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Reaction of Silyl Enol Ethers with Xenon Difluoride in MeCN: Evidence for a Nonclassical Radical Cation Intermediate

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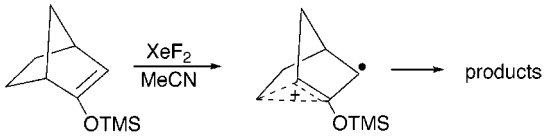
ABSTRACT



The reactions of xenon difluoride in MeCN solution in Pyrex flasks with a series of TMS enol ethers have been investigated. The types of products formed are dependent on the structures of individual enol ethers, but under these conditions all products are consistent with a mechanism involving single electron transfer to un-ionized XeF_2 giving a radical cation and subsequent formation of an α-fluoroketone, together with some ketone formation. The results suggest that if the radical cation is particularly stable, fluorodesilylation leads to radical formation, and solvent-derived products are then observed. Using other solvents, such as $CFCl_3$ and C_6F_6, much more complex mixtures of products are obtained, and this is attributed to a different mode of reaction of xenon difluoride involving ionization to FXe^+.

Using TMS derivatives that avoid the formation of HF, we have reported evidence that uncatalyzed reactions of xenon difluoride are dependent upon the nature of both the reaction solvent and vessel.[1] In glass flasks and solvents other than MeCN, the reactive species appears to be FXe^+,[2] which is isoelectronic with FI and which reacts as an electrophile.[3,4] In nonvitreous flasks (e.g., FEP) or in glass flasks using MeCN as solvent, the reactive species appears to be the un-ionized XeF_2 which reacts as a one-electron oxidizing agent. We have also shown that under very specific reaction conditions positron-emitting [^{18}F]fluoride ion exchanges with commercially available XeF_2 to give MeCN solutions of labeled [^{18}F]xenon difluoride for use in positron emission tomography (PET).[5,6] A better understanding of the reaction mechanisms of XeF_2[7] will enhance its value as a selective [^{18}F] and [^{19}F] fluorinating agent. To provide further evidence for our mechanistic proposals[1] and to further explore the one-electron oxidation mode of reaction of XeF_2 in MeCN/glass, which is a particularly convenient reaction medium, we have investigated the reactions of a selected series of TMS enol ethers with XeF_2 and now report the results and mechanistic conclusions.

A limited number of reactions of TMS enol ethers with XeF_2 to form α-fluoroketones have previously been reported. Four steroid ethers in $CF_2ClCFCl_2$/MeCN solutions at room temperature without a catalyst gave good isolated yields of the fluoroketones with α-stereoselectivity.[8] These authors concluded that radical involvement was unlikely and proposed a mechanism in which un-ionized XeF_2 reacted as a

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(1) Ramsden, C. A.; Smith, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 6842.
(2) Schrobilgen, G. J. In *Synthetic Fluorine Chemistry*; Olah, G. A., Chambers, R. D., Prakash, G. K. S., Eds.; John Wiley & Sons: New York, 1992; pp 1−30.
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(5) Aigbirhio, F. I.; Pike, V. W.; Smith, R. G.; Ramsden, C. A. *J. Nucl. Med.* **1998**, *39*, 231P.
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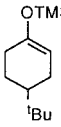
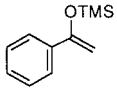
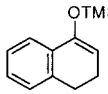
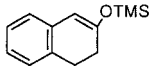
two-electron oxidizing agent. Using the same conditions but with a TBDMS enol ether, a monofluoro ketone peptide isostere has been prepared in 71% yield.[9] Fluorination of an estrone derivative in CH_2Cl_2 gave a product with a much lower yield (44%) but also with α-stereoselectivity.[10] The ethers of cycloalkanones are reported to give good yields of fluoroketones in CH_2Cl_2 with a trace of pyridinium poly(hydrogen fluoride) catalyst.[11] We have investigated the TMS enol ethers shown in Table 1. These were selected to give a broad range of structural types, and we have observed significant differences in their reactions. In general, MeCN solution gives the best results and we propose that under these condition they all react via an initial SET.

