Elemental Fluorine: Not Only for Fluoroorganic Chemistry!

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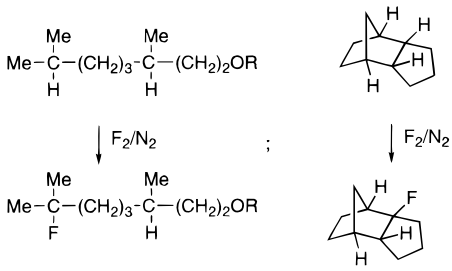
Introduction

Fluorine, the most chemically reactive element of the periodic table, was isolated more than a century ago by Moissan who received a Nobel prize for this achievement.[1] Its synthetic potential, however, remained largely hidden for almost a century. Fluoroorganic chemistry began to flourish starting with the "Manhattan Project", and soon organofluorine compounds took center stage in many fields of chemistry: fluoropolymers, surfactants, lubricants, herbicides, pesticides, special gases and solvents, numerous drugs, and much more. Still, the use of F_2 for construction of fluorine-containing materials, not to mention for general use in any other branch of organic chemistry, was an alien notion to most scientists. The dominant legend held that it was too reactive for controllable and selective reactions, and definitely too dangerous. Even today, when a reaction involving fluorine is described in the literature, there are always somewhat apologetic comments about the difficulties in handling this element and the alleged dangers associated with it. Of course, all this is part of a deeply rooted prejudice. Basic precautions such as working in a ventilated area, diluting the fluorine with an inert gas, and providing simple traps of soda-lime, alumina, or the like for the unreacted F_2 are sufficient for conducting any laboratory experiment with confidence. Unlike many other reagents, to the best of our knowledge, fluorine has not been involved in any fatal incident.

About 25 years ago I, then a freshly graduated student, attended a very impressive lecture by Professor D. H. R. Barton, who was awarded a Nobel prize a year earlier. He described the novel chemistry of the then rarely used CF_3OF. At the end of the talk, I humbly approached this great chemist and asked how he conducted these marvelous experiments. Barton looked at me slightly amused, and instead of describing complicated and frightening reaction protocols, just said "in glass vessels, my young friend". A few years later, I was fortunate to be able to conduct my postdoctoral studies under his and Hesse's[2] supervision in Cambridge, MA. There we started experimenting with elemental fluorine, and right from the beginning it was clear that F_2 could be used as a unique fluorinating agent, especially in electrophilic substitutions of tertiary, unactivated C−H bonds.[3]

Shlomo Rozen was born in 1942 in Bulgaria and moved to Israel as a child. He received his Ph.D. from the Hebrew University in Jerusalem, under the supervision of I. Shahak and the late E. D. Bergmann. He spent 3 years in the Research Institute for Medicine and Chemistry, Cambridge, MA, with D. H. R. Barton, R. H. Hesse, and M. M. Pechet. In 1976 he joined the School of Chemistry at the Tel Aviv University where he assumed the position of Professor of Chemistry in 1989. On numerous occasions during the last 15 years, he has held the position of a visiting scientist at the Central Research Department of the Du Pont Co. His main goal in chemistry is to demonstrate that elemental fluorine is a very useful reagent in general organic chemistry, as well as in fluorine chemistry, and chemists should discard their unjustified fear and prejudice against this long known but much neglected element.

Later, after I joined Tel Aviv University, we studied this process in detail,[4] and two examples are shown in eq 1. Hundreds of papers have appeared since, the



(1)

authors trying to accomplish activation of sp^3 C−H bonds using various organometallic reagents (hoping eventually to achieve a catalytic process), but the selectivity of fluorine has yet to be matched.

Fluorine-Free Products

In the last 15 years or so we have developed quite a few new reagents, all made *in situ* from fluorine. We have used them extensively for fluorinations, and some of their reactions are described in our previous Account.[5] With time, we came to realize that there are two strong driving forces associated with fluorine which could be utilized for reactions that could lead to fluorine-free products! The first concerns fluorine-containing intermediates which can easily eliminate HF. Less obvious is the second route to fluorine-free compounds based on *in situ* formation of reagents from F_2 which behave in a somewhat unfamiliar way since they contain a moiety loosely attached to the most electronegative element—fluorine.

This Account deals with some of the new synthetic possibilities offered by a direct or indirect employment of this halogen in organic chemistry. Equation 2 summarizes schematically most of the transformations which will be covered. It should be noted that, with the exception of the topic described in the first part, all other reactions do not require the isolation of an intermediate product, nor is it necessary to isolate the secondary reagents made from fluorine. These reactions, which start and finish with fluorine-free substrates and products, can therefore be considered as one-pot reactions.

Creating Olefins at Unreactive Sites

Steroids are a good example where fluorine has been used to create olefins at initially saturated sites

(1) Moissan, H. *Ann. Chim. Phys.* **1891**, *19*, 272.
(2) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.
(3) Barton, D. H. R.; Hesse, R. H.; Markwell, R. E.; Pechet, M. M.; Rozen, S. *J. Am. Chem. Soc.* **1976**, *98*, 3036.
(4) (a) Rozen, S.; Ben-Shoshan, G. *J. Org. Chem.* **1986**, *51*, 3522. (b) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769. (c) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 4928. (d) Rozen, S.; Gal, C. *J. Org. Chem.* **1988**, *53*, 2803.
(5) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307.

