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HOF·CH_3CN: Probably the Best Oxygen Transfer Agent Organic Chemistry Has To Offer

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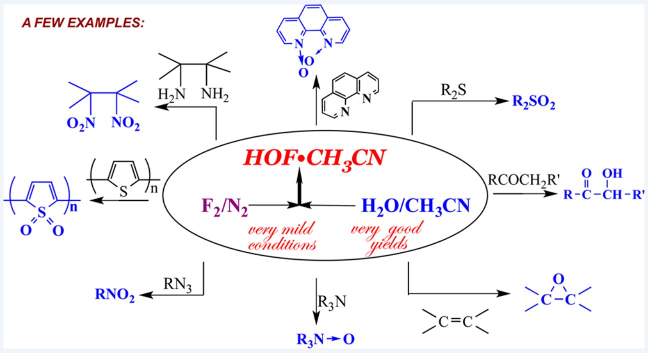


CONSPECTUS: The complex HOF·CH_3CN is readily obtained by bubbling dilute fluorine into aqueous acetonitrile solution. It does not have to be purified or isolated, and its solution can react as is, after the concentration has been establish by any iodometric method. It is the only reagent possessing a distinctive positive oxygen species. This enables electrophilic oxygen transfer with results no other reagent can match. HOF·CH_3CN demonstrates its ability in epoxidations that either could not be performed before or could only obtained 5 orders of magnitude slower. This complex is also an excellent tool for oxygenation of compounds at the α position of a carbonyl, including the synthesis of some hard-to-come-by indanediones, which are important for fingerprint visualization on paper. HOF·CH_3CN proves itself as a very efficient reagent for oxygenating tertiary nitrogen atoms both in aliphatic (including azides) and in aromatic amines, which could not be accomplished despite many attempts in the last 50 years. Oxygenation of two tertiary nitrogen atoms in the same molecule also becomes feasible as demonstrated for various phenanthrolines, bipyridines, diazafluorenones, and quinoxalines. It was also used to oxygenate primary amines, and because of the exceptionally mild conditions, it could transform vicinal aliphatic diamines to vicinal dinitro derivatives as well as amino acids to the corresponding nitro ones, practically unknown transformations before. Its ability to react with azines and hydrazones and convert them to the original carbonyls helped to establish these groups as good protecting tools for a variety of carbonyls.

HOF·CH_3CN excels in oxygenation of various sulfur and selenium compounds that could not be oxygenated in the past. The selectivity of the oxidation is quite good, and if there are alcohols, double bonds, and sulfides in the same molecule, usually the sulfur atom will be attacked first. Of special interest is the reaction with oligothiophenes resulting at will in either [all]-*S,S*-dioxooligothiophenes or in partially oxygenated ones. Some of these last derivatives have the narrowest HOMO−LUMO gap of all oligothiophenes tested, a very desirable feature. This reagent can also oxidize thiols or disulfides to either sulfonic or sulfinic acids at will, all in seconds and in very high yields.

Since the oxygen atom of HOF·CH_3CN originates in water, it is very easy and relatively inexpensive to introduce the heavy oxygen isotope in many sites of a variety of molecules, some of them quite important. The ^{18}O tirapazamine and any desirable alcohol, R(Ar)^{18}OH, are two examples.

■ INTRODUCTION

Up to about 30 years ago, elemental fluorine was a neglected agent as far as organic chemistry was concerned. Plenty of legends and prejudices were associated with it touching a sensitive core of fears based on its high reactivity. In the first half of the 20th century a few organic chemists tried to employ F_2, but most results did not encourage others to follow.[1] It was described by some as "extremely hazardous" relying on unfounded stories of others. Before continuing, however, let us clarify that fluorine is less toxic than chlorine,[2] and in the rare event of a leak, it cannot spread much, unlike chlorine or bromine, since it will react with most substances in its vicinity such as walls, wood, humidity, and so on. Constructing a simple vacuum line[3] from brass or monel in order to dilute the fluorine with N_2 or He or purchasing prediluted F_2 turns this element into a reagent that requires only a well ventilated area and good common sense, as do thousands of other reagents in chemistry.

One of the chemistry giants of the 20th century, Professor Sir Derek Barton, had been fascinated with fluorine chemistry and encouraged the author of this Account to start experimenting with this first halogen.[4] Soon we realized that diluted fluorine is a controllable reagent and its success depends on the efficiency of absorbing the heat released by any reaction of this element with organic substrates. We have also realized that reactions with F_2 have huge synthetic potential and started to develop, for example, regio- and stereospecific processes for fluorination and for activation of organic molecules at sites no other reagent could reach.[5−7]

Soon we concluded that secondary agents that have been constructed with fluorine could serve in a variety of fluorination reactions such as trifluoroacetyl hypofluorite,[8] acetyl hypofluorite,[9] and the real bromine and iodine fluorides,[10,11] including

Received: March 7, 2014
Published: May 28, 2014

dx.doi.org/10.1021/ar500107b | *Acc. Chem. Res.* 2014, 47, 2378−2389

BrF_3,[12] to mention just a few. In the mid 1980s, when we worked with acetonitrile as a solvent, which was either not dried or contained some methanol, we came across two reagents that did not produce any organofluorine derivative and yet resulted in clean products. We found that one of the reagents was methyl hypofluorite,[13] while the other proved to be a very important offspring of F_2, the acetonitrile complex of the hypofluorous acid, $HOF{\cdot}CH_3CN$, the main theme of this Account.[14] This reagent can be obtained in concentrations of up to 0.5 M just by bubbling nitrogen-diluted fluorine (10−15%) through aqueous acetonitrile (10% water in CH_3CN). Its composition has been proven by several analytical measurements including cryogenic X-ray diffraction.[15] Several theoretical works have been published on it with conclusions that were in good agreement with the experimental values. Martin carried out extensive ab initio and density functional studies and showed that indeed there is a strong hydrogen bond between the hydrogen atom of the HOF and the nitrogen of the acetonitrile. His calculations also suggested that the OH moiety acquires HO^+ character in the transition state for oxygen transfer.[16] Srnec dubbed the $HOF{\cdot}CH_3CN$ as an amazingly effective and universal reagent. One of his main theoretical contributions was the conclusion that a pair of HOF molecules seemed to be the best arrangement for the oxygen transfer process.[17]

