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α-FLUORINATION OF KETONES BY XENON AND IODOBENZENE DIFLUORIDES: A STEREOCHEMICAL EVIDENCE DEMONSTRATING THEIR MECHANISTIC DIFFERENCES

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Summary: Xenon difluoride reacts smoothly with various steroid silyl enol ethers in the absence of any acid catalyst to afford stereoselectively α-oriented α-fluoroketones in good yields while iodotoluene difluoride reacts rather sluggishly with these silyl enol ethers to competitively produce β-oriented α-fluoro ketones, elimination and other nucleophilic substitution products. The observed stereochemical contrast clearly suggests an electrophilic and nucleophilic mechanism for these reactions, respectively.

In order to extend our recent study[1] on α-fluorination of ketones and also to develop a new convenient synthetic reagent for the reaction, we were interested in examining the reactivities and mechanistic features of various difluoride fluorinating agents, in particular, xenon (XeF_2) and iodobenzene difluorides (IBDF) as tamed molecular fluorine analogues with enol derivatives. These reagents have been known to react, as mild fluorinating agents, with electron-rich olefins[2,3] in the presence of certain catalysts[4] but have not been used for a long time for the synthesis of α-fluoro ketones, unlike the extensively employed perchloryl fluoride[5] and fluoroxy compounds.[6] Recently, Kagan et al.[7] and Zupan et al.[8] successfully used xenon hexafluoride intercarlate ($C_{19}XeF_6$) and xenon difluoride, respectively, for this purpose. However, the fluorination mechanism of these reagents, especially the latter, remains to be established, as stereochemistries of the reactions are not known and HF catalyst is used. In addition, to our knowledge, IBDF has not been used for the α-fluorination of ketones.

In order to clearly define the stereochemistries of the reactions[9] with xenon and iodobenzene difluorides, steroid silyl enol ethers (1-TMS~4-TMS)[10] derived from 17β-hydroxy-5α-androstan-3-one acetate (1), 5-pregnen-3,11,20-trione 3,20-bisethylene ketal (2) 3β-hydroxy-5α-spirostan-12-one acetate (3), and 3β-hydroxy-5-androsten-17-one acetate (4), were chosen as substrates (see part structures).

On treatment[11] with XeF_2 without catalyst, compounds 1-TMS~4-TMS were stereoselectively converted into sterically less hindered α-oriented α-fluoro ketones in isolation yields of 60 to 75% (see Table I). These reactions were facile and completed in a few hours at room temperature. The results summarized are: (1) Radical involvement at any stage of the reaction appeared unlikely as neither the rates nor the nature of the products were affected by the

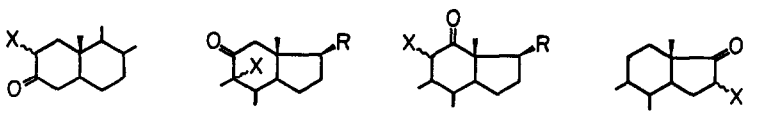
radical scavenger oxygen.[6a] (2) All the fluoro ketones obtained in high yields had similar stereochemistries and locations of fluorine as those in the preceding reactions[5,6] with CF_3OF and $FClO_3$. (3) Control experiments[12] clearly showed that these fluoro ketones were kinetically controlled primary products and not thermodynamically controlled secondary products. (4) The silyl enol ethers studied (1-TMS~4-TMS), which required no catalyst for the reaction, appeared to be more reactive than the corresponding enol acetates.[8]

Next, three (p)-substituted iodobenzene difluorides (Z = CH_3, H, Cl) were prepared by known methods[14] and their reactivities were examined in reactions with 1-TMS. (p)-Iodotoluene difluoride (Z = CH_3: ITDF) produced the highest yield, 37.5%, of fluorination products, 1a and 1b, although this yield was not satisfactory (see Table 1). As the ^{19}F nmr measurement of the crude products showed that the fluorination yield decreased notably with increasing electronegativity of the substituent in the benzene ring (in sequence, CH_3 > H > Cl), ITDF was used as a fluorinating agent. The compounds (1-TMS~4-TMS) treated with ITDF[11] gave the various oxidation products summarized in Table I. The significant results were: (1) Unlike the reaction with XeF_2, the reactions with 1-TMS and 4-TMS preferably produced β-oriented α-fluoro ketones, 1b and 4b. A control experiment unambiguously demonstrated that 4b was a kinetically controlled primary product and not a secondary product derived from the thermodynamically less stable ketone, 4a.[14] In addition, since 1b was found to be thermodynamically less stable than 1a, it was obviously considered to be a kinetically controlled product.[15] (2) The reaction became very sluggish at sterically hindered tertiary centers and elimination and/or hydroxylation[16] displaced fluorination. (3) Like the reaction with XeF_2, oxygen did not affect the reaction.