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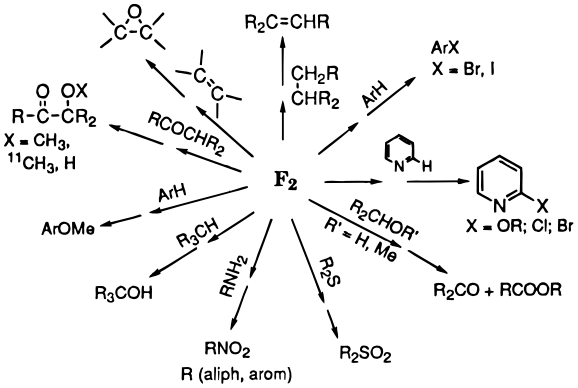
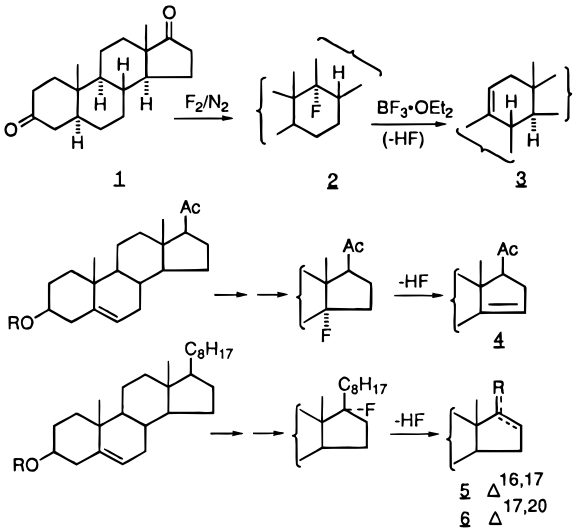


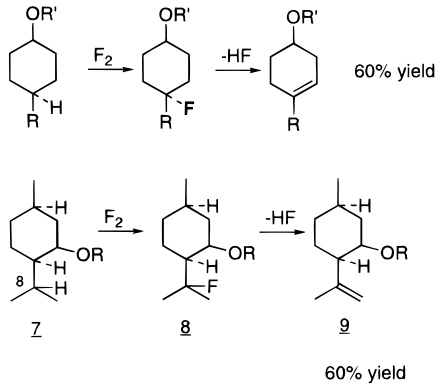
(2)

remote from any activating groups. In quite a few cases it has been shown that it is possible to introduce double bonds at the 9−11, 14−15, 16−17, and 17−20 positions. Thus, fluorination of 3,17-androstandione (**1**) produced the 9α-fluoro derivative **2**, which under treatment with BF_3·OEt_2 formed the $\Delta^{9,11}$-olefin **3** in 60% yield. Similarly, $\Delta^{14,15}$-pregnenolone (**4**) and a mixture of $\Delta^{16,17}$- and $\Delta^{17,20}$-cholesterol (**5** and **6**) have been prepared from the corresponding parent compounds (eq 3).[6]



(3)

While one other notable method, Breslow's elegant remote control oxidation,[7] is also applicable for creating double bonds in the rigid steroidal skeleton, it is not easy to introduce a double bond in other types of compounds at sites lacking a functional group in the immediate vicinity. Hundreds of reactions are recorded in *Chemical Abstracts* for the simple 4-alkylcyclohexanol system, but none with a transformation on the 4-position. Fluorine, under conditions where it acts as an electrophile, selectively substitutes the tertiary hydrogen to form the corresponding 4-fluoro compounds. These are easily dehydrofluorinated, resulting in 4-alkyl-3-cyclohexenol derivatives ready for further transformations. Similarly, menthol (**7**) could be fluorinated with good regioselectivity at the 8-position (**8**) and subsequently be dehydrofluorinated to give an isopulegol derivative (**9**) (eq 4).[4b] Two types of dehydrofluorinating agents could be employed in the above reactions, acidic and basic. BF_3·OEt_2 or anhydrous HF is quite efficient, but proceeds through an E1 mechanism, in some cases causing rearrangements typical for carbocations. These rearrangements could be avoided when bases were used. In such reactions the elimination is of the E2 type, although the less common syn elimination (E2BH) seems to be dominant. The two basic agents which we have examined were NaOH and MeMgI, the yields with the latter usually being considerably higher.

