

## HOF·CH<sub>3</sub>CN, an excellent oxygen transfer agent\*

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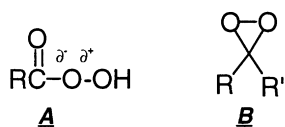
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**Abstract:** A short review on the new oxygen transfer agent HOF·CH<sub>3</sub>CN is presented. Although very potent, this reagent is used under very mild reaction conditions, a fact that enables it to perform transformations of which other reagents are incapable. It epoxidize any double bond, including very deactivated ones, in short reaction times and high yields. It also efficiently oxidizes amines to nitro derivatives and transform sulfides, even highly deactivated ones, into the corresponding sulfones. It is also useful for hydroxylation  $\alpha$  to a carbonyl of many ketones, esters and acids. HOF·CH<sub>3</sub>CN is easily prepared by bubbling mixtures of fluorine and nitrogen through aqueous acetonitrile [1–12].

In recent years the HOF·CH<sub>3</sub>CN complex has proven to be probably the best oxygen transfer agent. Its uniqueness is based on the oxygen atom being bonded to the only element with higher electronegativity—fluorine, turning the oxygen into a strong electrophile. Its reactions have been shown to be ionic in nature and are usually complete in a few minutes at temperatures ranging from 0°C to 25°C.

HOF·CH<sub>3</sub>CN is easily prepared in a matter of minutes in a glass reactor by bubbling about 10% F<sub>2</sub> in N<sub>2</sub> through an aqueous acetonitrile solution (10% H<sub>2</sub>O in CH<sub>3</sub>CN) at 0°C. Concentrations of 0.25–0.5 M are readily achieved and are monitored by any iodometric titration method. No isolation, purification or other manipulation of the reagent are required. Contrary to the general belief, working with fluorine is no more complicated than working with any other corrosive gas such as chlorine, especially as premixed mixtures of 10% F<sub>2</sub> in N<sub>2</sub> are now commercially available.

One of the major uses of the HOF·CH<sub>3</sub>CN reagent is an epoxidation of practically any type of olefin, deactivated or not. Practically all current direct epoxidation methods use reagents possessing the peroxy moiety. The reason for this is the high electronegativity of oxygen and hence the relative ease of inducing a small positive pole on the adjacent oxygen atom, especially if helped by additional factors, such as resonance stabilization of a leaving carboxylic group (**A**) or strain relief in the small dioxirane ring (**B**) (Scheme 1) [1].

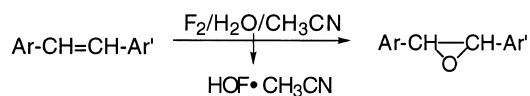


Scheme 1

HOF·CH<sub>3</sub>CN enjoys a permanent positive pole on the oxygen turning it into a very strong electrophile indeed. It takes less than a minute for *trans* or *cis* stilbene (**1**) or (**2**) to react with the reagent at 0°C producing *trans* or *cis* stilbene oxide (**3**) or (**4**), respectively, in higher than 90% yield. Substituted stilbenes were successfully epoxidized, even with very electron deficient double bonds as in *trans* 4,4'-dinitrostilbene (**5**), which produced (**6**) in 70% yield (Scheme 2) [2].