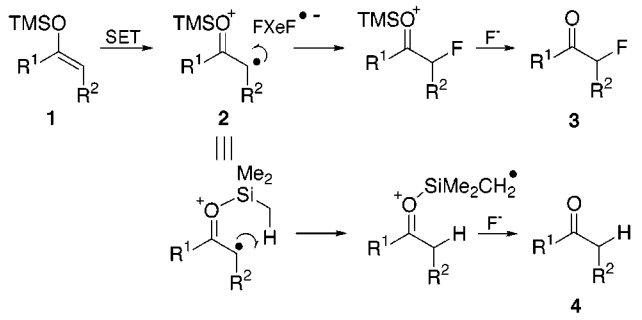
Table 1. Reaction of TMS Enol Ethers with XeF_2

Enol ether 1	Solvent	Product Yield (%) 3	4	Other
a 	MeCN	100	0	0
b 	MeCN	100	0	0
	$CFCl_3$/MeCN (9:1)	41	11	48[c]
	$CFCl_3$	55	8	37[c]
	C_6F_6	56	0	44[c]
c 	MeCN	74 (1.1)[a]	20	6[d]
	C_6F_6	11	0	89[c]
d 	MeCN	38	24	38[e]
e 	MeCN	38	53	9[c]
	C_6F_6	28	72	0
f 	MeCN	90	4	6[d]
	C_6F_6	78	19	4[d]
g 	MeCN	14	52	34[f]
	$CFCl_3$/MeCN (9:1)	36	22	42[f]
	$CFCl_3$	13	23	64[c]
	C_6F_6	11	48	41[c]
h 	MeCN	59 (0.5)[b]	41	0
	$CFCl_3$/MeCN (9:1)	49 (0.8)	33	19[c]
	$CFCl_3$	41 (0.8)	30	29[c]
	C_6F_6	45 (0.5)	36	9[c]
i 	MeCN	25 (7.3)[b]	17	58[f]
	$CFCl_3$/MeCN (1:1)	55 (8.2)	25	20[f]
	$CFCl_3$/MeCN (3:1)	59 (8.8)	30	11[f]
	$CFCl_3$/MeCN (9:1)	57(13.3)	29	14[f]
	$CFCl_3$	68 (7.5)	23	9[c]
	C_6F_6	42 (9.5)	10	48[c]

[a] *trans:cis* ratio; [b] *exo:endo* ratio; [c] complex mixture of products; [d] *gem* difluoride; [e] starting material; [f] see text.

All reactions of the enol ethers **1** (Table 1) were carried out under identical conditions using Pyrex flasks and a reaction time of 1 h. Product composition was monitored immediately after reaction by ^1H and ^{19}F NMR and GC-MS, and major products were fully characterized. We have previously reported[1] the clean reaction of 1-((trimethylsilyl)-oxy)cyclohexene **1b** in MeCN solution, which clearly gives results superior to those of other solvents (Table 1). Under the same conditions the cyclopentene derivative **1a** gave a quantitative yield of 2-fluorocyclopentanone **3a**. When the 4-*tert*-butylcyclohexene derivative **1c** was investigated in MeCN, the fluoroketone **3c** was accompanied by ketone **4c** (20%). A similar yield of ketone was obtained when 1,1-dimethyl-2-(trimethylsilyl)oxypropene **1d** was used, and the corresponding styrene derivative **1e** gave acetophenone **4e** as the major product. We interpret all these results in terms of the mechanism in Scheme 1. Initial SET, presumably via

Scheme 1



a short-lived electron donor−acceptor (EDA) complex, gives radical cation **2** together with the radical anion $XeF_2^{\bullet-}$. The latter may act as fluorinating agent with formation of Xe^0 and F^- or may lose F^- to give $XeF^{\bullet}$[12] which delivers fluorine to the radical cation. The liberated fluoride ion then acts as desilylating agent. Alternatively, the radical cation may undergo a 1,5-hydrogen transfer which leads to ketone **4** after desilylation. Under these conditions there are no significant amounts of HF in the reaction mixture and HF-mediated ketone formation is unlikely. When reactions were carried out in CD_3CN solution, no deuterium was incorporated into ketones **4**, supporting the view that the ketones are formed by an intramolecular mechanism (Scheme 1). This mechanism is also consistent with the lack of stereoselectivity observed for the *t*-Bu derivative **1c**. The *trans/cis* product ratio is presumably determined by the probabilities of the XeF_2 molecule (r_{XeF} 2.0 Å; Xe atomic radius 2.2 Å) approaching either face of the enol ether and not by the energies of alternative transition states involving partially formed C−F bonds.