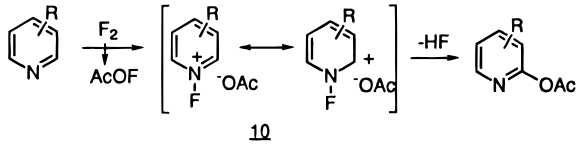


(4)

Activation of Heterocyclic Systems

Among the new reagents we have developed based on fluorine, we have succeeded in making acetyl hypofluorite, AcOF.[8] This was the first molecule to contain both O−F and C−H bonds, previously considered not possible because of potential HF elimination. It was made *in situ* from F_2 and sodium acetate, and we used it extensively for fluorination.[9] When we applied this reagent to various pyridines, we obtained some interesting results suggesting that AcOF can be used for direct regiospecific substitution of hydrogen in the pyridine nucleus, a procedure which usually requires harsh conditions and has a poor outcome.[10]

Since the fluorine atom in acetyl hypofluorite is a strong electrophile, it attacks the pyridine nitrogen atom, creating a positively charged *N*-fluoropyridine intermediate. This activates the nucleus to nucleophilic attack, and in the absence of other nucleophiles, it reacts with the acetate ion. HF elimination and restoration of aromaticity then take place, forming 2-acetoxypyridines in 60−90% yield (eq 5).[11] The



(5)

reaction is carried out at low temperature and takes less than 1 min. Substituents at the 3- or 4-position do not interfere, although with a few exceptions, substituents at the 2-position are not compatible with the reaction. Quinoline and pyrazine derivatives were also successfully reacted.

When other potential nucleophiles are present, the outcome of the reaction changes accordingly. Methylene chloride is known to create a loose complex with

(6) Alker, D.; Barton, D. H. R.; Hesse, R. H.; James, J. L.; Markwell, R. E.; Pechet, M. M.; Rozen, S.; Takeshita, T.; Toh, H. T. *Nouv. J. Chim.* **1980**, *4*, 239.

(7) Breslow, R.; Brandl, M.; Hunger, J.; Adams, A. D. *J. Am. Chem. Soc.* **1987**, ***109***, 3799.

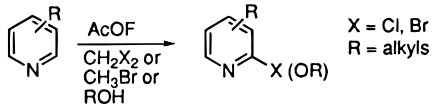
(8) Rozen, S.; Lerman, O.; Kol, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443.

(9) Rozen, S. in *The Chemistry of Halides, Supplement D2*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons Ltd.: 1995; Chapter 12, p 629.

(10) Chichibabin. A. E. *Chem. Ber.* **1923**, *56*, 1879. Tomasik, P.; Woszczyk, A. *Tetrahedron Lett.* **1977**, *25*, 2193.

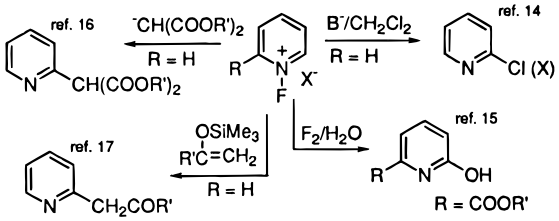
(11) Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* **1987**, *109*, 3789. Rozen, S.; Hebel, D. *Heterocycles* **1989**, *28*, 249.

the pyridine ring.[12] After the formation of the *N*-fluorocarbocation **10**, the ring interacts with the chlorine atom to form the corresponding 2-chloro derivative. The competition between chlorination and acetoxylation (eq 5) seems to depend both on the electron availability of the C−Cl bond and on its strength. Thus, unlike the results with methylene chloride, only acetoxylation is observed with both $CHCl_3$ and alkyl chlorides, but a very good yield of 2-bromo derivative is obtained in the presence of either CH_2Br_2 or CH_3Br. With primary alcohols present, the nucleophilic oxygen attacks the *N*-fluorocarbocation, forming 2-alkoxypyridine (eq 6).[13]



(6)

The idea of activating heterocyclic systems via N−F intermediates quickly flourished. Umemoto reacted the stable *N*-fluoropyridinium triflate with methylene chloride to form mixtures with 2-chloropyridine as a major component through a suggested carbene mechanism.[14] Van Der Puy used the reaction to hydroxylate various pyridinecarboxylates[15] in 50−70% yields, and Gakh showed that carbanions could also be used to alkylate the 2-position, although in 30−40% yields.[16] Later Strekowski used trimethylsilyl enol derivatives, improving the yield of the C-substitution (eq 7).[17]



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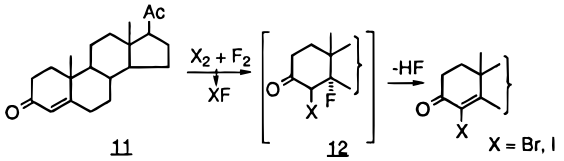
Bromination and Iodination of Deactivated π-Centers

Fluorine is an amazingly versatile reagent. It has been used for radical,[18] electrophilic,[19] and even nucleophilic fluorinations. The last group of reactions uses, *in situ*, the easily prepared reagents BrF[20] and IF.[21] The bromine and iodine atoms in these reagents are therefore strong electrophiles. They can react even with deactivated double bonds as in enones, progesterone (**11** in eq 8) serving as an example. Although it is possible to detect the intermediate adduct **12**, gentle heating or crystallization results in