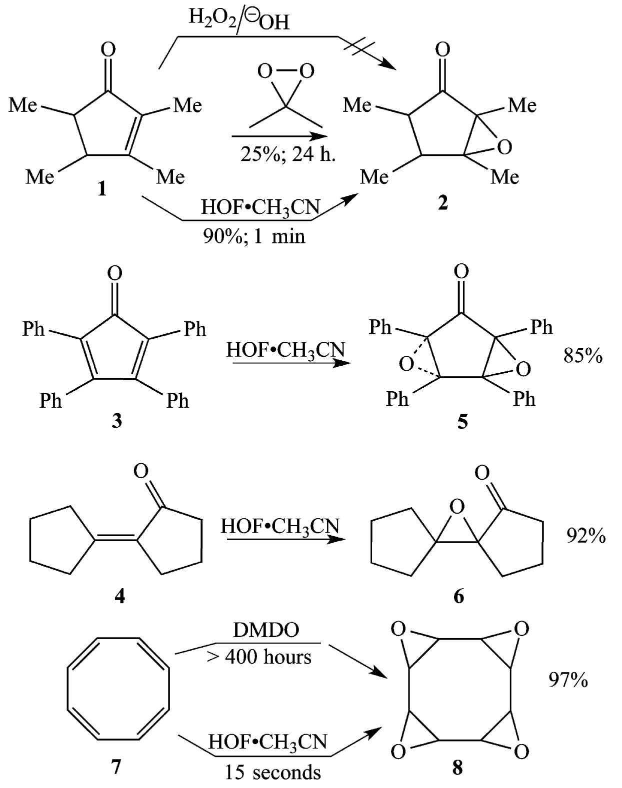
Hypofluorous acid itself was first made and isolated in low yields by Appelman already in the early 1970s by passing F_2 above the surface of very cold ice.[18] Most of its physical properties were measured, but the cumbersome synthesis and isolation and extremely low stability severely limited its use in organic synthesis. We were lucky to discover that acetonitrile complexes with this acid, increasing its lifetime to a few hours at 0 °C or room temperature and even a few days at −78 °C. This acquired stability enabled us to use this complex in a large variety of reactions without much time limitation and carry them out in standard, open to air, glass vessels. It also should be noted at this stage that no isolation or purification of the $HOF{\cdot}CH_3CN$ complex is necessary and its concentrations could be conveniently determined by any iodometric method. While reactions between H_2O and F_2, as well as between $HOF{\cdot}CH_3CN$ and most substrates, produce HF, the presence of water and the very short reaction times (seconds to few minutes) prevented the acid from damaging the glass reaction vessels.

Some of the first reactions of F_2 leading to synthesis of fluorine-free molecules have been already included in our previous Account.[19] This Account describes novel processes associated with $HOF{\cdot}CH_3CN$ leading to materials that usually cannot be obtained by any other means.

■ EPOXIDATIONS

The first set of reactions performed with $HOF{\cdot}CH_3CN$ were epoxidations of a few simple olefins. Although they are obtained rapidly and in excellent yields, epoxidation methods have been known for more than a century. Still, there were some classes of olefins that were very difficult or even impossible to epoxidize. Thus, for example, epoxides of tetra-substituted and especially electron depleted double bonds have rarely been described, and when they were, they had been prepared by multistep reactions over prolonged times and in low yields. Typical examples can be found in Scheme 1. *cis*-2,3,4,5-Tetramethyl-2-cyclopentenone (**1**) resisted epoxidations by basic H_2O_2, gave 2% of the epoxide **2** with *meta*-chloroperoxybenzoic acid (MCPBA) and gave 25% of the epoxide when brought in contact with dimethyldioxirane (DMDO) for 24 h. Repeating the reaction of this olefin with $HOF{\cdot}CH_3CN$ at room temperature for a minute resulted in the epoxide **2** in higher than 90% yield. Similarly, tetraphenylcyclopentadienone (**3**) and 2-cyclopentylidenecyclopentanone (**4**) were converted to the corresponding diepoxides **5** and **6** in 85% and 92% yields, respectively (Scheme 1).[20] Another interesting comparison with DMDO is the epoxidation of cyclooctatetraene (**7**). In the past, it was fully epoxidized to the tetraoxide **8** by excess of dioxirane, but that was achieved only after 17 days (almost 15 × 10^5 s). The $HOF{\cdot}CH_3CN$ achieved similar results, but one hundred thousand times faster (15 s).[21]

Scheme 1

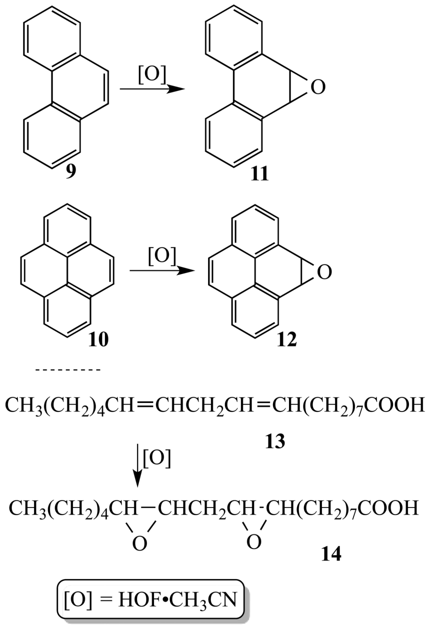


Phenanthrene (**9**) or pyrene (**10**) could also be epoxidized to the corresponding **11** and **12** in good yields and in seconds.[22] Unsaturated unprotected carboxylic acids either resisted direct epoxidation or required very long treatment with various peracids in the presence of heavy metals producing the epoxides in 50−70% yield at best. $HOF{\cdot}CH_3CN$ epoxidized such acids in very high yield and in minutes as evident from the reaction of linoleic acid (**13**) producing **14** almost quantitatively in 3 min (Scheme 2).[23]

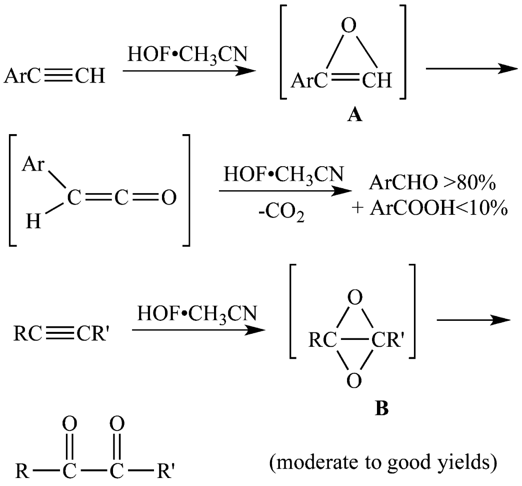
Acetylenes have also been subjected to this oxygen transfer reagent. The mono- (A) and bisepoxides (B) were assumed to be intermediates en route to the final products which, in the case of terminal acetylenes, were mainly rearranged aldehydes and, in the case of internal ones, were mainly 1,2-diketones (Scheme 3).[24]