It is not clear why acetophenone enol ether **1e** gives the ketone as major product, in contrast to aliphatic ether **1d**. We assume that the ratio of fluoroketone **3** to ketone **4** is determined by factors which include the relative stability of the radical cation and conformational flexibility. In this context the behavior of the isomeric tetralone derivatives **1f** and **1g** in MeCN is significant. Reaction of α-tetralone TMS enol ether **1f** gave an excellent yield of fluoroketone **3f** and only a small amount of α-tetralone **4f**. In contrast *β*-tetralone

(9) Garrett, G. S.; Emge, T. J.; Lee, S. C.; Fischer, E. M.; Dyehouse K.; McIver, J. M. *J. Org. Chem.* **1991**, *56*, 4823.
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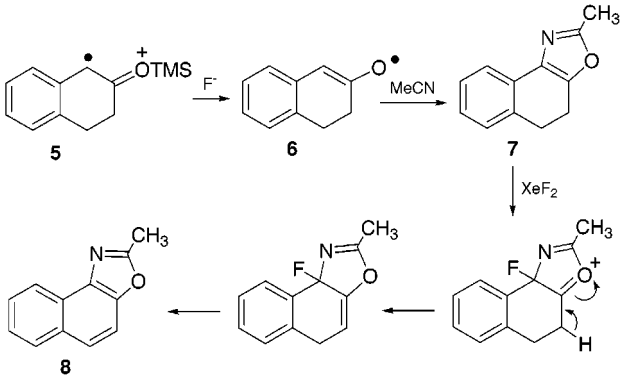
isomer **1g** gave a poor yield of fluoroketone **3g**, and *β*-tetralone **4g** was the major product. We interpret these observations in terms of differences in the stabilities of the intermediate radical cations **2f** and **2g**. In intermediate **2f** the aromatic ring is cross-conjugated with the enol radical whereas in isomer **2g** the radical is conjugated with the ring, leading to greater stabilization and delocalization of spin density. We assume that conjugated radical **2g** does not react so readily with the fluorinating agent, which diffuses away, and intramolecular hydrogen transfer predominates. A similar rationalization, supported by time-resolved spectroscopy, has been proposed to account for differences in the thermal reactions of tetralone enol ethers **1f** and **1g** with tetranitromethane.[13] In this case the EDA complex of ether **1g** appears to be stable in solution and does not dissociate to the radical cation.

A further feature of the reaction of *β*-tetralone derivative **1g**, which is not observed for substrates **1a**−**f**, is the high yield of solvent-derived products in MeCN solution. In particular, two products were identified by GC-MS as having the oxazole structures **7** (16%) ($M^{\bullet+}$ *m*/*z* 185) and **8** (24%) ($M^{\bullet+}$ *m*/*z* 183). The ^{1}H NMR of the product mixture showed two methyl singlets at *δ* 2.1and *δ* 2.2. When CD_3CN was the solvent, these singlets were absent and the molecular weights increased by three mass units ($M^{\bullet+}$ *m*/*z* 188 and 186), consistent with the incorporation of one molecule of nitrile solvent. We propose that these solvent-derived products arise because of the longer lifetime of resonance-stabilized benzylic radical cation **5** which subsequently undergoes fluorodesilylation to give the highly reactive radical **6** (Scheme 2). Radical **6** immediately undergoes [3 + 2] cycloaddition