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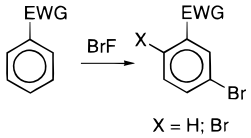
quantitative loss of HF, producing 4-bromo (or 4-iodo) progesterone.[22]

The most important reaction in this category, however, is aromatic halogenation. Bromination of benzene or activated aromatic compounds is a straightforward process requiring only Br_2. Deactivated aromatic rings are a different story. In such cases, a strong polarizing coreagent such as $AlCl_3$ is needed, usually in stoichiometric amounts, creating disposal problems. Bromine monofluoride, being a considerably polarized agent already, does not need Friedel−Crafts catalysts. When reacted with benzoic acid or benzaldehyde at −45 °C, it forms the corresponding *m*-bromo derivatives in nearly quantitative yields (eq 9).[23] Using excess BrF usually resulted in clean

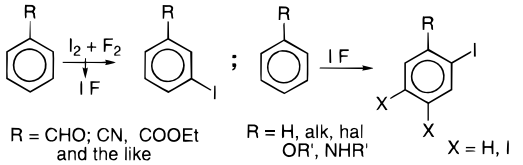


(9)

dibromination (eq 9).[24] It is worth noting that even the highly deactivated *m*-dinitrobenzene formed 3,5-dinitrobromobenzene in higher than 90% yield.

The above reactions require a solvent, at least for the preparation of BrF. This requirement can be waived in many cases if BrF_3 is used. Although a commercial reagent, it can be prepared easily without any solvent using the appropriate molar ratio of the elements. For aromatic bromination with this reagent, an equimolar amount of Br_2 has to be added, creating the equilibrium $BrF_3 + Br_2 \rightleftharpoons 3BrF$.[25]

Aromatic iodination is usually a challenging process. Although less reactive than ClF and BrF, the IF molecule is polarized enough to accomplish aromatic iodinations.[26] It requires longer reaction times than the parallel reactions with BrF, but monoiodination could eventually be achieved in good yields (eq 10).



(10)

With mildly activated rings, di and triiodination could also be achieved.[27] Recently, radiochemists used this reaction with radioactive ^{123}I and ^{131}I isotopes for use in positron emitting tomography (PET).[28]

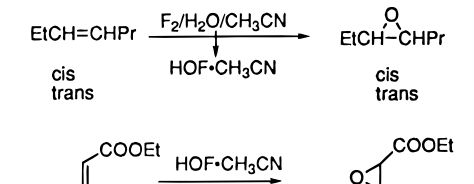
Fluorine, Water and Acetonitrile: $HOF{\cdot}CH_3CN$ Chemistry

One of the most versatile reagents we have developed so far is the $HOF{\cdot}CH_3CN$ complex made simply

(12) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand., Ser. B* **1984**, *38*, 469.
(13) Hebel, D.; Rozen, S. *J. Org. Chem.* **1988**, *53*, 1123. Hebel, D.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 6298.
(14) Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705. Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1989**, *54*, 1726.
(15) Van Der Puy, M.; Nalewajek, D.; Wicks, G. E. *Tetrahedron Lett.* **1988**, *29*, 4389.
(16) Gakh, A. A.; Kiselyov, A. S.; Semenov, V. V. *Tetrahedron Lett.* **1990**, *31*, 7379.
(17) Kiselyov, A. S.; Strekowski, L. *J. Org. Chem.* **1993**, *58*, 4476.
(18) Lin, W. H.; Clark, W. D.; Lagow, R. J. *J. Org. Chem.* **1989**, *54*, 1990. Hung, M. H.; Farnham, W. F.; Feiring, A. E.; Rozen, S. *J. Am. Chem. Soc.* **1993**, *115*, 8954.
(19) Rozen, S. In *Synthetic Fluorine Chemistry*; Olah, G. A., Chambers, R. D., Prakash, G. K. S., Eds.; J. Wiley & Sons: New, York, 1992; p 143.
(20) Rozen, S.; Brand, M. *J. Org. Chem.* **1986**, *51*, 222.
(21) Rozen, S.; Brand, M.; Zamir, D.; Hebel, D. *J. Am. Chem. Soc.* **1987**, *109*, 896. Rozen, S; Zamir, D. *J. Org. Chem.* **1991**, *56*, 4695.
(22) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342.
(23) Rozen, S.; Brand, M. *J. Chem. Soc., Chem. Commun.* **1987**, 752.
(24) Rozen, S.; Brand, M.; Lidor, R. *J. Org. Chem.* **1988**, *53*, 5545.
(25) Rozen, S.; Lerman, O. *J. Org. Chem.*, **1993**, *58*, 239.
(26) Rozen, S.; Zamir, D.; Menahem, Y.; Brand, M. *J. Org. Chem.* **1988**, *53*, 1123.
(27) Rozen, S.; Zamir, D. *J. Org. Chem.* **1990**, *55*, 3552.
(28) Thinius, O.; Dutscka, K.; Coenen, H. H. *Tetrahedron Lett.* **1994**, *35*, 9701.

by passing fluorine through aqueous acetonitrile.[29] Although HOF itself has been known for more than 20 years,[30] it has found little use in synthetic chemistry, since it decomposes rapidly at temperatures above −100 °C. By forming a loose complex with acetonitrile,[31] it is stabilized and can exist for a few hours at 0 °C, long enough to run a variety of reactions comfortably. HOF·CH_3CN is not much of a fluorinating agent, but it is unique in the sense that it possesses a strong electrophilic oxygen atom. It is probably the best oxygen transfer agent organic chemistry has to offer today.