A few years ago Sandford developed a continuous flow methodology using microreactors to form various epoxides by the above reagent in high yields. It seems that such a method is preferred over the batch reactions and has much to offer when large scale syntheses are proposed.[25]

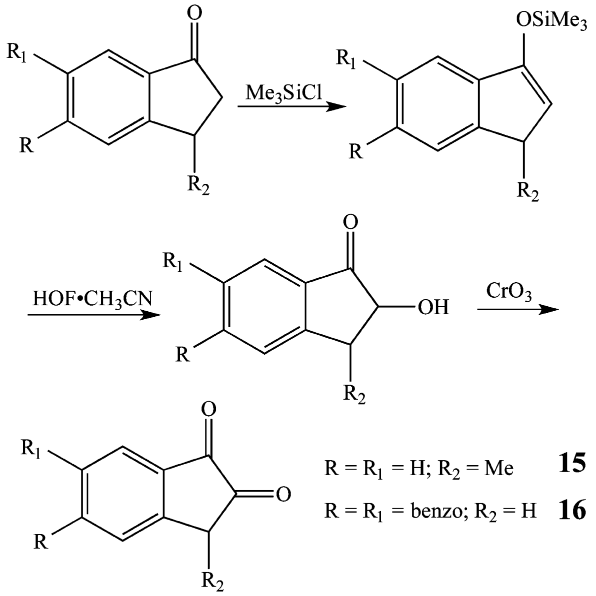
Scheme 2



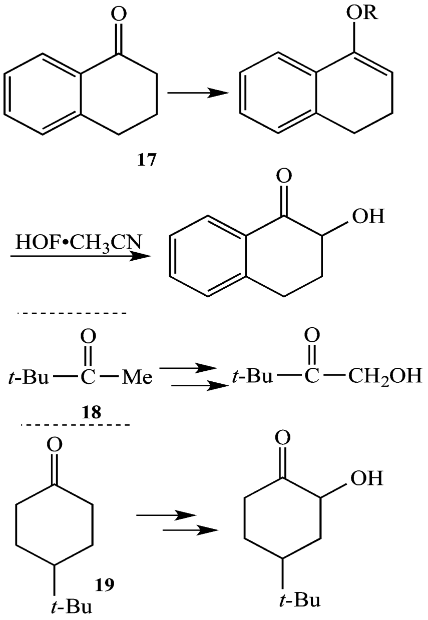
Scheme 3



Scheme 4



Scheme 5



■ *α*-HYDROXY CARBONYLS

At one time, we were approached by the Israeli Police Crime Investigation Department asking to find a general synthesis for some indanediones, which were making their debut as important ingredients for fingerprint visualization on paper.[26] Quite a few derivatives (e.g., **15** and **16**) however, could not be prepared by conventional methods. The HOF·CH_3CN helped through hydroxylation of the corresponding enol derivative, followed by a simple oxidation of the formed hydroxy ketone to produce the desired compounds (Scheme 4).[27]

Obviously, the reaction is not confined to indanones. Tetralone (**17**), pinacolone (**18**), or 4-*t*-butylcyclohexanone (**19**) are a few additional examples of a wide variety of aromatic, aliphatic, and cyclic ketones, most of which hydroxylated in 5 min and in >90% yield (Scheme 5).[28]

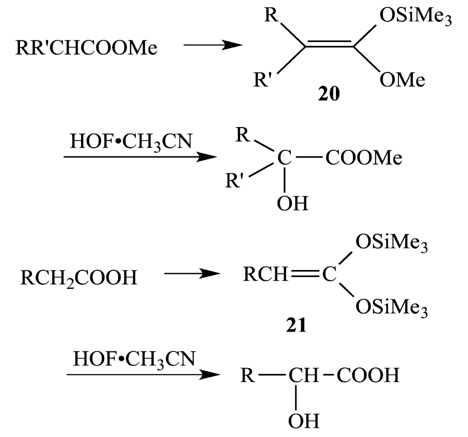
This reaction is also operative in very good yields for both esters and free carboxylic acids. In the first case, the reaction proceeds through the corresponding trimethylsilyl ketene acetals **20**, while bis(trimethylsilyl acetals) **21** had to be prepared when free carboxylic acids were the substrates (Scheme 6).[29]

■ OXYGENATION OF THE NITROGEN AND PHOSPHORUS ATOMS

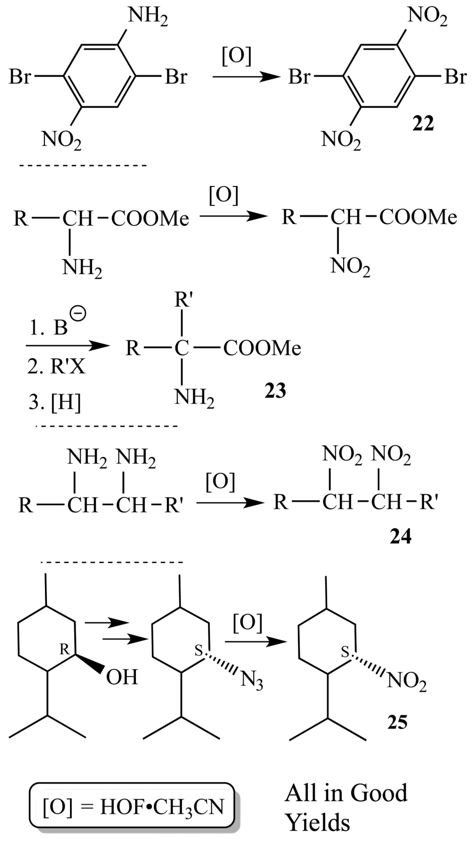
From Amines and Azides to Nitro Compounds

Quite a few years ago, we described the clean oxidation of simple aromatic[30] and aliphatic amines[31] to their corresponding nitro derivatives. Tour has continued this line of research and produced several dinitroarenes (**22**), some of which were good candidates for electronic devices (Scheme 7).[32] While understandably simple amines are relatively easy to oxidize, it is not so with amino acids since the usual harsh conditions required caused either decarboxylation or deamination. HOF·CH_3CN transfers oxygen in very short reaction times and under very mild conditions, so we were able to oxidize most amino acids to

Scheme 6



Scheme 7



the corresponding α-nitro ones. This presented a good opportunity to prepare α-alkylamino acids (**23**) believed to be important in the fight against Parkinson's and Alzheimer's diseases (Scheme 7).[33,34]