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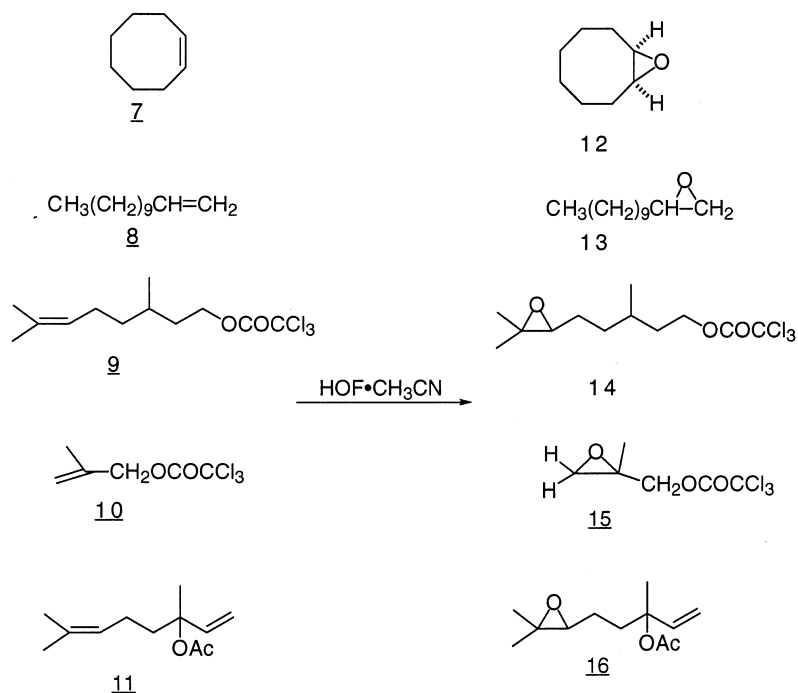
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<u>1</u>	Ar = Ar' = Ph ( <i>trans</i> )	<u>3</u>
<u>2</u>	Ar = Ar' = Ph ( <i>cis</i> )	<u>4</u>
<u>5</u>	Ar = Ar' = <i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ( <i>trans</i> )	<u>6</u>

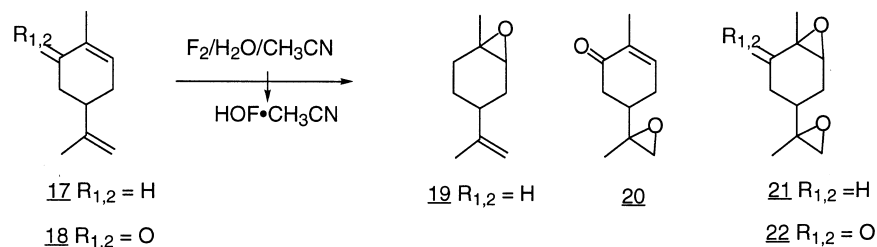
## Scheme 2

The epoxidation is not confined to benzylic olefins. Cyclooctene (**7**), 1-dodecene (**8**), β-citronellol trichloroacetate (**9**), methallyl alcohol trichloroacetate (**10**) and linalyl acetate (**11**) to name just few, were instantaneously converted to the corresponding epoxides **12–16** in excellent yields (Scheme 3).



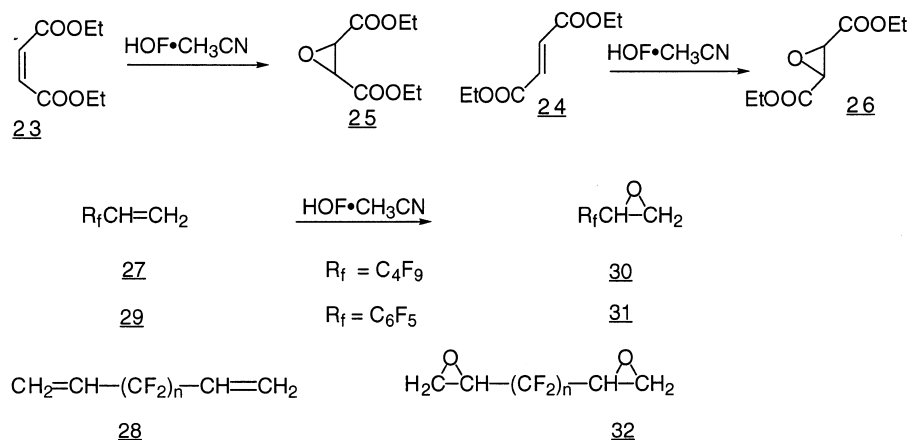
## Scheme 3

In the case of a molecule with more than one double bond the more electron rich one can be selectively epoxidized. Limonene (**17**) and R(-) carvone (**18**) demonstrate this selectivity and the products proved to be 1,2-epoxylimonene (**19**) and 2-methyl-5-(2-methyloxiranyl)-2-cyclohexene-1-one (**20**), respectively. Using excess reagent led to limonene and carvone dioxides **21** and **22** (Scheme 4).



