Oxidative Cleavage of Methyl Ethers Using the HOF·CH_3CN Complex

Shlomo Rozen,* Sharon Dayan, and Yifat Bareket

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel

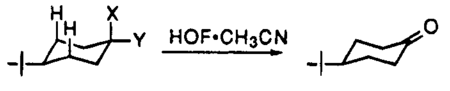
Received June 29, 1995⊗

HOF·CH_3CN complex, made easily by bubbling fluorine diluted with nitrogen through aqueous acetonitrile, proved to be a suitable oxidizer for various methyl ethers. Secondary ethers are oxidized to ketones and even to lactones via Baeyer–Villiger type of oxidation. The reaction is ionic, and the reagent's electrophilic oxygen attacks the relatively electron rich C–H bond α to the ether moiety. It was found that the more sterically hindered is the C–H bond in question, the slower the reaction. In cases where this bond is an electron poor one as in benzoin methyl ether (**9**), no reaction takes place. When labeled $H^{18}OF·CH_3CN$ is used on a ^{16}O methyl ether, the resulting ketone possesses only the heavier oxygen isotope. Primary methyl ethers are somewhat slower to react, but they too were oxidized in very good yields to acids via the corresponding aldehydes.

The HOF·CH_3CN complex is proving itself to be an outstanding oxidizer, since the powerful electrophilic oxygen is bonded to the most electronegative atom—fluorine. Oxidation of various heteroatoms and aromatics, tertiary hydroxylations and epoxidation of practically any type of double bond are some of its recorded successes.[1] HOF·CH_3CN is easily prepared by bubbling either commercial or self-prepared mixtures of 10%–15% F_2 in nitrogen through aqueous acetonitrile. It offers very mild conditions: a range of reaction temperatures between 0 and 25 °C during times lasting from a few seconds to 3–4 h for most stubborn cases.[2] We are aware of the fact, as one reviewer pointed out, that the "use of F_2 would deter most chemists of using the HOF·CH_3CN method". This attitude, however, is changing quite rapidly since it lacks any real foundations. In any event, oxidizing procedures based on the HOF·CH_3CN complex, offer safe, heavy metal free, and environmentally friendly oxidizing opportunities. Synthetically speaking, often the results obtained with this reagent could not be duplicated by other methods. We present here yet another use of this oxidizing complex in converting primary and secondary methyl ethers to acids and ketones, respectively.

Oxidative cleavage of ethers is rarely described in the literature. A few publications deal specifically with benzyl ethers[3] and ketals,[4] while others promote reagents such as UF_6,[5] nitrates on silica gel[6] and, more recently, dimethyldioxirane reacting with some steroidal ethers.[7]

When *trans*-4-*tert*-butylcyclohexanol methyl ether (**1**) was reacted with a ~5-fold excess of HOF·CH_3CN in the presence of NaF, 4-*tert*-butylcyclohexanone (**2**) was obtained in 90% yield. With the cis isomer **3**, however, the reaction was faster, and only an ~3-fold excess of the oxidant was needed for the same results.[8] When *endo*-2-norborneol methyl ether (**4**) served as the substrate, a 2-fold excess of the oxidant was sufficient to convert it into 2-norbornanone (**5**) in 80% yield, while with *exo*-2-norborneol methyl ether (**6**) an 18 times excess had to be used to get similar results.

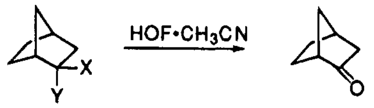


1 X = H; Y = OMe

3 X = OMe; Y = H

2

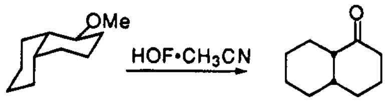
oxidation of 3 and 4 is faster than 1 and 6



4 X = H; Y = OMe

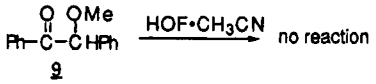
6 X = OMe; Y = H

5



7

8



9

Although some of the previously described ether oxidation reactions seem to proceed via a radical pathway,[6,9] the reaction with HOF·CH_3CN appears to be of ionic

---

⊗ Abstract published in *Advance ACS Abstracts*, November 1, 1995.

