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An Efficient α-Hydroxylation of Carbonyls Using the HOF•CH3CN Complex

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Abstract: The complex HOF•CH_3CN, made directly from fluorine and aqueous acetonitrile, was used for α-hydroxylation of various ketones, esters and acids via their trimethyl silyl enol ethers. The reaction is usually complete in a few minutes at room temperature or below and has high yields.

In the last 15 years of his life Professor Barton devoted a considerable effort to develop various oxidation processes aimed at oxidizing unactivated sites of organic molecules. These were collectively known as "Gif Chemistry".[1] Since Barton's research on fluorine chemistry[2] greatly influenced one of us[3], we would like to present here work which combines the two fields and demonstrates how elemental fluorine, although somewhat indirectly, can be efficiently used in oxidation of carbons next to carbonyl groups, through the corresponding enols, turning them into the respective α-hydroxy derivatives.

HOF•CH_3CN complex is easily prepared, by bubbling nitrogen diluted fluorine through aqueous acetonitrile, and does not require any isolation or purification prior to reaction. This reagent proved to be an exceptionally efficient oxygen transfer agent and reacts under very mild conditions even with very weak nucleophiles which do not usually react with other agents in this category such as dimethyldioxirane or various peracids. It epoxidizes olefins[4] including very electron deficient ones,[5] oxidizes amines,[6] ethers,[7] sulfur containing compounds including perfluoroalkyl sulfides,[8] and other functional groups.[9]

There have been many different approaches for synthesizing specific α-hydroxy carbonyl derivatives[10] of importance. One of the pioneers in this field was Rubottom who oxidized silyl enol ethers with either MCPBA[11] or $Pb(OAc)_4$.[12] More recent studies demonstrated that methyltrioxorhenium and hydrogen peroxide can also be used for the same purpose.[13] With the development of the HOF•CH_3CN complex an opportunity presented itself for a new excellent

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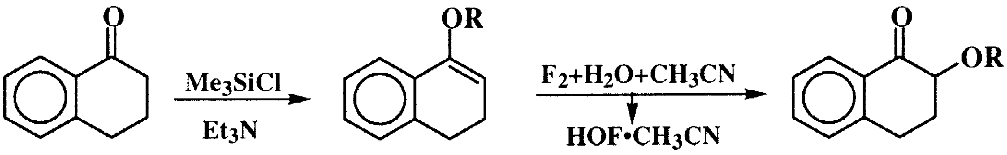
general synthetic method for hydroxylation of almost any type of carbonyl compound in a two step reaction sequence, usually with excellent yields.[14]

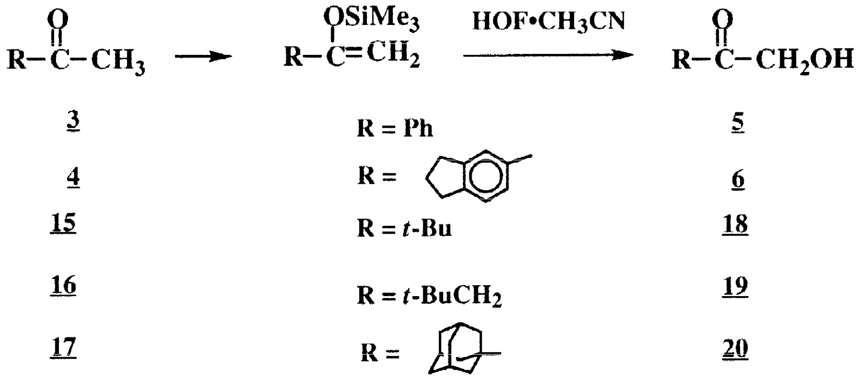
Since the hydroxylium moiety of HOF•CH3CN is strongly electrophilic, it should react quickly with any electron rich site. Reactions with metal enolates fail because of the presence of water and HF in the HOF•CH3CN solution. Reactions with trapped enols, however, such as trimethylsilyl enol ethers were found to be very satisfactory. Treating trimethylsilyl enol ether of tetralone (1) with HOF•CH3CN at room temperature for five minutes resulted in α-hydroxytetralone (2)[10] in higher than 90% yields. Similarly, the silylenols ethers of other benzylic carbonyls such as acetophenone (3) and 5-acetyl indane (4) formed the corresponding α-hydroxy compound 5[15] and the previously undescribed 6, each reaction proceeding in 95% yield. Under the same conditions the trimethylsilyl enol ether of 2-indanone (7) gave mainly tars through opening of the sensitive oxygenated 5-membered ring, but reacting at 0 °C for one minute only, produced 1-hydroxy-2-indanone (8)[16] in 85% yield.