These results clearly demonstrated that the two fluorination reactions proceeded by different mechanisms. Thus, we propose an electrophilic fluorination mechanism for the reaction with XeF_2 and a mechanism involving an iodonium ion intermediate[3] and its subsequent S_N2 nucleophilic substitution or β-proton elimination by either fluoride or hydroxide anion for the reaction with IBDF.

Comparison of the two proposed mechanisms for the reactions with XeF_2 and ITDF (see the reaction sequences in equations 1 and 2) shows that XeF_2 is a source for electrophilic fluorine in equation 1 and ITDF that for a nucleophilic fluorine in equation 2. Also, in the reaction with ITDF the subsequent nucleophilic attack of the fluoride anion on the intermediate occurs in S_N2 manner with inversion of configuration. In these schemes, the reagents are suggested to be more favorably approach the double bond from the less hindered side according to the stereochemistries of the products obtained. Given the sophisticated stereochemical explanation described by House[17] for halogenation of steroid enol derivatives, the mechanism presented here can rationally account for all the experimental results obtained, although other mechanistic possibilities[18] still remain.

In conclusion, XeF_2 was found to be a very useful and convenient electrophilic fluorinating agent for the synthesis of α-fluoro ketones. Also, the one-step nucleophilic fluorination of enol derivatives with ITDF is new and is expected to produce stereoisomeric α-fluoro ketones of physiological importance, as exemplified by the reaction with 4-TMS.



1 a: X=2α-F
b: X=2β-F
c: X=Δ1(2)

2 a: 9α-F
b: 9β-F

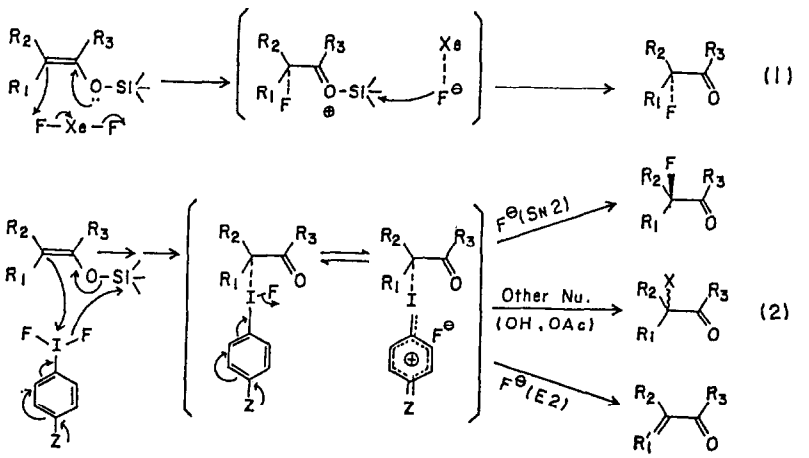
3 a: 11α-F
b: 11β-F
c: Δ9(11)

4 a: 16α-F
b: 16β-F

Table I. Products[a] and Stereochemistries of Reactions with XeF_2 and ITDF

compound	product (XeF_2)	yield isol. (%)	mp[d] (°C)	selectivity (α/β)[c]	product (ITDF)	yield (%)	mp[d] (°C)	selectivity (α/β)[c]
1-TMS	1a + 1b[b]	76.8(N_2)	190-194	4/1	1a + 1b[b] + 1c	37.5 17.0		4/6
2-TMS	2a	71.6(N_2) 77.2(O_2)	185-186	no 2b	no reaction (2-TMS recovered)			
3-TMS	3a	58.9(N_2)	~305(dec)	no 3b	3c	67.5	219-221	
4-TMS	4a + 4b	64.2(N_2) 68.8(O_2)	204-205[e]	9/1	4 + 4b	22.5 22.5	162-164	no 4a

[a] The details of structural elucidation will be reported in the full paper. ^{19}F nmr data of these products were: 1a: δ (int. C_6F_6) -32.2 (dm, J 47.0); 1b: -21.2 (m, J 47.0); 2a: -15.1 (m); 3a: -26.0 (dd, J 47.0); 4a: -23.0 (dt, J 48.9); 4b (q, J 50.8). [b] Compounds 1b could not be isolated. [c] The selectivities were determined with crude reaction products. [d] Melting points are uncorrected. [e] $Mp^{lit.}$ 205 °C: see Nakanishi, S.; Jensen, E. V. J. Org. Chem. 1962, 27, 702.



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REFERENCES AND NOTES

(1) Tsushima, T.; Nishikawa, J.; Sato, T.; Tanida, H.; Tori, K.; Tsuji, T.; Misaki, S.; Suefuji, M. Tetrahedron Lett. 1980, 21, 3593. The part 1 report on α fluorination of ketones, J. Org. Chem., in press. This is part 2 of the series.