The hypofluorous acid−acetonitrile complex reacts with practically any type of double bond to produce the corresponding epoxide at room temperature. This is a stereoselective reaction, and the initial configuration of the olefin is preserved in the product. With regular olefins, the reaction takes a few seconds with yields well above 90%. Enones[32] or (perfluoroalkyl)-ethenes,[33] which usually cannot be directly epoxidized by orthodox methods, require longer reaction times, although high yields are also eventually achieved here as well (eq 11). A free hydroxyl group or an unprotected carboxylic acid does not interfere with this epoxidation process,[34] in contrast to some other methods where such groups contend with direct epoxidation.[35] Electron rich π-centers such as enols also react very well to produce α-hydroxy ketones through an epoxy intermediate. Enol acetates, silyl enol ethers, and methyl enol ethers can all serve as substrates, and the yields are usually higher than 90% (eq 12).[36]



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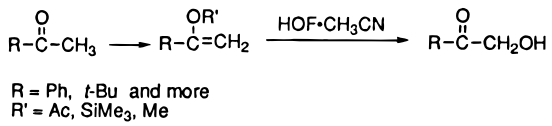
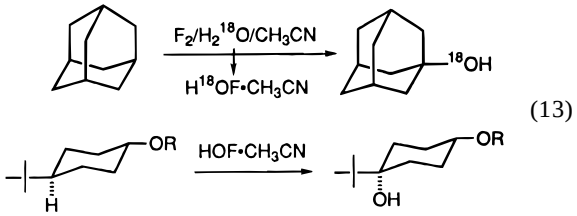


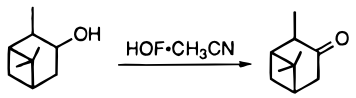
(12)

Since the oxygen atom in HOF·CH_3CN is electrophilic in nature, it can react with relatively electron rich sp^3 C−H bonds, representing yet another way for activating unactivated molecules. This reaction resembles very much a parallel process with F_2 which has already been mentioned.[4] It is worth noting that, if ^{18}O-labeled water is used, the resulting hydroxyl will contain this heavy oxygen isotope (eq 13).[37]



(13)

The HOF·CH_3CN complex can assume the role of a more conventional oxidizer as well. It oxidizes secondary alcohols in a matter of minutes to ketones with yields between 85% and 95% by abstracting the hydride-like hydrogen α to the hydroxyl group. Since the oxidation is carried out between 0 °C and room temperature (rt), almost no side reactions are recorded. Even acid-sensitive systems like 3-pinalol are converted to the corresponding ketones in high yields (eq 14).[38] Prolonged reaction times of up to 4 h at rt



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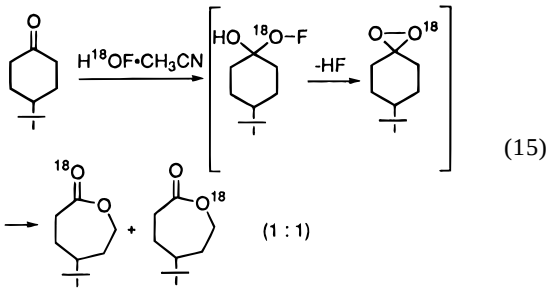
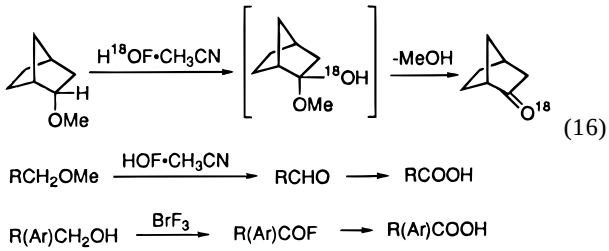
led to good yields of the respective ester through a Baeyer−Villiger-type oxidation of the intermediate ketone. It is interesting that the mechanism of these oxidations (eq 15), as proved by labeling experiments,



(15)

resembles the mechanism proposed by Baeyer himself (for reactions with peracids) almost a century ago,[39] and later proven to be wrong.[40]

Secondary and primary methyl ethers can undergo this oxidation reaction as well, although a large excess of the reagent is needed. The reaction proceeds through the abstraction of the hydrogen α to the etheric oxygen atom to form hemiketals. This has been proven by again using $H_2{}^{18}O$ (eq 16). The carbonyl in the product did not contain the original methoxy oxygen, but its heavier isotope ^{18}O. Primary ethers were oxidized to the acids through the corresponding aldehydes, in better yields than the parallel primary alcohols (eq 16).[41] It should be noted that