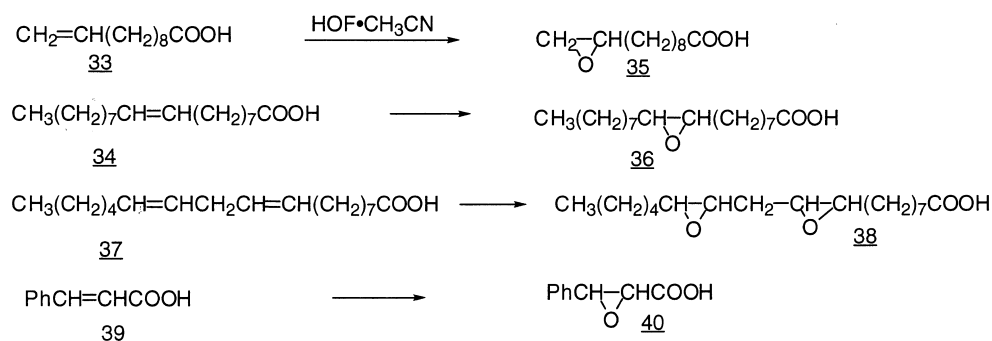
## Scheme 4

The double bonds in diethyl maleate (**23**) and fumarate (**24**) are very electron deficient. Still with a large excess of HOF·CH<sub>3</sub>CN *cis* (**25**) and *trans* (**26**) diethyl epoxysuccinate were, respectively, obtained in good yields [3]. The same situation is present in many polyfluoro olefins of which some are important intermediates in the synthesis of surfactants, oligomers and polymers with special properties. Thus 1,1,2-3*H*-perfluorohex-1-ene (**27**), polyfluorinated dienes such as **28** or pentafluorophenylethene (**29**), which could not be efficiently epoxidized by any other method, were converted into their epoxides **30–32** with this reagent which is made from fluorine and water (Scheme 5) [4].



Scheme 5

There are known difficulties with direct epoxidation of unprotected acids and many reagents require esterification as the first step. This is not the case with the HOF·CH<sub>3</sub>CN.  $\Delta^{10}$ -Undecanoic as well as oleic acid (**33** and **34**) reacted in a matter of 3 min, and the only organic products found were the corresponding epoxy acids (**35** and **36**) obtained in 90% yield. Linoleic acid (**37**) with its two double bonds had been bis-epoxidized in the past by reacting it with a variety of peracids, achieving yields of 35% after many hours. Applying twofold excess of HOF·CH<sub>3</sub>CN formed the diepoxide **38** in a clean reaction (90% yield) in 3 min. The electron poor *trans*-cinnamic acid (**39**) was also reacted to give the sensitive epoxide **40** in higher than 90% yield (Scheme 6) [5].

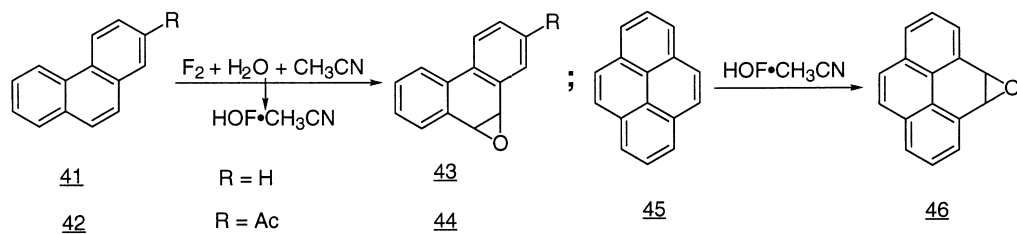


Scheme 6

Another important group of labile organic compounds whose chemistry and biological properties have given rise to a great deal of interest are polynuclear arene oxides. Several preparation routes have been attempted, but the epoxidation yields seldom exceeded 40–50%. The HOF·CH<sub>3</sub>CN complex seems to be useful here as well.