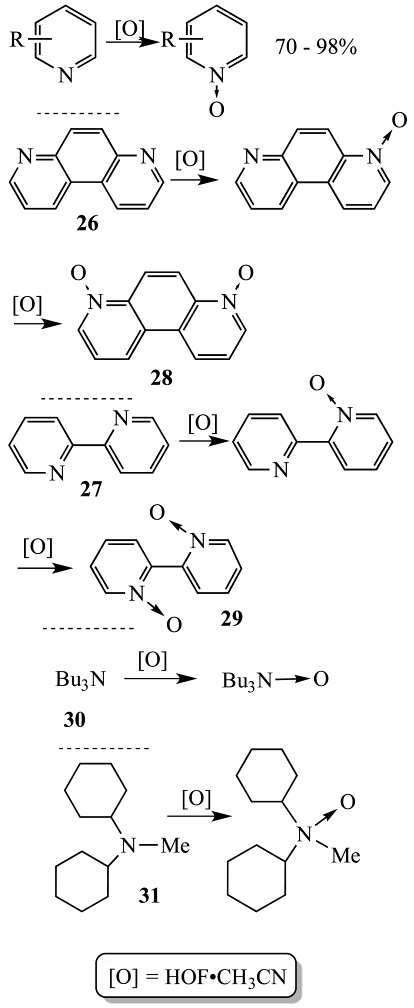
HOF·CH_3CN was also able to oxidize aliphatic vicinal diamino groups to vicinal dinitro ones (**24**) in very good yields. It should be noted that this is not an easy task, and in the past 1,2-dinitro derivatives could only be made by addition of dinitrogen tetraoxide (N_2O_4) to olefins with low yields (Scheme 7).[35]

An important and somewhat related reaction is the novel transformation, exclusive to the HOF·CH_3CN, of azides to nitro compounds in very good yields and with retention of configuration (e.g., menthol **25**) (Scheme 7).[36,37]

The Reactions of HOF·CH_3CN with Tertiary Amines

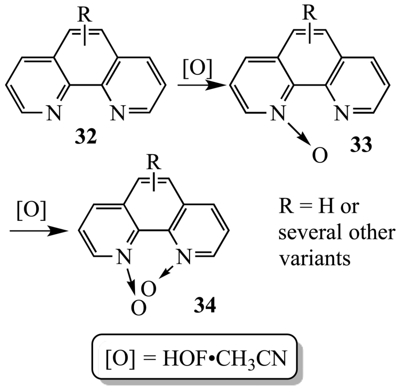
Being an electrophile, the oxygen in HOF·CH_3CN easily forms *N*-oxides with tertiary amines, either aliphatic or aromatic. Pyridine, 4,7-phenanthroline (**26**) or 2,2-bipyridine (**27**) were transformed after treatment with one mole-equivalent of HOF·CH_3CN to the corresponding mono *N*-oxides, but using excess of the reagent gave the respective *N*,*N*-dioxide **28** and **29** in good yields. Tertiary aliphatic amines also form effortlessly the tertiary *N*-oxides as demonstrated by tributylamine (**30**), *N*,*N*-dicyclohexyl-*N*-methylamine (**31**) and quite few other tertiary amines (Scheme 8).[3]

Scheme 8



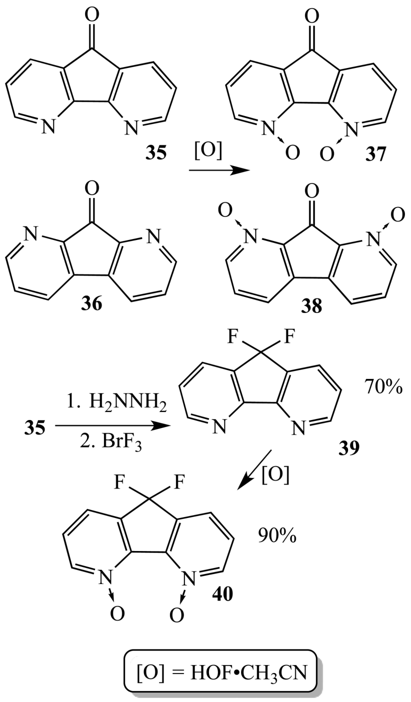
Maybe the most impressive result from this reagent was demonstrated by its reaction with 1,10-phenanthroline **32**. For decades, chemists including Woodward and Corey have tried in vain to prepare 1,10-*N*,*N*-dioxophenanthroline (**34**), but all they got was the mono-*N*-oxide **33** since there is no space in the bay area of **32** to accommodate two oxygen atoms. When HOF·CH_3CN was reacted with **32** for 5 min, the mono-*N*-oxide **33** was obtained in high yield. However, increasing the amount of the reagent to about 3-fold excess resulted instantaneously in the elusive 1,10-*N*,*N*-dioxophenanthroline **34** in higher than 60% yield. The lack of space for the two oxygens was addressed by deforming the phenanthroline and taking it out of planarity forming in the process the smallest known helicene.[38] It should be pointed out that other derivatives of **32** did not pose any resistance either and all formed the corresponding *N,N*-dioxides (Scheme 9).[39]

Scheme 9



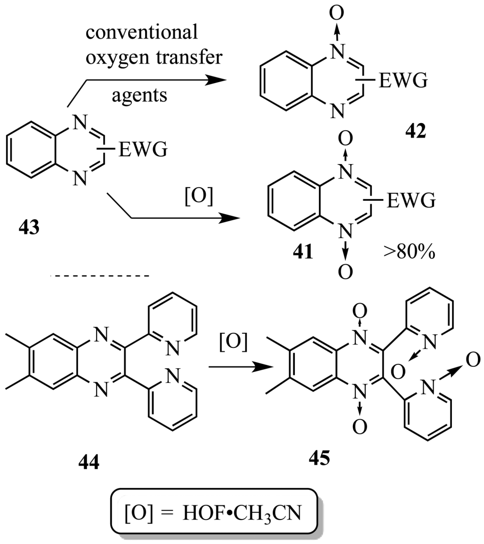
A somewhat related situation was met with diazafluorene compounds, which are of considerable interest in connection with various organic electronic devices. It was challenging to oxidize both nitrogen atoms in certain diazafluorenones such as **35** and **36**. As with **34** most of the *N,N*-dioxodiazafluorenones could not be prepared by orthodox oxidizing agents, but HOF·CH_3CN helped to form the *N,N*-dioxo derivatives **37** and **38** in short reaction times and in 90−95% yield. Even when the carbonyl in such compounds was replaced by the strong electron-withdrawing CF_2 group as in **39**,[40] it was still possible to attach two oxygen atoms to the two nitrogens and form the desirable **40** in 90% yield (Scheme 10).[41]