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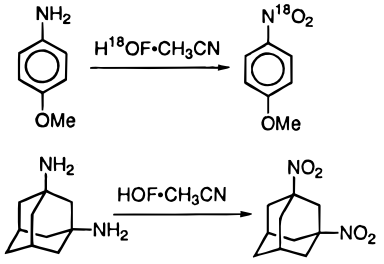
(29) Rozen, S.; Brand, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 554.
(30) Appelman, E. H. *Acc. Chem. Res.* **1973**, *6*, 113.
(31) Appelman, E. H.; Dunkelberg, O.; Kol, M. *J. Fluorine Chem.* **1992**, *56* , 199.
(32) Rozen, S.; Kol, M. *J. Org. Chem.* **1990**, *55*, 5155.
(33) Hung, M. H.; Smart, B. E.; Feiring, A. E.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 3187. Hung, M. H.; Rozen, S.; Feiring, A. E.; Resnick, P. R. *J. Org. Chem.* **1993**, *58*, 972.
(34) Rozen, S.; Bareket, Y.; Dayan, S. *Tetrahedron Lett.* **1996**, *37*, 531.
(35) Sattler, A.; Haufe, G. *Liebigs Ann. Chem.* **1994**, 921.
(36) Rozen, S.; Bareket, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 627.
(37) Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325.
(38) Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169.
(39) Baeyer, A. V.; Villiger, V. *Chem. Ber.* **1899**, *32*, 3625.
(40) Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* **1953**, *75*, 5595.
(41) Rozen, S.; Dayan, S.; Bareket, Y. *J. Org. Chem.* **1995**, *60*, 8267.

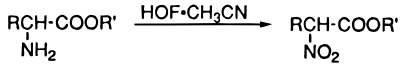
primary alcohols can be oxidized to acids by reacting them with BrF_3, first forming the corresponding acyl fluorides.[42] Somewhat similar oxidations of this type have been reported in the past.[43]

Other oxygen transfer reactions involving aromatic[44] and aliphatic[45] amines led to a fast and near quantitative formation of the respective nitro compounds. The use of $H^{18}OF{\cdot}CH_3CN$ resulted in labeling both nitro oxygen atoms (eq 17).



(17)

There are, of course, other ways to oxidize the above amines, but when it comes to more sensitive molecules such as amino acids, most of the known methods do not work. The oxidizing conditions are too harsh and the substrate loses either the amino or the carboxylic group.[46] Thus, α-nitro acids are made by combining two fragments such as nitroacetate and an alkyl halide.[47] The unique combination of $HOF{\cdot}CH_3CN$, a powerful oxidant and yet a reagent able to react under the mildest conditions, is behind its success in this area as well. Any amino acid (or ester) we tried was successfully converted to the respective α-nitro acid (or ester). Since the amino moiety reacts faster than the hydroxyl group, even unprotected ethyl serine was converted to ethyl 2-nitro-3-hydroxypropanoate (R = $HOCH_2$ in eq 18). As with most other oxygen transfer



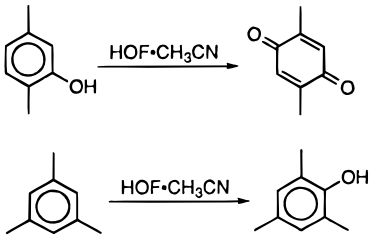
(18)

R = $HOCH_2$; $MeOOC(CH_2)_n$; $PhCH_2$; and more

reactions involving $HOF{\cdot}CH_3CN$, the typical reaction time was around 1−2 min, with yields ranging from 80% to 95%.[48]

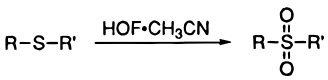
This reagent is also able to react with aromatic rings, although in this case the yields rarely exceeded 50%. When reacting phenols such as thymol, the quinone was immediately formed. Quinones were also formed from anthracene and phenanthrene, while aromatics with no hydrogens ortho or para to each other (such as mesitylene) have been hydroxylated to the corresponding phenol (eq 19). Destruction of aromaticity and consequent epoxidation of the remaining double bonds were also observed.[49]

Oxidizing sulfides to sulfones is a well-established procedure. The transformation, however, usually requires lengthy treatment with oxidants which con-



(19)

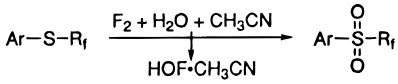
tain polluting heavy metals such as $KMnO_4$[50] or osmium tetroxide.[51] The use of various peroxides at high temperatures, and of dimethyl dioxirane,[52] was also recorded. $HOF{\cdot}CH_3CN$ will also perform this task. Quantitative yields, reaction temperatures of 0 °C, and contact times of around 5 min describe the outcome and conditions of all reactions we tested. These included various aromatic sulfides, benzylic and cyclic ones. Even the steric hindrance of the sulfur atom in di-*tert*-butyl sulfide did not effect sulfone formation (eq 20).[53]



(20)