[1] (a) Rozen, S.; Bareket, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1959 (thiophene oxidation). (b) Kol, M.; Rozen, S. *J. Chem. Soc., Chem. Commun.* **1991**, 567 (amine oxidation). (c) Hung, M. H.; Smart, B. E.; Feiring, A. E.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 3187 (fluoroolefin epoxidation). (d) Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325 (CH activation).

[2] Such prolonged reaction times were recorded for tertiary hydroxylations (ref 1b), epoxidation of extremely electron poor double bonds (ref 1c), and certain Baeyer–Villiger oxidations (ref 10).

[3] Angibeaud, P.; Defaye, J.; Gadelle, A.; Utille, J. P. *Synthesis* **1985**, 1123.

[4] Nishiguchi, T.;Ohosima, T.; Nishida, A.; Fujisaki, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1121 and references therein.

[5] Olah, G. A.; Welch, J. *J. Am. Chem. Soc.* **1978**, *100*, 5396.

[6] Nishiguchi, T.; Bougauchi, M. *J. Org. Chem.* **1989**, *54*, 3001.

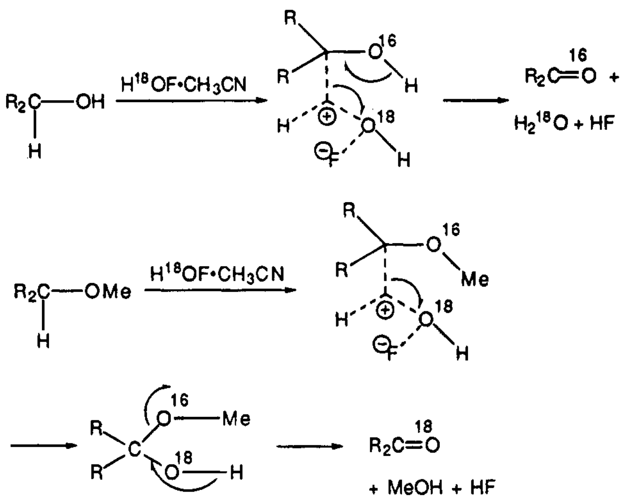
[7] Heerden, F. R.; Dixon, J. T.; Holzapfel, C. W. *Tetrahedron Lett.* **1992**, *33*, 7399.

[8] In the case of HOF·CH_3CN complex, as with the cases of other reagents such as AcOF or MeOF which have limited stability at the reaction temperatures, an excess of a reagent does not have the usual meaning. Completing a reaction in 1 min by using a 2-fold excess does not necessarily mean that by prolonging its time to 10 min a much smaller excess will be required. We still do not know all the factors governing the decomposition rate of the reagent during the reaction, and it may vary from one experiment to another. Thus, all the numbers associated with the excess of the reagent in this work should be considered as general guidelines and not necessarily as absolute values.

[9] Ferrer, M.; Baeza, F. S.; Casas, J.; Messeguer, A. *Tetrahedron Lett.* **1994**, *35*, 2981.

0022-3263/95/1960-8267$09.00/0

Scheme 1

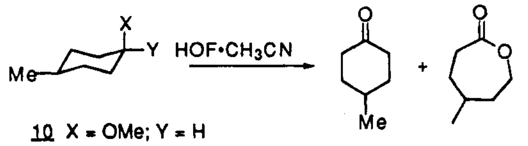


nature. On the one hand we have carried out the oxidation reaction of **4** in the presence of radical scavengers such as oxygen and dinitrobenzene and on the other under strong sun lamp irradiation. In both cases the outcome was essentially identical as in the absence of these factors.