Scheme 10



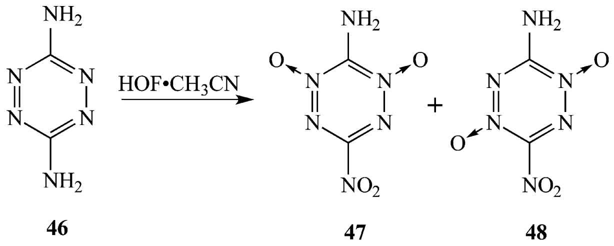
Another important pharmaceutical family of compounds containing two nitrogen atoms is the quinoxaline *N,N*-dioxo derivatives **41** used as antibacterial agents. Usually after the first oxidation forms **42** (e.g., with $K_2S_2O_8$), it becomes quite difficult to attach an additional oxygen to the second nitrogen atom because its basicity decreases considerably. If on top of that the original molecule possesses an extra electron-withdrawing group (**43**), such double oxidation becomes impossible, but not for the HOF·CH_3CN complex. This reagent oxidized both nitrogen atoms in various quinoxalines bearing electron-donating groups (EDGs), electron-withdrawing groups (EWGs), or aromatic rings, all in very good yields. An interesting demonstration is provided by 6,7-dimethyl-2,3-di(2-pyridyl)quinoxaline (**44**) where all four nitrogen atoms were oxygenated (**45**) in 80% overall yield (Scheme 11).[42]

Scheme 11



Since HOF·CH_3CN can oxidize both primary and tertiary nitrogens, it was used by Hiskey to prepare energetic materials. One of the starting compounds was 1,4-diaminotetrazine (**46**), which produced upon contact with the reagent molecules having both nitro and *N*-oxide moieties (**47**) and (**48**), which proved to be powerful explosives (Scheme 12).[43]

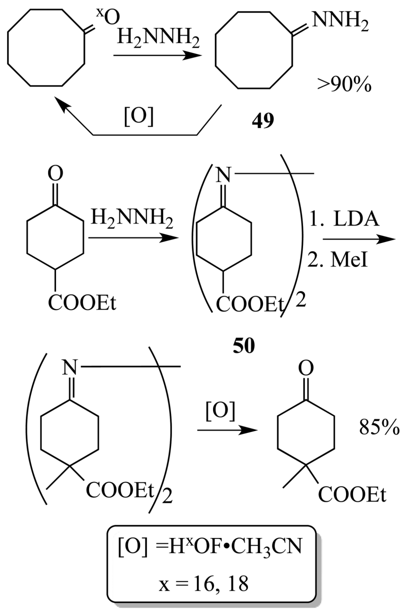
Scheme 12



The formation of stable hydrazones and azines from carbonyls is very easy and proceeds with almost quantitative yields. The main disadvantage for using these derivatives as protecting groups is the difficulty to reclaim the original carbonyls. HOF·CH_3CN solves this problem in a remarkable way. Both hydrazones (**49**) and azines (**50**) react with the reagent in seconds to generate the carbonyls usually in very good yields. This reaction offers also a good way for constructing carbonyls with the ^{18}O isotope (Scheme 13).[44]

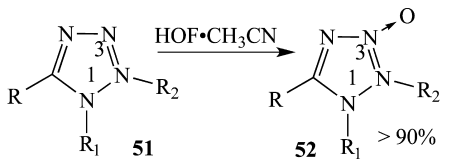
The tetrazole ring (**51**) can be found in quite a few drugs. It was agreed though, that this heterocycle could not be oxidized because of its low HOMO.[45] Again an opportunity was provided for the HOF·CH_3CN to perform another first in organic

Scheme 13



synthesis. The strong electrophilic oxygen of the reagent was able to attach itself to the *N*-3 atom (**52**) in a wide variety of tetrazole derivatives (Scheme 14).[46]

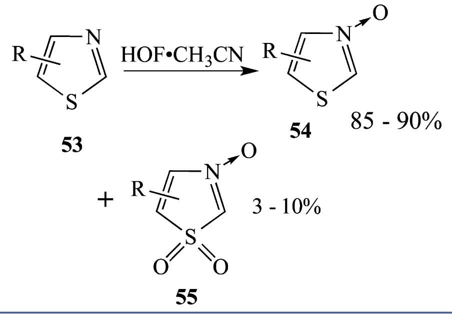
Scheme 14



R_1 = H; R_1, R_2 = various substituents or
R, R_1 = various substituents; R_2 = H

The family of thiazole derivatives (**53**) has been also subjected to oxygenation because of its important role in certain antibiotics. When its members were reacted with HOF·CH_3CN, only the nitrogen atom was affected, and the thiazole *N*-oxides (**54**) were rapidly formed in good yields. A small portion (<10%) of the corresponding *N,S,S*-trioxo derivatives (**55**) could also be detected, but they are soluble in water and hence easy to remove (Scheme 15).[47]

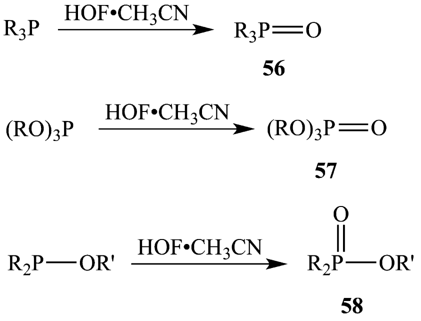
Scheme 15



Oxygenation of Various Phosphorus Containing Compounds

Although several reagents can oxidize the phosphorus atom, Shreeve showed that HOF·CH_3CN can readily perform this oxygen transformation faster and in good yields. Thus, phosphines, phosphites, and phosphinites were transformed into the corresponding phosphine oxides (**56**), phosphates (**57**), and phosphinates (**58**) (Scheme 16).[48]

Scheme 16



OXYGENATION OF THE SULFUR AND SELENIUM ATOMS

Oxygen Transfer to Sulfur Compounds

Oxidation of sulfides to sulfones is a very old procedure in organic chemistry. However, when it comes to electron deficient sulfides (e.g., Rf-S-R(Ar) Rf > CF_3), all common reagents fail to produce sulfones in satisfactory yields since their oxygen atoms are not sufficiently strong electrophiles. With HOF·CH_3CN, perfluoroalkyl aryl(alkyl) sulfides (**59**) were transformed for the first time to the corresponding sulfones (**60**) quickly and in very high yields (Scheme 17).[49] This ability was also exploited for constructing the CF_3, $CF_2{}^{18}F$, important for PET studies[50] and terminal difluoroolefins (**64**)[51] via dithioesters (**61**), difluorosulfones (**62**), and the olefins (**63**) (Scheme 17).