R, R' = various Ar and Alk
including R = R' = *t*-Bu

While there are several alternatives for the oxidation of common sulfides, the situation differs drastically when electron-depleted ones are considered. The family of aryl perfluoroalkyl sulfides is such an example. Extreme conditions employing chromic anhydride or concentrated H_2O_2/trifluoroacetic anhydride[54] were used with limited success. The true potential of the $HOF{\cdot}CH_3CN$ complex could be realized here in full. Perfluoro-*n*-butyl *p*-tolyl sulfide (**13**), bis(perfluorophenyl) sulfide (**14**), and even the most hindered perfluoro-*tert*-butyl *p*-fluorophenyl sulfide (**15**) were all converted to the corresponding sulfones in higher than 90% yield, although a longer than usual reaction time of about 20 min was required (eq 21).[55]



13 Ar = *p*-$CH_3C_6H_4$; R_f = n-C_4F_9

14 Ar = R_f = C_6F_5

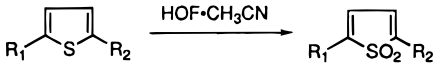
15 Ar = *p*-FC_6H_4 ; R_f = $C(CF_3)_3$

(21)

The unique combination of the $HOF{\cdot}CH_3CN$ complex's excellent ability to transfer oxygen atoms and the mild conditions under which such reactions take place help reach goals otherwise almost impossible to achieve. This was already demonstrated in the case of oxidation of amino acids[48] and is further emphasized in the reactions with thiophenes leading to the corresponding *S*,*S*-dioxides. In the past the synthesis of such oxidized thiophenes has not been easy. The main

(42) Rozen, S.; Ben-David, I. *J. Fluorine Chem.* **1996**, *76*, 145.
(43) Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* **1989**, *44*, 6095.
(44) Kol, M.; Rozen, S. *J. Chem. Soc., Chem. Commun.* **1991**, 567.
(45) Rozen, S.; Kol, M. *J. Org. Chem.* **1992**, *57*, 7342.
(46) Acharia, R. C.; Saran, N. K.; Rao, S. R.; Das M. N. *Int. J. Chem. Kinet.* **1982**, *14*, 143. Laloo, D.; Mahanti, M. K. *J. Chem. Soc., Dalton Trans.* **1990**, 311.
(47) Gogte, V. N.; Natu, A. A.; Pore, V. S. *Synth. Commun.* **1987**, *17*, 1421.
(48) Rozen, S.; Bar-Haim, A.; Mishani, E. *J. Org. Chem.* **1994**, *59*, 1208 .
(49) Kol, M.; Rozen, S. *J. Org. Chem.* **1993**, *58*, 1593.
(50) Gokel, G. W.; Gerdes, H. M.; Dishong, D. M. *J. Org. Chem.* **1980**, *45*, 3634.
(51) Pribe, W.; Gynkiewicz, G. *Tetrahedron Lett.* **1991**, *32*, 7353.
(52) Murray, R. W.; Jeyaraman, R.; Pilley, M. K. *J. Org. Chem.* **1987**, *52*, 746.
(53) Rozen, S.; Bareket, Y. *Tetrahedron Lett.* **1994**, *35*, 2099.
(54) (a) Kondratenko, N. V.; Popov, V. I.; Kolomeitsev, A. A.; Saenko, E. P.; Prezhdo V. V.; Lutskii, A. E.; Yagupolskii, L. M. *Russ. J. Org. Chem. (Engl. Transl.)* **1980**, *16* , 1049. (b) Robson, P.; Smith, T. A.; Stephens R.; Tatlow, J. C. *J. Chem. Soc.* **1963**, 3692.
(55) Beckerbauer, R.; Smart, B. E.; Bareket, Y.; Rozen, S. *J. Org. Chem.* **1995**, *60*, 6186.

obstacle arises from the difficulty in overcoming the aromatic stabilization, and once this is achieved the usually harsh conditions of oxidation encourage dimerization and other secondary reactions. With the electron-rich 2,5-dimethylthiophene (**16**), oxidation could be carried out with MCPBA[56] although in 52% yield and with long reaction times. HOF·CH_3CN gives the same product with higher than 95% yield and in less than 5 min. In 2,5-dibromothiophene (**17**), the sulfur atom is more electron poor, and peracids were no longer usable. Only dimethyldioxirane was able to convert it into the *S*,*S*-dioxide derivative, but in only 27% yield and with a reaction time of several days.[57] The reaction with HOF·CH_3CN was carried out at room temperature for 20 min and the product obtained in 95% yield. Thiophenes with stronger electron-withdrawing groups are usually beyond the oxidizing power of common oxidizers, since under the harsh conditions required the dioxides undergo secondary reactions. Indeed, 2,5-dichlorothiophene (**18**) has never been oxidized before, but a 2-fold excess of HOF·CH_3CN at room temperature for 20 min was sufficient to transform it into the corresponding *S*,*S*-dioxide in high yield (eq 22).[58]