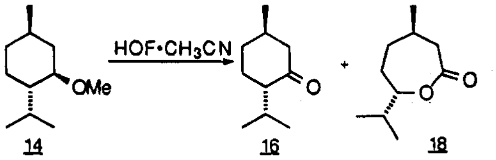
We believe that as with the previously described alcohol oxidation,[10] the electrophilic oxygen in $HOF\cdot CH_3CN$ attacks the electron rich C−H bond α to the oxygen atom in the ether moiety forming a two-electron three-centered nonclassical ion (see Scheme 1) which is characteristic of electrophilic attacks on saturated centers.[11] Such a pathway is facilitated eventually by the consecutive HF elimination step. The addition of NaF helps absorb some of the HF present, which otherwise would partially protonate the methyl ether oxygen and lower the electron density of the adjacent CH bond. In its absence larger amounts of oxidant are usually required. According to the proposed mechanism the oxidation rate is dictated by steric factors around the C−H bond in question, and obviously the approach to the axial hydrogen in **1** and to the endo one in **6** is more hindered than in the corresponding more easily oxidized isomers **3** and **4**. Similar reasoning explains the slow oxidation (10-fold excess of $HOF\cdot CH_3CN$) of *cis*-decalin-2-ol methyl ether **7**, where the approach to the axial hydrogen α to the methoxy group is quite hindered. Nevertheless, **7** was converted to *cis*-2-decalone (**8**) in 75% yield. In compounds where the CH bond α to the methoxy group is more electron depleted than usual, as in benzoin methyl ether (**9**), the electrophilic oxygen of the $HOF\cdot CH_3CN$ complex could not attack this bond efficiently and no reaction took place even after prolonged treatment with large excess of the oxidant.

An additional support for the proposed mechanism is found through labeling experiments. In the past we have used the $HOF\cdot CH_3CN$ complex for oxidation of alcohols to ketones.[10] By working with an ^{18}O labeled oxidant we have shown that the resultant carbonyl oxygen atom is the same as in the unlabeled alcohol, suggesting that while the hydride-like C−H bond α to the hydroxyl moiety was attacked by the oxidant's electrophilic oxygen, the hydroxyl proton was then eliminated before having a chance for complete formation of the corresponding *gem*-diol (see Scheme 1). In contrast, oxidizing ethers such as **4** with $H^{18}OF\cdot CH_3CN$ resulted in a full incorporation of the ^{18}O isotope in the carbonyl's ketone. Since no alcoholic proton elimination is possible in this reaction, a hemiketal is formed which then decomposes to the corresponding ketone by elimination of MeOH, with complete incorporation of the labeled ^{18}O atom and formation of ^{18}O-**5** [MS: $m/e = 112$ (M^+)].

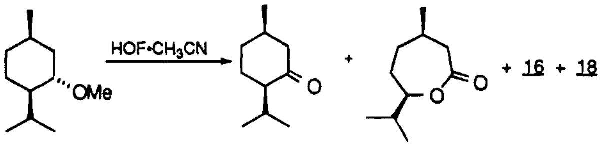
As with alcohols,[10] it is difficult in some cases, for reasons not yet completely understood, to stop the oxidation at the ketone level and a lactone formation is observed in a Baeyer−Villiger type of reaction. Thus, *cis*-4-methylcyclohexanol methyl ether (**10**) was fully consumed after treatment with a 5-fold excess of $HOF\cdot CH_3CN$ at room temperature, producing a 40% yield of 4-methylcyclohexanone **11** along with an additional 50% yield of the corresponding lactone (**12**) [MS: $m/e = 128$ (M^+)].[12] Obviously, if desired, either **10** or **11**, and for this matter any alcohol and ketone mentioned in this work, could be easily converted to **12** and any other corresponding lactone, by prolonging the reaction time. The isomeric *trans*-4-methylcyclohexanol methyl ether (**13**) gave similar results, but the amount of the oxidizer used had to be doubled in accordance with our previous findings on the influence of steric effects on this reaction. The same trend was observed with menthol (**14**) and isomenthol (**15**) methyl ethers. For complete conversion of **14** an about 12 times excess of the $HOF\cdot CH_3CN$ complex was needed, while half of this was sufficient for a full conversion of **15** where the attacked hydrogen is equatorial in some important contributing conformers. In both cases right from the beginning, both the corresponding ketones (**16** or **17** [MS: $m/e = 154$ (M^+)][13]) and lactones (**18** or **19**[14]) were obtained, the ratio of lactone/ketone increasing with the reaction time. It should be noted that while the oxidation of **14** is very clean and only **16** (30% yield) and **18** (65% yield) were obtained, the reaction with **15** resulted in a mixture of both ketones **16** and **17** (5% and 10% yield, respectively) along with both lactones **19** (53% yield) and **18** (26% yield). Apparently, some of the isomenthone **17** was converted under the reaction conditions to the more thermodynamically stable menthone **16** through enolization, enabling the consequent formation of the corresponding lactone as well.