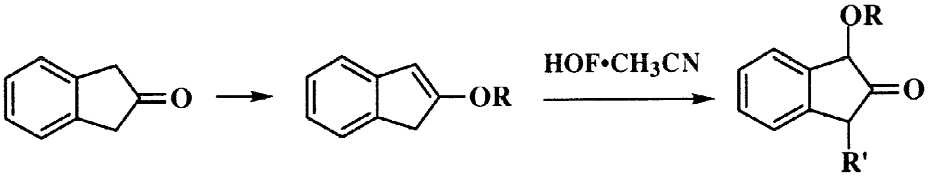


1

R = SiMe3
R = Ac

2 R = H
38 R = Ac



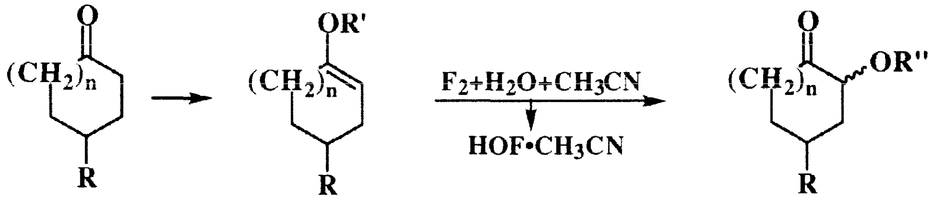


7

R = SiMe3
R = Ac

8 R = R' = H
40 R = Ac; R' = H
41 R = Ac; R' = OAc

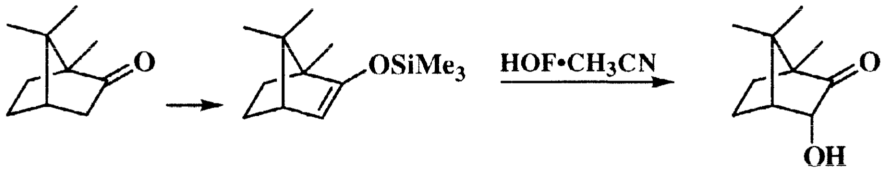
The cyclic and bicyclic ketones such as cyclooctanone (9), 4-t-butylcyclohexanone (10) and camphor (11) also reacted smoothly with HOF•CH_3CNcomplex to form α-hydroxycyclooctanone (12),[17] 2-hydroxy-4-t-butylcyclohexanone (mixture of isomers) (13)[18] and endo-α-hydroxycamphor (14)[19] in 85, 90 and 80% yield. Aliphatic ketones did not present any surprises either and pinacolone (15), 4,4-dimethyl-2-pentanone (16) and 1-acetyladamantane (17) were converted, via their trimethylsilyl enol ethers into the α-hydroxy derivatives 18,[20] 19[21] and 20[22] in 95, 90 and 80% yield respectively.



9 R = H; n = 3
10 R = *t*-Bu; n = 1

R' = $SiMe_3$
R' = Ac

12 R = H; R" = H; n = 3
13 R = *t*-Bu; R" = H; n = 1
39 R = *t*-Bu; R" = Ac; n = 1



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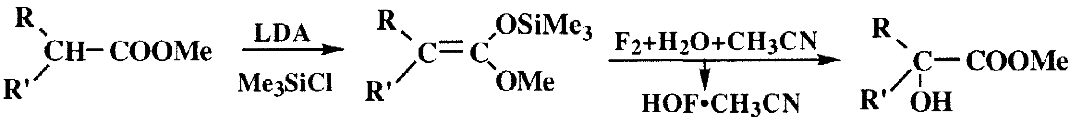
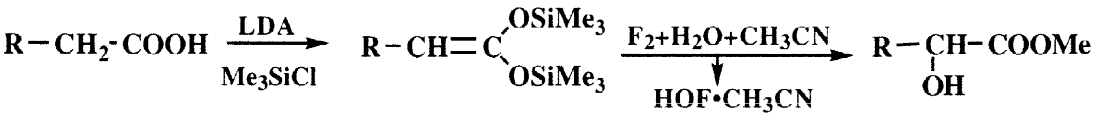
14