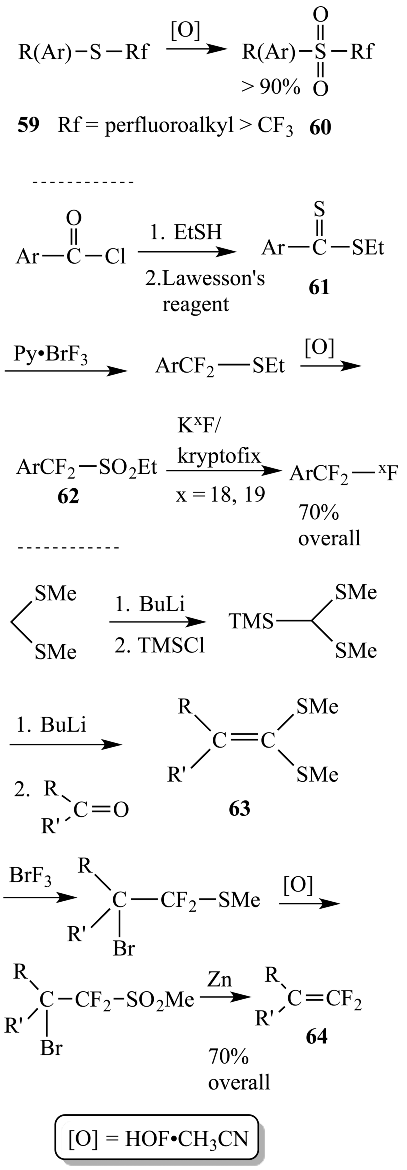
Although hydroxyls and olefins do react with HOF·CH_3CN,[52] sulfides usually react faster as demonstrated by **65** and **65a** (Scheme 18). Another observed important phenomenon was the formation of sulfones from sulfides with almost no sulfoxides to be detected. This is due to hydrogen bonds forming a cluster of HOF molecules thus ensuring that the second electrophilic oxygen is always in the vicinity of the reacting sulfur (**66**, Scheme 18). Such clusters can be broken by adding protic solvents enabling formation of sulfoxides (**67**, Scheme 18).[17,53]

The difference in reactivity is also demonstrated by the reaction of HOF·CH_3CN with various thioglycosides converted to glycosyl sulfones. When **68** was reacted, the sulfur at 2 was oxidized forming **69** without affecting the aromatic nitrogen or sulfur atoms (Scheme 19).[54]

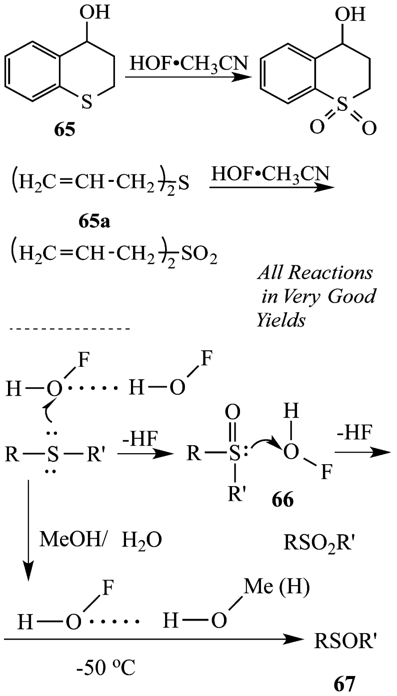
Sulfides were not the only sulfur containing substrates subjected to the oxygen transfer reactions. Thiols (**70**) and disulfides (**71**) were also successfully reacted with HOF·CH_3CN. In seconds at 0 °C, they were converted to sulfonic acids (**72**) in very good yields. At −40 °C, however, the respective sulfinic acids (**73**) were formed (Scheme 20).[55]

The very mild conditions characteristic of all HOF·CH_3CN reactions, combined with the reagent's extraordinary ease of transferring oxygen atoms, offer an entry to reactions that are usually denied to orthodox oxidizing agents. The formation of α-nitro acids from amino acids (see Scheme 7) is one example and transferring episulfides **74** to episulfones (**75**) is another. Very few derivatives of this family are known, and they are

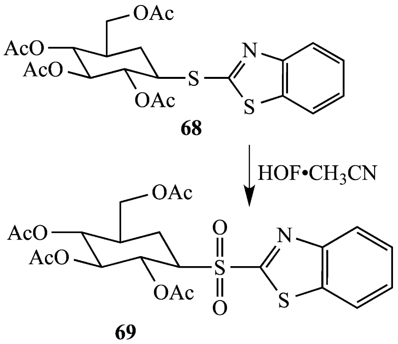
Scheme 17



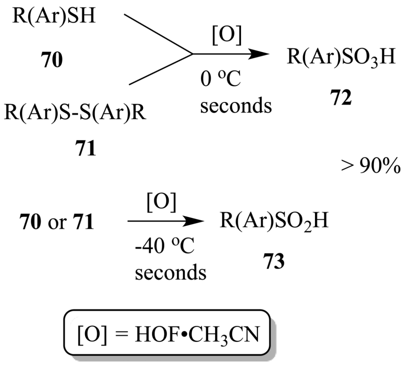
Scheme 18



Scheme 19



Scheme 20



usually made by total synthesis or in a single case by hexafluorodimethyldioxirane in low yields. HOF·CH_3CN provides a general route for preparing episulfones in seconds at 0 °C and in 80−90% yield (Scheme 21). Since it is easy to prepare this reagent with the ^{18}O isotope and since it is possible to prepare episulfoxides (**76**) with common peracids, one can readily make episulfones with an exact combination of the oxygen isotopes. Heating episulfones can release S^xO^yO (x and y being any combination of 16 and 18), rare molecules that despite many attempts could not be made in a well-defined composition before (Scheme 21).[56]

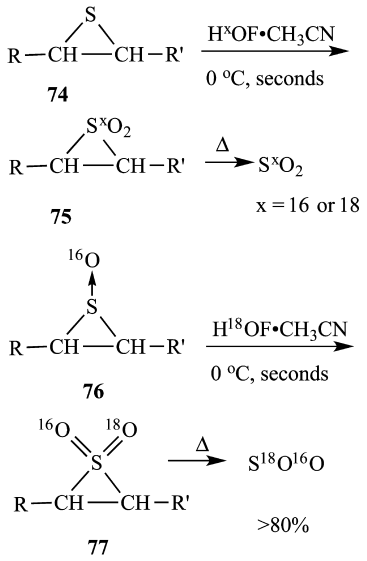
Oxygen Transfer to Organoselenium Compounds