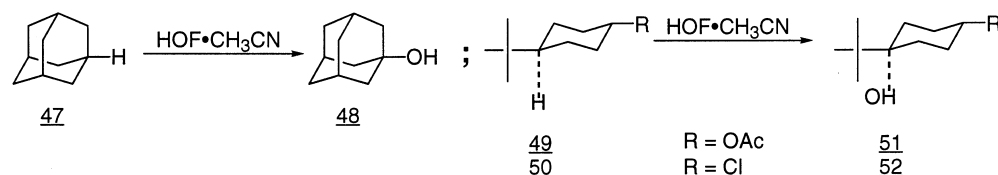
Phenanthrene (**41**) and 2-acetyl phenanthrene (**42**) were reacted with HOF·CH<sub>3</sub>CN for 30–60 s forming the desired oxides **43** and **44** in 80% yield. Pyrene (**45**) seems to be even more reactive and it took

only 5 s to obtain pyrene-4,5-oxide (**46**) in 80% yield (65% conversion), considerably higher than in any other published method (Scheme 7) [6].



**Scheme 7**

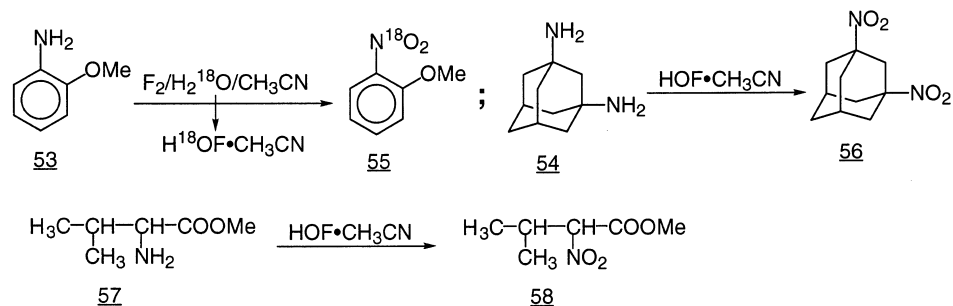
Like the electrophilic  $F_2$ , the hydroxylum pole of  $HOF \cdot CH_3CN$  can react with a tertiary, relatively electron rich CH bond, with a full retention of configuration. Thus, when adamantane (**47**) is treated with the oxidative solution, only a tertiary hydrogen is substituted resulting in 80% yield of 1-adamantanol (**48**). Molecules with electron withdrawing groups somewhat deactivate the tertiary CH bond, but in many cases not enough to completely prevent the reaction. The cases of *trans* acetoxy- or chloro-4-*t*-butylcyclohexane (**49** or **50**) which were hydroxylated with a full retention of configuration in 35% yield forming **51** or **52**, demonstrate this trend (Scheme 8).



**Scheme 8**

$HOF \cdot CH_3CN$  was also utilized for oxidation of various amines, both aliphatic and aromatic, to the corresponding nitro derivatives. In general the reactions are very fast and the yields excellent. A couple of representative examples are 2-methoxyaniline (**53**) and 1,3-diaminoadamantane (**54**) which were transformed into the respective nitro derivatives **55** and **56**. It should be noted that in all cases  $H_2^{18}O$  could be used as shown for the preparation of methoxynitrobenzene (**55**) in which two heavy oxygen atoms bonded to the nitrogen atom were incorporated [7].

On the one hand  $HOF \cdot CH_3CN$  is a powerful reagent, but on the other it reacts under very mild conditions. This helped to oxidize for the first time practically any amino acids to the desired  $\alpha$ -nitro acid. Thus the methyl ester of valine (**57**) was transformed into methyl 2-nitro-3-methylbutanoate (**58**) in 5 min and in higher than 80% yield (Scheme 9) [8].

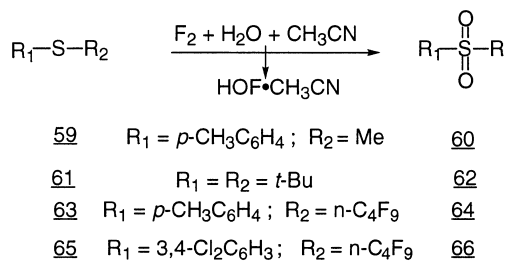


**Scheme 9**

Oxidizing sulfides to sulfones is a well established procedure. The transformation however, requires either lengthy treatment with metal containing oxidants or the use of various peroxides including