Esters can also be converted to their α-hydroxy derivatives under similar conditions, although preparing their alkyl trimethylsilyl ketene acetals using trimethylsilyl chloride requires pretreatment with a strong base such as LDA. Reacting these ketene acetals with HOF•CH_3CN gave the α-hydroxy esters in excellent yields. A 95% yield of methyl mandelate (21)[23] was obtained in a 5 minutes' reaction from the trimethylsilyl ketene acetal of methyl phenylacetate (22). Similarly, methyl heptanoate (23) and methyl 3-adamantylpropanoate (24) were converted into their α-hydroxy derivatives 25[24] and 26 in 90 and 85% yield. Methyl 2-propylpentanoate (27), a secondary ester, was successfully hydroxylated at the tertiary position forming the previously undescribed methyl 2-hydroxy-2-propylpentanoate (28) in 90% yield.



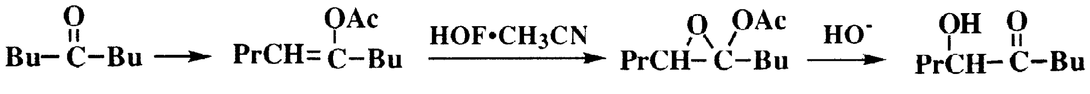
22	R = H; R' = Ph	21
23	R = H; R' = $CH_3(CH_2)_4$	25
24	R = H; R' = 	26
27	R = R' = $CH_3(CH_2)_2$	28

It is also possible to use acids as substrates, although the yields are somewhat lower and it is necessary to first prepare the carboxylic corresponding ketene bis(trimethylsilyl acetals) which requires two equivalents of LDA and trimethylsilyl chloride. These ketenes are much more sensitive to hydrolysis by the acidic aqueous media in which the HOF•CH3CN is present and a considerable portion of the reactant undergoes hydrolysis back to the starting acid. Still, undecanoic and isovaleric acids (29) and (30) were converted to the 2-hydroxyundecanoic (31)[25] and 2-hydroxyisovaleric (32) acids in 60 and 75% yield respectively in a short reaction time. As in the previous cases aromatic rings were accommodated and phenyl acetic acid (33) was converted into mandelic acid (34) in 50% yield. In all cases the only by-product obtained was the starting acid.



29	R = $CH_3(CH_2)_8$	31
30	R = *i*-Pr	32
33	R = Ph	34

We believe that the first step of the reaction is the epoxidation of the π region of the captured enol. While the resulting epoxide cannot be isolated when working with trimethylsilyl enol ethers because of rapid hydrolysis, especially in the presence of fluoride anions, the more stable enol acetates offer a good opportunity to identify the transient epoxide. Thus, from the enol acetate of 5-nonanone (35) we isolated in good yield 5-acetoxy-4,5-epoxynonane (36)[26] (a mixture of stereoisomers) which could be hydrolyzed under basic conditions to 4-hydroxy-5-nonanone (37).[27] With the enol acetates of tetralone (1), 4-t-butylcyclohexanone (10) or 2-indanone (7) the corresponding α-acetoxy carbonyl derivatives 38, 39[14] and 40,[28] which are the rearranged form of the intermediate gem-acetoxy epoxide, were formed in 50, 65 and 80% yield, along with the respective α-hydroxy derivatives. When 40 was subjected again to enolization with *i*-propenyl acetate a single enol acetate was formed although in 50% only. It was then treated again with HOF•CH3CN to form the 1,3-diacetoxy-2-indanone (41) in 88% yield. This is in contrast to the case of trimethylsilyl enolization of 1-hydroxy-2-indanone which resulted in a mixture of enols and did not produce any trioxygenated indanone.



35 36 37

EXPERIMENTAL

^{1}H NMR spectra were recorded with Bruker AC-200 with $CDCl_3$ as solvent and Me_4Si as an internal standard. The proton broad band decoupled ^{13}C NMR spectra were recorded at 90.5 MHz. Here too, $CDCl_3$ served as a solvent and TMS as internal standard. High resolution mass spectra were measured with a VG micromass 7070H instrument. IR spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets on a Nicolet 205 FTIR spectrophotometer.