Organoselenium compounds are easily oxidized to selenoxides, but unlike organosulfur derivatives, there is no general protocol for forming selenones (R_2SeO_2) because of the vigorous conditions needed, which can cause thermal instability. As in many other cases, HOF·CH_3CN finds an unique role here as well. Treating selenides (**78**) with a slight excess over 2 equiv of the reagent produced the generally unknown selenones (**79**). Only when very electron depleted selenides, such as bis(pentafluorophenyl)selenide (**80**), served as a substrate, the corresponding selenoxide (**81**) was obtained exclusively (Scheme 22).[57]

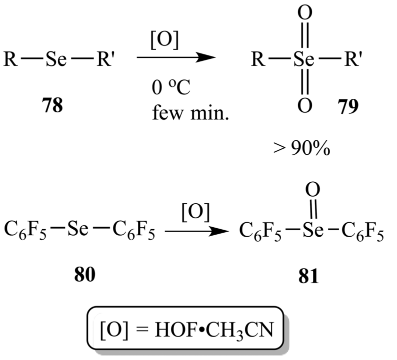
■ THE *S,S*-DIOXOOLIGOTHIOPHENES

Oligothiophenes are probably the most important group in today's research in organic chemistry. Tens of thousands of

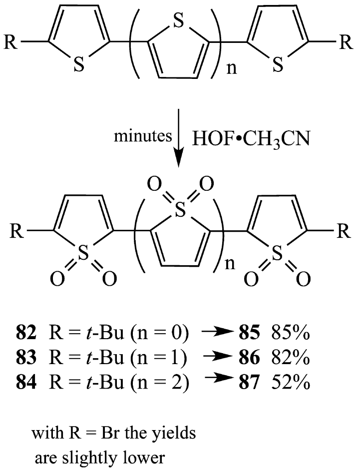
Scheme 21



Scheme 22



Scheme 23



publications have appeared in the last 15 years on this subject alone, mainly because of the electronic conjugation between the individual heteroaromatic rings. This increases their potential to be used in electronics based on organic materials. The very same aromaticity, however, hampers to some extent the full electronic conjugation along the oligomer. Already in the 1980s, it was postulated that if the aromaticity would be destroyed, the resulting polyene will have better electronic properties based on the HOMO−LUMO gap, ionization potential, and electron affinity. This could be achieved, the theory claimed, by oxidizing all sulfur atoms in the oligomer.[58] The only problem was that this prediction could not be verified since no oxygen transfer agent was able to attach oxygen atoms to all sulfur atoms in terthiophene and higher oligomers. Only some of the sulfur atoms, especially at the end rings, could be oxidized. This task was therefore assigned to the HOF·CH$_3$CN complex.

HOF·CH$_3$CN reacted successfully with dithiophenes (**82**), terthiophenes (**83**), and quaterthiophenes (**84**) to produce in good yields the all-*S*,*S*-dioxide derivatives (**85**, **86**, and **87**) with HOMO−LUMO gap indeed considerably reduced (Scheme 23).

Hawker used soluble [all]-*S*,*S*-dioxothiophenes made with HOF·CH$_3$CN as monomers for polymerization via microwave assisted Stille coupling to narrow the polymer band gap.[59] He also spun films from such semiconducting polymers and studied extensively spectroscopic phenomena, concluding that these polymers have lower optical and electrical band gaps.[60]

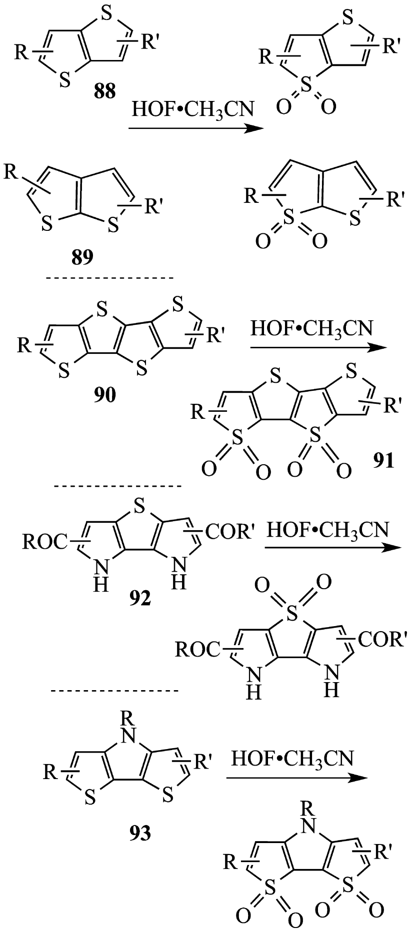
Compared with the starting oligothiophenes, the actual HOMO−LUMO gaps were indeed reduced for every [all]-*S*,*S*-dioxo derivative by 0.7−0.86 eV, in good agreement with the results obtained by DFT calculations.[61] More measurements, including electrochemical studies and extensive Raman spectroscopy were also performed. The main conclusion was that they resembled polyenes but were much more thermally stable.[62]

Bi-, tri-, or polycyclic fused oligothiophenes, being of the [3,2-*b*] (**88**) or [2,3-*b*] (**89**) family, were also subjected to reactions with HOF·CH$_3$CN. In no case could both adjacent rings be oxidized. It seems, and DFT calculations confirm, that once one sulfur was oxygenated, the basicity of the second was so reduced that no electrophile could attack it. In tricyclic or higher fused oligothiophenes (**90**), the oxidation took place on alternate sulfur atoms (**91**). Fused thienopyrrols, **92** or **93**, have also been treated with HOF·CH$_3$CN, and only the sulfur atoms were oxidized despite the presence of EWGs. What may have been of some help is the nearby NR group, which activates the sulfur atom by conjugation (Scheme 24).[63−65]

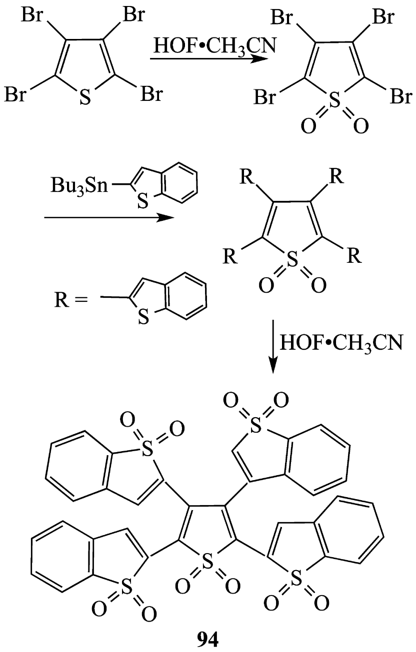
Two additional issues remained unresolved in the field of oligothiophenes prior to reactions with HOF·CH$_3$CN. The first dealt with the interesting category of star oligothiophenes, a group of compounds showing promising characteristics for development of electronic materials based on organic compounds. It was of interest to prepare [all]-*S*,*S*-oxygenated star oligothiophenes. Several members of this family were prepared, and the [all]-*S*,*S*-dioxo-2,3,4,5-tetrabenzothienylthiophene (**94**) made in a few steps can serve as an example (Scheme 25).[66]

