seven* products are obtained upon attempted oxidation of cinnamaldehyde in dilute nitric acid, four of which were identified as phenylacetaldehyde, phenylglyoxal, phenylglyoxylic acid, and benzaldehyde.[12]

Scheme I. Conversion of Cinnamaldehydes to Arylmalondialdehyde Tetramethylacetals



(a) R = R' = H, 79%
(b) R = 4-CH_3O, R' = H, 84%
(c) R = 4-O_2N, R' = H, 63%
(d) R = H, R' = CH_3, 83%
(e) R = 3-O_2N, R' = CH_3, 50%

We wish to report the remarkable effectiveness of methanol/trimethyl orthoformate (MeOH/TMOF) (1:1) or of TMOF alone as solvents for certain TTN-mediated oxidations. Reactions such as the above, which fail in the usual solvents, proceed rapidly and cleanly in MeOH/TMOF; in addition, strikingly different products are obtained with some substrates in MeOH/TMOF rather than MeOH itself. These results are summarized below.

We have found that cinnamaldehydes rearrange cleanly with TTN/MeOH/TMOF to give arylmalondialdehyde tetramethylacetals. It is remarkable that this conversion proceeds in good yield even when the migrating group is *p*-nitrophenyl (see Scheme I). This transformation proceeds by an initial TTN-catalyzed conversion of the cinnamaldehyde to its dimethylacetal;[13] the oxidative rearrangement which then follows methoxythallation is analogous to the TTN-mediated rearrangement of styrene to phenylacetaldehyde.[9]

The above arylmalondialdehyde synthesis from cinnamaldehydes constitutes a potentially general synthetic method for the conversion of an aryl CHO into a *tert*-butyl substituent. Thus, benzaldehyde was converted into α-methylcinnamaldehyde by aldol condensation with propionaldehyde. Oxidative rearrangement with TTN/MeOH/TMOF then gave methylphenylmalondialdehyde tetramethylacetal. Acid-catalyzed exchange with ethanedithiol, followed by reduction under Wolff–Kischner conditions, gave *tert*-butylbenzene. This conversion can obviously be readily adapted to the synthesis of *gem*-dimethyl derivatives of the type $ArC(CH_3)_2R$, a substitution pattern laborious to introduce by classical methods.

Although cinnamic esters have been reported to react slowly or not at all with TTN/MeOH,[12] we have found that these substrates, in analogous fashion to cinnamaldehydes, are smoothly rearranged with TTN/MeOH/TMOF or TTN/TMOF to methyl α-(dimethoxymethyl)arylacetates. Some typical conversions are reported in Scheme II.

Acetophenone rearranges smoothly to methyl phenylacetate on treatment with 1 equiv of TTN in MeOH.[10] With MeOH/TMOF as solvent, however, *2* mol of TTN are consumed, and the product is methyl α-methoxyphenylacetate. Methyl phenylacetate itself is not an intermediate in this conversion, since it is recovered unchanged under the reaction conditions. We have been able to show that α-methoxystyrene (from TTN-catalyzed loss of methanol from acetophenone dimethylketal) and the trimethyl orthoester of phenylacetic acid are both intermediates in this conversion, which therefore