General Procedure for Working with Fluorine

Fluorine is a strong oxidant and a very corrosive material. An appropriate vacuum line such as outlined in the following scheme should be constructed in a well ventilated area. After evacuation of the line, nitrogen is added up to about 5 psi above atmospheric pressure, followed by an appropriate amount of F_2, usually about 5-7 psi. More nitrogen is introduced building up a total pressure of 60-70 psi. We assume a rapid mixing of N_2 and F_2 takes place in the secondary cylinder B. For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, simplifying somewhat the process. If elementary precautions are taken, work with fluorine is relatively simple and we have had no bad experiences working with it.

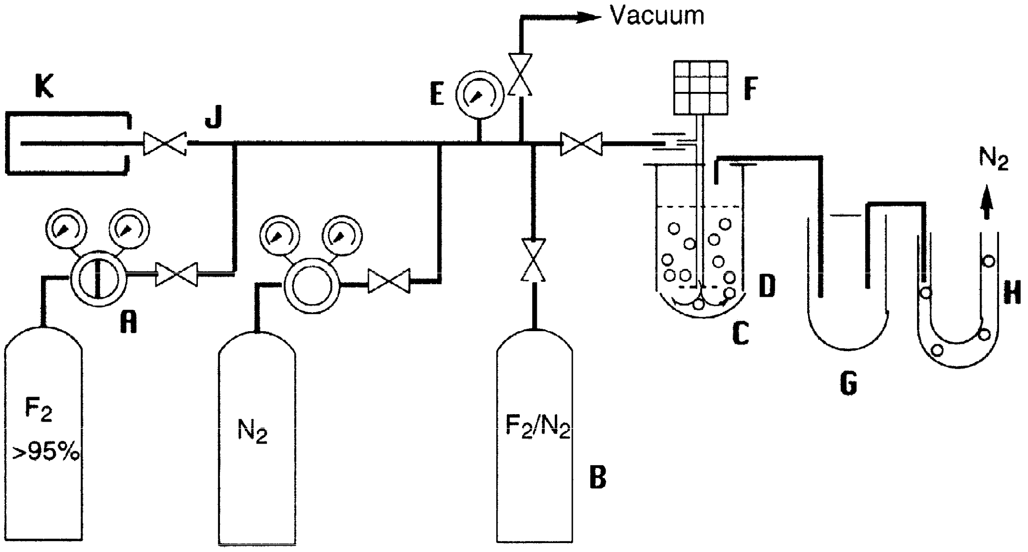
General Procedure for Producing the Oxidizing Agent $HOF{\bullet}CH_3CN$

Mixtures of 10% F_2 with nitrogen were used in this work. They were passed at a rate of about 400 mL per minute through a cold (-10 °C) and vigorously stirred mixture of 400 mL CH_3CN and 40 mL H_2O. The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.4 - 0.5 mol/liter.

Synthesis of trimethyl silyl enol derivatives

All derivatives were prepared from the corresponding carbonyl compounds by standard procedures such as reactions with trimethylsilyl triflate or chloride and Et_3N for ketones,[29] The enol derivatives were usually obtained in nearly quantitative yields and used without any further purification. LDA and trimethylsilyl chloride were used for esters and excess of LDA and trimethylsilyl chloride for acids,[30] the resulting ketene acetals were distilled under low pressure. Using this method we could achieve yields around 70%.

Our setup for working with pure fluorine



A, E: Regulator and pressure gauges suitable for work with fluorine (Matheson).

B: A secondary cylinder of a known volume made from either brass or monel (it can be a cylinder which has been already passivated for fluorine). Once the desired gas mixture is obtained the main fluorine cylinder is shut-off.

C: Glass reaction vessels are fine.

D, F: An optional way of mixing is using a vibromixer with either stainless steel or monel hollow shaft equipped with a disk having conic holes (Braun Biotech). Such a setup is especially efficient for a solid dispersion and creates fine gas bubbles.

G: Small soda-lime trap for consumption of any unreacted fluorine.

H: Small gas bubbler indicating free gas flow throughout the system (commercialy available flowmeters for fluorine and other gases can also be used).

J: All valves and lines are made from either brass or monel.