10 X = OMe; Y = H
13 X = H; Y = OMe
11 **12**



14 **16** **18**



15 **17** **19**

---

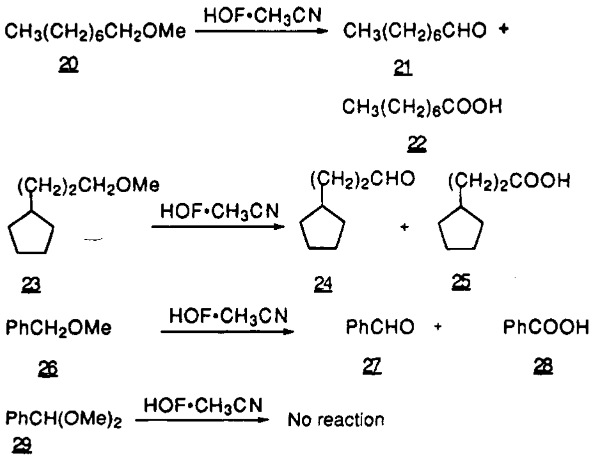
[10] Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169.

[11] (a) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769. (b) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 4928. (c) Olah, G. A.; Prakash, G. K. S.; Williams, R. E.; Field, L. D.; Wade, K. *Hypercarbon Chemistry;* Wiley: New York, 1987.

Primary methyl ethers have also been reacted with $HOF\cdot CH_3CN$ complex usually with very good results. For example, monitoring the reaction of 1-octanol methyl ether (**20**) with the oxidant showed that octanal (**21**) and octanoic acid (**22**) were formed almost simultaneously, and by the time a full conversion of the ether was achieved (using around 18 molar excess of $HOF\cdot CH_3CN$), a 20% yield of the aldehyde and 75% yield of the acid were the only organic components in the reaction mixture. A full Baeyer–Villiger type of oxidation of the aldehyde to the acid was achieved by using even greater oxidant excess. It should be noted that in a competitive reaction between octanal (**21**) and the methyl ether (**20**) it could be shown that while the aldehyde reacts somewhat faster than the ether, the differences are not striking. Thus, when a mixture of equimolar amounts of **21** and **20** was treated with a relatively small amount of oxidant, more than 50% of the aldehyde compared to only 30% of the methyl ether were consumed.

The alicyclic 3-cyclopentylpropanol methyl ether (**23**) was converted to the corresponding aldehyde **24** and acid **25** in 15% and 70% yields, respectively, without affecting the tertiary center which potentially could be a competitive reaction site participating in tertiary hydroxylation.[1d] Nor do aromatic rings interfere with the ether oxidation through excessive attack on the ring,[15] as demonstrated by benzyl alcohol methyl ether (**26**). Although the reactions here are particularly slow and more than 18-fold excess of $HOF\cdot CH_3CN$ was used, when full conversion was reached a clean reaction mixture was obtained containing 35% benzaldehyde (**27**) along with 45% benzoic acid (**28**). Here again, by continuing the reaction time, all the aldehyde could be converted into benzoic acid.