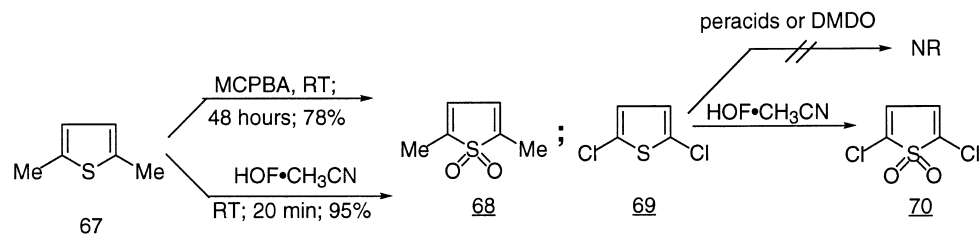
dimethyldioxirane. In addition the completion of the reactions may require many hours and high temperatures. The HOF·CH<sub>3</sub>CN complex is an excellent oxidant for sulfur atoms and it rapidly oxidizes practically any sulfide to the corresponding sulfone in very high yields at room temperature or below. Methyl-*p*-tolyl sulfide (**59**) was oxidized to the corresponding sulfone **60** in quantitative yield in 4–6 min. Aliphatic sulfides behave similarly and even the sterically hindered *tert*-butyl sulfide (**61**) was easily converted to the corresponding sulfone **62**.

While there are a number of alternatives for oxidizing sulfides, there is practically none for clean oxidation of very electron deficient ones. There have been reports of attempts to oxidize perfluoroalkyl sulfides to sulfones with oxidants such as chromic anhydride or concentrated H<sub>2</sub>O<sub>2</sub> in trifluoroacetic acid/trifluoroacetic anhydride, but even these potent oxidants were not very efficient. The HOF·CH<sub>3</sub>CN complex did succeed where the other oxidants failed, although large excesses of the reagent were employed and long reaction times of up to 10–30 min were required. Thus, perfluorobutyl *p*-tolyl sulfide (**63**) was converted into the sulfone **64** and similarly the even more electron depleted 3,4-dichlorophenyl perfluorobutyl sulfide (**65**) was oxidized to the corresponding sulfone **66** (Scheme 10).



**Scheme 10**

Oxidizing the heteroatom of thiophenes is challenging since there are two complementing difficulties involved. On the one hand the reaction has to overcome a substantial aromatic stabilization, requiring relatively harsh conditions. On the other, the nonaromatic *S,S*-dioxide products are sensitive to Diels–Alder and other *ene* and *diene* reactions strongly facilitated by high temperatures and prolonged reaction times. As with the oxidation of amino acids described above, HOF·CH<sub>3</sub>CN is powerful enough to act quickly and at the same time under the mildest possible conditions. For example, 2,5-dimethylthiophene (**67**), was oxidized in the past to the *S,S*-dioxide **68** with either MCPBA (hours, 78% yield) or dimethyldioxirane (90% yield). With HOF·CH<sub>3</sub>CN, higher than 95% yield of **68** was obtained in a few minutes. With 2,5-dichlorothiophene (**69**), the sulfur atom is more electron depleted and is beyond the oxidizing power of the traditional oxidizers. HOF·CH<sub>3</sub>CN oxidized it at room temperature to 2,5-dichlorothiophene-*S,S*-dioxide (**70**) in 70% yield in about 30 min (Scheme 11) [9].