(2) For the reactions with XeF_2, see (a) Filler, R. Israel J. Chem. 1978, 17, 71 and references cited therein. (b) Zupan, M.; Šket, B. J. Org. Chem. 1978, 43, 696 and references cited therein. (c) Shackelford, S. A. Tetrahedron Lett. 1977, 4265.

(3) For the reactions with IBDF, see: (a) Carpenter, W. J. Org. Chem. 1966, 31, 2688 and references cited therein. (b) Gregorcic, A.; Zupan, M. J. Chem. Soc., Perkin Trans. 1 1977, 1446. (c) Zupan, M.; Pollak, A. J. Chem. Soc., Chem. Commun. 1975, 715. (d) Patric, T. B.; Scheibel, J. J.; Hall, W. E.; Lee, Y. H. J. Org. Chem. 1980, 45, 4492 and references cited therein.

(4) Anhydrous HF, trifluoroacetic acid, and BF_3-etherate were known as catalysts.

(5) (a) Nakanishi, S.; Morita, K.; Jensen, E. V. J. Am. Chem. Soc. 1959, 81, 5259. (b) See also references cited in Chamberlin, J. W. "Steroid Reactions, and Outline for Organic Chemists"; Djerrasi, C., Ed.; Holden-Day: San Francisco, 1963; pp 164-167 and Hudlicky, M. "Chemistry of Organic Fluorine Compounds: A Laboratory Manual"; Ellis Horwood: Chichester, 1976; pp 83-93.

(6) (a) Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. Chem. Commun. 1968, 804. (b) Barton, D. H. R. Pure Appl. Chem. 1970, 21, 285 and references cited therein. (c) Hesse, R. H. Israel J. Chem. 1978, 17, 60. (d) Middleton, W. J.; Bingham, E. M. J. Am. Chem. Soc. 1980, 102, 4845.

(7) Yemul, S. S.; Kagan, H. B. Tetrahedron Lett. 1980, 277.

(8) Zajc, B.; Zupan, M. J. Chem. Soc., Chem. Commun. 1980, 759.

(9) See the following work with the same strategy, Barrett, A. G. M.; Barton, D. H. R.; Tsushima, T. J. Chem. Soc., Perkin Trans. 1 1980, 639.

(10) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. J. Org. Chem. 1969, 34, 2324.

(11) As a typical procedure: XeF_2 (128 mg) was added to a stirred solution of 1-TMS (203 mg) in 4 ml of a 1:1 mixture of $CF_2ClCFCl_2$ and CH_3CN under nitrogen at room temperature. After 4 h, the reaction mixture was poured into a cold diluted aqueous sodium sulfite solution (3%) and extracted with ethyl acetate. The organic layer was then thoroughly washed with water, dried, and evaporated to afford a crude crystalline product mixture (163 mg, the 4:1 mixture of 1a and 1b shown by ^1H- and ^{19}F-NMR). Crystallization (CH_3OH and CH_2Cl_2) afforded clean fluorinated ketones (135 mg, 1a slightly contaminated with 1b). Repeated recrystallization gave a pure sample of 1a of constant mp 190-194 °C; mp[lit.] 196: see ref (5a). The reactions with ITDF were similarly carried out except for the use of ethyl acetate instead of acetonitrile and a longer reaction time of 1-2 days.

(12) On treatment with XeF_2 under the same conditions as those used for the reaction, 1b and 4b were recovered unchanged. 1a and 4b were thermodynamically more stable than 1b and 4a, respectively.

(13) Three known methods were examined: (a) Dimroth, O.; Bockemuller, W. Ber. 1931, 64B, 516, (b) Ref (3a) and (c) Ref (3b). We found method (a) gave the best results.

(14) On treatment with ITDF under the same conditions as those used for the reaction, 4a was totally recovered unchanged.

(15) The formation of 1a appears to be due to partial acid-catalyzed isomerization of 1b by a small amount of HF produced by the elimination reaction.

(16) Hydroxylation products were obtained in the reaction with other steroid compounds. Details will be published in the full paper.

(17) (a) House, H. O. "Modern Synthetic Reaction", Second ed.; W. A. Benjamin, Inc.: Menlo Park, California, 1972; pp 469-471.

(18) Three different mechanisms are conceivable for both of the fluorination reactions: (1) the one involving an enolate intermediate, (2) concerted cyclic one, and (3) the one involving initial electrophilic attack toward the double bond by either fluorine or a central atom (xenon or iodine). We speculate here the involvement of an enolate intermediate in the reaction with IBDF but not in the reaction with XeF_2, as the protonated product, 4, was detected only in the former reaction. The details of mechanistic aspects of the two reactions will be discussed in the full paper.

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