Unlike most of the other methyl ethers, benzaldehyde dimethyl acetal (**29**) was resistant to oxidation with $HOF\cdot CH_3CN$, since the CH bond α to the two methoxy groups is an electron poor one and hence not susceptible to an electrophilic attack by the $HOF\cdot CH_3CN$ oxygen atom. This supports the proposed mechanism and resembles the case of the benzoin methyl ether (**9**), already mentioned above.



Experimental Section

^1H NMR spectra were recorded with a 200 MHz machine with $CDCl_3$ as solvent and Me_4Si as an internal standard. GC/MS was used to record the mass spectra. FTIR spectra were recorded as neat films in $CHCl_3$ solution or in KBr pellets. All methyl ethers were prepared according to the literature[16] in very good yields.

General Procedure for Working with Fluorine. Fluorine is a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or monel in a well-ventilated area should be constructed for working with this element. For more experimental details, see, for example, ref 17. For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, simplifying the whole process. The reactions themselves can be carried out in glass vessels. 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 $HOF\cdot CH_3CN$. Mixtures of about 10% F_2 with nitrogen were used in this work. The gas mixture was prepared in a secondary container before the reaction was started. This mixture was then passed at a rate of about 400 mL per minute through a cold (−15 °C) mixture of 400 mL of CH_3CN and 40 mL of H_2O. The formation of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was titrated with thiosulfate. It is thus possible to achieve concentrations of more then 1 mol/L of the oxidizing reagent which at room temperature has a half-life of about 3-4 h. Experiments with $H_2{}^{18}O$ were performed in a smaller reaction vessel containing 1 g of labeled water in 10 mL of CH_3CN. A total of 6.6 mmol of $H^{18}OF\cdot CH_3CN$ was thus obtained and reacted with 214 mg (1.7 mmol) of **4**.

General Oxidation Procedure. About 3 mmol of an ether was dissolved in 20 mL of $CHCl_3$ at 0 °C and mixed with 3 g of NaF, forming a suspension. An excess of 3 mol equiv (9 mmol) of the oxidizing $HOF\cdot CH_3CN$ in aqueous CH_3CN was then added in one portion. The reaction was allowed to warm to room temperature and after 5 min checked for the disappearance of the starting material. If needed, another portion of 3 mol equiv of the reagent was added until a higher than 90% conversion was achieved. The reaction mixture was then neutralized with saturated sodium bicarbonate solution, extracted with CH_2Cl_2, and washed again with $NaHCO_3$ and water until neutral. The organic layer was dried over $MgSO_4$, the solvent evaporated, and the oxidized product isolated usually through chromatography. Although the mass balance of most reactions was higher than 90%, some tars and minor oxidative unidentified fragments were also formed and easily removed during the purification process. All products are known and compared either with authentic samples or their spectral properties compared with those reported in the literature. In every case excellent agreement was found.

Acknowledgment. This research was supported by the Israel Science Foundation administrated by the Israel Academy of Science and Humanities.

JO951182W

---

(12) Starchen, P. S.; Phillips, B. *J. Am. Chem. Soc.* **1958**, *80*, 4079.

(13) Takano, S.; Inomata, K.; Tomita, S.; Yanase, M.; Samizu, K.; Ogasawara, K. *Tetrahedron Lett.* **1988**, *29*, 6619.

(14) Lactone **18** is commercial. The isomeric **19** has a M/S: *m/e* = 170 (M^+) and is described in the literature: Asakawa, Y.; Matsuda, R.; Tori, M.; Hashimoto, T. *Phytochemistry* **1988**, *27*, 3861.

(15) Kol, M.; Rozen, S. *J. Org. Chem.* **1993**, *58*, 1593.

(16) Johnston, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

(17) Hebel, D.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 6298.