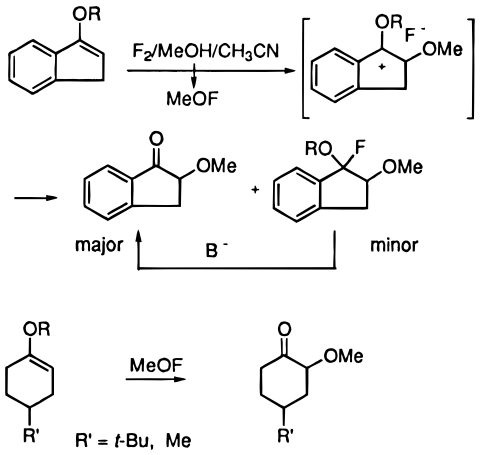


(22)

16 $R_1 = R_2 = Me$
17 $R_1 = R_2 = Br$
18 $R_1 = R_2 = Cl$

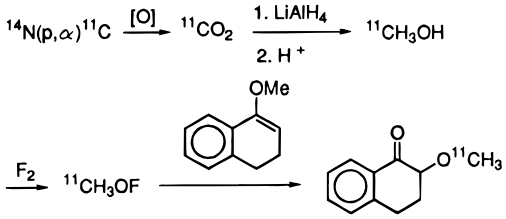
MeOF: The Smallest Unknown, until Recently, Organic Molecule

The only three smallest organic molecules which have not been made until recently were MeHe, MeO-He, and MeOF. At the beginning of this decade only the helium derivatives remained elusive.[59] What really helped the synthesis of methyl hypofluorite, which we wanted to prepare for more than 10 years, was our experience with the stabilizing effect of acetonitrile on the hypofluorous acid discussed above. Passing fluorine through a mixture of methanol and acetonitrile produced MeOF, which was later isolated and fully characterized.[60] Methyl hypofluorite is also unique because it is the only molecule which possesses a strong, electrophilic methoxylium species, which in analogy to the electrophilic fluorine, was represented as "MeO^+", leaving the oxygen-bound fluorine to act as a nucleophile. MeOF adds itself across many types of double bonds to produce CF−COMe adducts,[61] but what is more relevant to this Account is its reaction with electron rich olefin centers such as enol derivatives. We found that while enol acetates, silyl enol ethers, and enamines do react with MeOF, the best results were achieved with methyl enol ethers. Benzylic, cyclic, and alicyclic methyl enol ethers reacted with methyl hypofluorite, and after a few seconds, the corresponding α-methoxy carbonyl derivatives were formed in good yields through an addition−elimination mechanism (eq 23).[62]



(23)

This reaction opened a new route for introducing the short-lived ^{11}C isotope (half-life 20 min) into molecules important for the fast-developing PET technique used for chemical and medical research and diagnosis. A typical experiment is outlined in eq 24. The whole reaction sequence takes less than 50 min with an overall radiochemical yield of 10%.[63]



(24)

Recently we have succeeded in also making the higher homologue *t*-BuOF,[64] but its chemistry is still under development.

In conclusion, it is our hope that a clear message is being passed to the organic chemistry community: *Do not be intimidated by elemental fluorine.* The actual work is performed in regular glassware and is simple to execute. The commercial availability of prediluted fluorine makes the work for the occasional user even easier. The synthetic potential of this "forgotten" reagent seems to be remarkable and waits to be fully discovered.

I am deeply indebted to the graduate students who have brought life to the work described here. Their names are to be found in the appropriate references. Part of this research was supported by the Israel Science Foundation administrated by the Israel Academy of Science and Humanities and by the USA-Israel Binational Science Foundation (BSF), Jerusalem, Israel.

AR950106C

(56) van Tilborg, W. J. M. *Synth. Commun.* **1976**, *6*, 583.
(57) Miyahara, Y.; Inazu, T. *Tetrahedron Lett.* **1990**, *31*, 5955.
(58) Rozen, S.; Bareket, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1959.
(59) The existence of MeOF was first reported during the 1990 ACS meeting: Rozen, S.; Hebel, D.; Kol, M. 199th ACS National Meeting, Boston, MA, 1990; FLUO-17 (see also: *Chem. Eng. News* **1990**, May 7, 62).
(60) Kol, M.; Rozen, S.; Appelman, E. *J. Am. Chem. Soc.* **1991**, *113*, 2648.
(61) Rozen, S.; Mishani, E.; Kol, M.; Ben-David, I. *J. Org. Chem.* **1994**, *59*, 4281.
(62) Rozen, S.; Mishani, E.; Kol, M. *J. Am. Chem. Soc.* **1992**, *114*, 7643.
(63) McCarthy, T. J.; Bonasera, T. A.; Welch, M. J.; Rozen, S. *J. Chem. Soc., Chem. Commun.* **1993**, 561. McCarthy, T. J.; Bonasera, T. A.; Welch, M. J.; Rozen, S. *J. Labelled Compd. Radiopharm.* **1994**, *35*, 106.
(64) Appelman, E. H.; French, D.; Mishani, E.; Rozen, S. *J. Am. Chem. Soc.* **1993**, *115*, 1379.