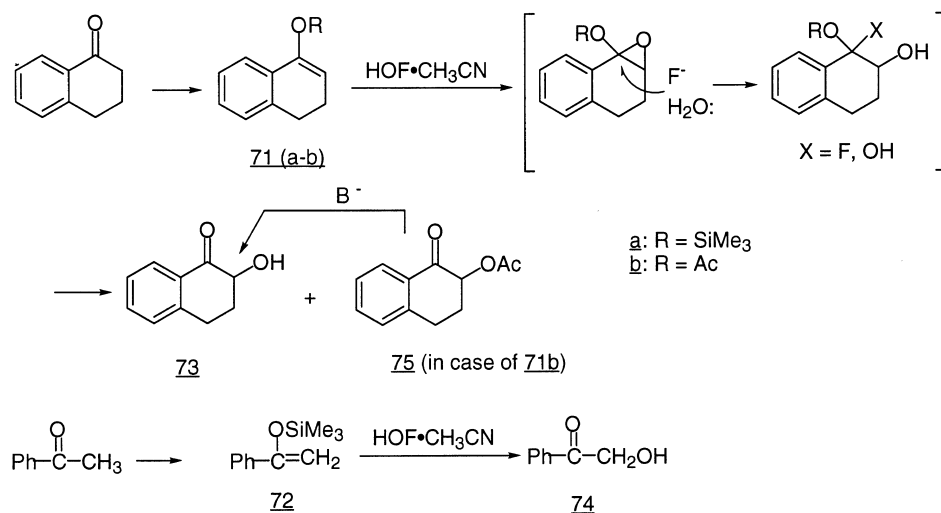


**Scheme 11**

The synthesis of  $\alpha$ -hydroxy carbonyl derivatives has been of continuous interest to organic chemists since the beginning of the century. Classical methods have been supplemented in more recent years by several polluting heavy metal containing oxidants. Here too, HOF·CH<sub>3</sub>CN plays a very positive role.

Benzylic enol derivatives such as tetralone trimethylsilyl enol ether (**71a**) or its enol acetate (**71b**) and acetophenone trimethylsilyl enol ether (**72**) were reacted at room temperature with the reagent forming  $\alpha$ -hydroxytetralone (**73**) and  $\alpha$ -hydroxyacetophenone (**74**) in higher than 90% yield, each in a matter of 5–10 min [10].

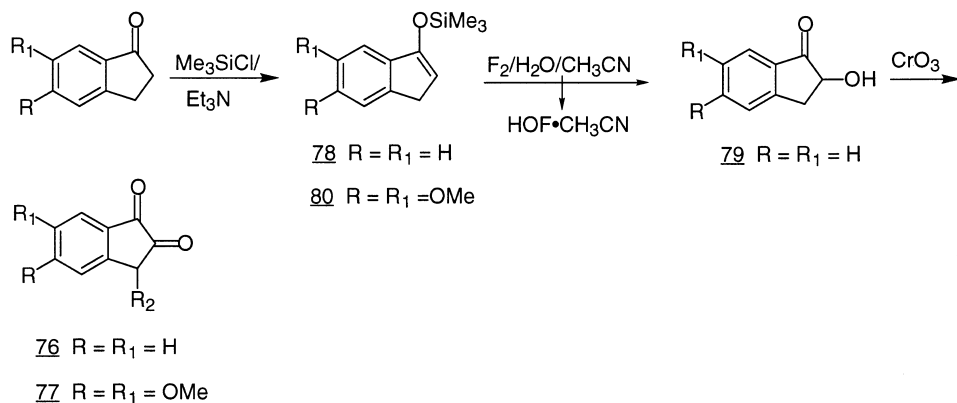
Although we have not isolated any intermediates in these reactions, it is quite likely that they proceed through the epoxidation of the enolic double bond. The epoxide is opened subsequently by either the nucleophilic fluoride ion or a water molecule present in the reaction mixture. This is supported by the isolation of the expected **73** in 50% yield along with 2-acetoxytetralone (**75**) which was also isolated in 50% yield. This second product resulted from a known type of rearrangement of enol acetate epoxides and could be hydrolyzed back to **73** bringing the overall hydroxylation yield to near quantitative (Scheme 12).



Scheme 12

Recently, it has been indicated that 1,2-indandione (**76**), and some of its derivatives, particularly 5,6-dimethoxy-1,2-indandione (**77**), can visualize latent fingerprints by direct fluorogenic reaction [11]. This immediately sprang a series of efforts to prepare such derivatives.

Several methods for preparing this family of compounds are described in the literature but none appears to be of general use. The  $\alpha$ -hydroxylation method described above found here an additional use. We prepared the trimethylsilyl enol ether of 1-indanone (**78**), and reacted it with HOF·CH<sub>3</sub>CN. The reaction was completed in 3–4 min forming 2-hydroxy-1-indanone (**79**) in good yield. The hydroxyl group was then oxidized with chromic acid forming the desired **76** in 65% overall yield from 1-indanone. This sequence of reactions was similarly efficient with other indanones including 5,6-dimethoxy-1-indanone (**80**) leading to **77** in good overall yield (Scheme 13) [12].



Scheme 13

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