The second question was about the number and ordering of the oxidized thiophene rings needed in the oligomeric chain. There were some predictions (which could not be verified at the time) that the best arrangement in quarterthiophene, for example, should consist of only two oxidized rings at the center of the molecule. We have prepared, for the first time, such compounds (**95**), and indeed their HOMO−LUMO gaps were the narrowest and the reduction potential highest compared with the starting materials or other partially oxidized oligothiophenes. It should be emphasized that the very good thermal stability also contributes to their promising potential (Scheme 26).[67] Very recently Campos partly oxygenated

Scheme 24

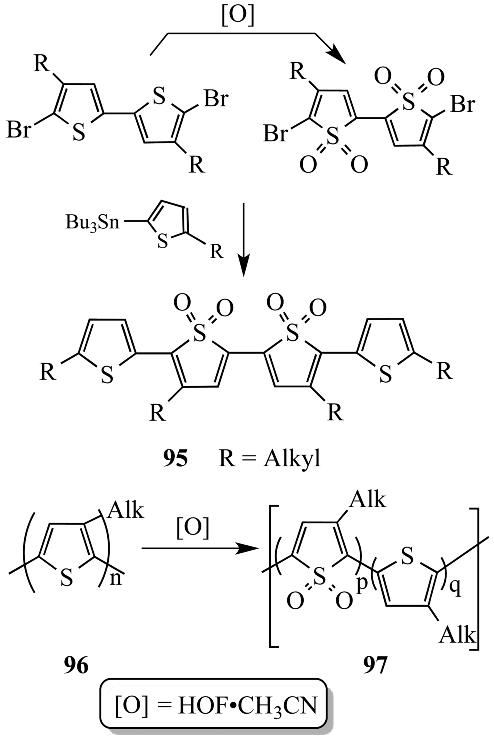


Scheme 25



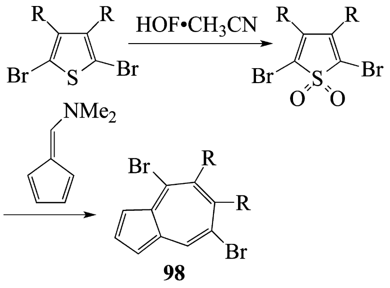
polythiophenes (**96**) to obtain chains having some *S,S*-dioxothiophene units (**97**). Such polymers exhibit low lying LUMO and hence a small band gap (Scheme 26).[68]

Scheme 26



An additional somewhat unexpected use of oxygenated thiophenes was described by Hawker and Campos who used them as tools for making azulenes (**98**), which were then incorporated into certain polymers (Scheme 27).[69]

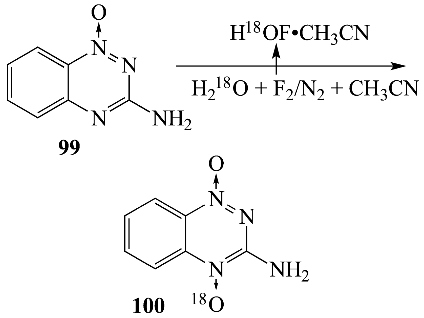
Scheme 27



■ WHEN THE INTRODUCTION OF THE ^{18}O ISOTOPE MATTERS

We have already seen in several cases that in all new oxygenation reactions leading to compounds that could not be made prior to the appearance of HOF·CH$_3$CN, one has a choice to introduce any oxygen isotope at will, since H$_2{}^x$O (x = 16, 17, 18) is the source for the electrophilic oxygen. One such important case was the synthesis of tirapazamine (**100** with both ^{16}O), which is in clinical trials as promising anticancer agent. For studying the mechanism by which this drug operates, it was crucial to prepare **100** with the heavier oxygen isotope. This was achieved by reacting the 1-oxide-3-amino derivative (**99**) with H^{18}OF·CH$_3$CN resulting in **100** in 70% yield (higher for derivatives other than the amine) (Scheme 28).[70]

Scheme 28



The second case consisted of alcohols having ^{18}O isotopes. Obviously there are numerous ways to make alcohols, but not a single one is suitable for introducing the heavy oxygen isotope in a one step reaction. This was recently achieved by reacting aryl (or alkyl) boronic acid (**101**) with $H^{18}OF\cdot CH_3CN$ to produce $Ar(R)^{18}OH$ (**102**) with higher than 90% yields (Scheme 29).[71]

Scheme 29

$$\underset{\mathbf{101}}{R(Ar){-}B(OH)_2} \xrightarrow{H^{18}OF\cdot CH_3CN} \underset{\mathbf{102}}{R(Ar){-}{}^{18}OH} \quad >90\%$$

CONCLUSION

Elemental fluorine was first isolated in 1886. For nearly a century, the chemical community missed somehow the opportunity to work with this element despite the enormous importance of fluorine-containing compounds in our life. Once the mythical fears of working with it are starting to fade away, one can discover the huge potential of this element not only for synthesizing fluorine-containing derivatives (pharmaceuticals, agriculture, polymers, and much more) but also for accessing fluorine-free organic materials that could not be made before, the main theme of this Account. We believe that the organic chemistry of F_2 is still in its infancy and many interesting surprises lay ahead of it.

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Funding

This work was supported by the Israel Science Foundation

Notes

The author declares no competing financial interest.

Biography

Shlomo Rozen was born in Bulgaria and immigrated to Israel as a small child. He received his Ph.D. from the Hebrew University of Jerusalem and then spent 3 years in the Research Institute for Medicine and Chemistry, Cambridge, MA, under D. H. R. Barton, R. H. Hesse, and M. M. Pechet, where he began work with elemental fluorine. In 1976, he joined the School of Chemistry at the Tel Aviv University were he assumed the position of Professor of Chemistry in 1989. On multiple occasions he had held a position of visiting scientist at the Central Research Department of the DuPont Company. His main goal in chemistry is to demonstrate that elemental fluorine and reagents derived from it are very useful in general organic chemistry, as well as in fluorine chemistry, and chemists should discard their unjustified fears and prejudice against this long known but somewhat neglected element.

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