K: Large soda-lime trap for discharging any unused 95% fluorine (serves also as an emergency trap in the unlikely event that the fluorine in the main cylinder has to be evacuated).

General Oxidation Procedure

About 10 mmol of an enol derivative was dissolved in 10-20 ml $CHCl_3$. The mixture was then cooled to 0 ^{o}C and added to 2-4 fold excess of the $HOF \bullet CH_3CN$ complex. After about 5-10 min the reaction mixture was warmed to room temperature, neutralized with saturated sodium bicarbonate solution, extracted with $CHCl_3$, dried over $MgSO_4$, and the solvent removed. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck). The spectral and physical properties of the non commercial known products, which are referenced, were compared with the literature reports. In every case excellent agreement was obtained. The physical properties of all new α-oxygenated compounds are given below.

Hydroxymethylene-5-Indanyl Ketone (6) was obtained in 95% yield as a white solid; mp 72 °C; IR: 1680, 3440 cm^{-1}; ^{1}H NMR: 7.78 (1H, s), 7.72 (1H, d, J = 8 Hz), 7.33 (1H, d, J = 8 Hz), 4.85 (2H, d, J = 4 Hz), 3.58 (1H, t, J = 4 Hz), 2.97 (4H, t, J = 7 Hz), 2.13 (2H, quintet, J = 7 Hz); MS: *m/e*, (CI) 177.091259 (MH)$^+$ calcd. for $C_{11}H_{13}O_2$ 177.091555 .Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.88; H, 6.59.

Methyl 2-Adamantyl-2-Hydroxy Acetate (26) was obtained in 85% yield; mp 51 °C; IR: 3460, 1733 cm^{-1}; ^{1}H NMR: 3.79 (3H, s), 3.62 (1H, d, J = 8 Hz), 2.74 (1H, d, J = 8 Hz), 2.0 - 1.9 (3H, m), 1.7 - 1.5 (12H, m); MS: *m/e*, 224.140096 (M)$^+$ calcd. for $C_{13}H_{20}O_3$ 224.141245 ; Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61, H, 8.99. Found: C, 68.29; H, 8.97.

Methyl 2-Hydroxy-2-Propylpentanoate (28) was obtained in 90% yield; oil; IR: 3540, 1740 cm^{-1}; ^{1}H NMR: 3.76 (3H, s), 3.27 (1H, s), 1.7-1.6 (4H, m), 1.58 - 1.35 (2H, m), 1.1 - 0.95 (2H, m), 0.9 (6H, t, J = 7Hz); MS: *m/e*, 174 (M)$^+$; Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.00, H, 10.60.

5-Acetoxy-4,5-epoxynonane (36)[26] was obtained as mixture of stereoisomers in 80% yield; oil; IR: 1752 cm^{-1}; ^{1}H NMR: 3.1 - 2.9 (1H, m), 2.09, 2.06 (3H, two s), 2.01 - 1.95 (2H, m), 1.57 - 1.3 (8H, m), 1.03 - 0.87 (6H, m); MS: *m/e*, 141 (M - OAc)$^+$. This compound was hydrolyzed to (37) by treatment with NaOH at 60 °C overnight.

1-Acetoxy-2-indanone (40) was obtained in 90% yield as a waxy solid; Although known,[28] no physical data was ever given. IR: 1737, 1764 cm^{-1}; ^{1}H NMR: 7.4-7.3 (4H, m), 5.98, (1H, s), 3.64, (2H, s), 2.17, (3H, s); MS: *m/e* 190 (M)$^+$.

1,3-Diacetoxy-2-indanone (41) was obtained as mixture of stereoisomers in 88% yield; IR: 1743, 1751, 1783 cm^{-1}; ^{1}H NMR: 7.5-7.3 (4H, m), 6.3 (3/2H, s), 5.86 (1/2H, s), 2.2 (9/2H, s), 1.98 (3/2H, s); MS: *m/e* 248 (M)$^+$.

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3. At the beginning of the 70's one of us (S. R.) joined Professor Barton's research group at the Research Institute for Medicine and Chemistry (RIMAC) in Cambridge MA. Enchanted by the

potential of the electrophilic fluorinating agents being developed there at that time, he continues to work on the subject till today. (See Rozen, S. *Acc. Chem Res.* **1988,** *21*, 307.)

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