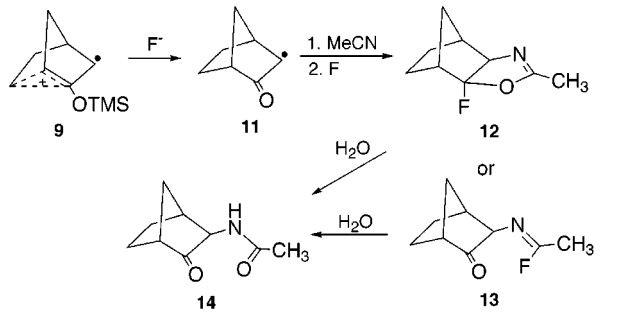
Scheme 2



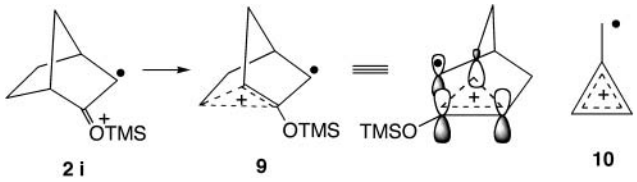
with MeCN and aromatizes (**6** → **7**). This mechanism of oxazole formation has precedent in the reported one-electron oxidation of enols in MeCN solution using Cu^{II} triflate.[14] Further oxidation, possibly mediated by XeF_2, leads to the fully conjugated product **8** (Scheme 2).

When the TMS ether of camphor **1h** was investigated, fluoroketone **3h** was accompanied by significant amounts of ketone **4h**. The *exo:endo* ratio of α-fluoroketone, determined by ^{19}F NMR,[15] was in the range 0.5−0.8 (Table 1). These ratios are in accord with the expected steric hindrance to approach of the alternative faces. The results with the corresponding norcamphor derivative **1i** were unexpected. Although the *exo:endo* ratio of α-fluoroketone isomers **3i** in various solvent systems is, as expected, significantly greater (7.3−13.3) than that for camphor, the lowest yield of fluoroketone was obtained using MeCN. Furthermore, in this solvent ketone products **3i** and **4i** are accompanied by a major solvent-derived product (ca. 25%) which after isolation and purification was identified as amide **14** (mp 159−160 °C) (Scheme 3). This result parallels the behavior of

Scheme 3



β-tetralone ether **1g**, and we propose that this is a second example in which the intermediate radical cation (i.e., **2i**) enjoys enhanced stability, in this case by adopting nonclassical structure **9**. Species **9** is isoconjugate with the methylenecyclopropene radical cation **10** which is aromatic.[16]



Formation of amide **14** is accounted for by the mechanism in Scheme 3, which parallels the *β*-tetralone mechanism (Scheme 2). Dilution of the acetonitrile solvent with Freon led to diminishing amounts of product **14** (Table 1), and use of CD_3CN gave a product incorporating CD_3CN ($M^{\bullet+}$ *m*/*z* 170 and CD_3CO^+ *m*/*z* 46). We propose that radical **11** adds to MeCN to give after fluorination either fluorooxazolidine **12** or acyclic fluoroimine **13**. Upon workup and prior to detection, product **12** or **13** is then rapidly hydrolyzed by adventitious water to the observed amide **14**. Some amide formation has previously been reported to occur in the photochemical fluorination of norbornene by XeF_2.[17] The

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(15) Middleton, W. J.; Bingham, E. M. *J. Am. Chem. Soc.* **1980**, *102*, 4845. Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *16*, 19.
(16) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum Press: New York, 1975; p 499.
(17) Hildreth, R. A.; Druelinger, M. L.; Shackelford, S. A. *Tetrahedron Lett.* **1982**, *23*, 1059.

mechanistic details of these reactions of MeCN with radicals requires further investigation.

In conclusion, these results support the view that in MeCN−glass XeF_2 reacts via one-electron oxidation. The stability of the radical cations formed from TMS enol ethers determines the subsequent reaction pathway: stabilization of radical cations leads to radical formation and addition to MeCN in competition with α-fluorination. Results using the TMS enol ether of norcamphor provide indirect evidence that this radical cation is stabilized, possibly by formation of nonclassical structure **9**. With some exceptions, other solvents give more complex mixtures and poorer yields of α-fluoroketones. This can be ascribed to participation of the ion FXe^+, probably formed at the glass−solvent interface.[1] The species FXe^+ may act as a fluorinating agent via electrophilic addition or via one-electron oxidation ($FXe^+ \rightarrow FXe^\bullet$) or may initiate rearrangement reactions.[3,4] All these modes of reaction of FXe^+ may account for the additional products formed in Pyrex flasks and solvents other than MeCN.

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Supporting Information Available: Experimental procedures, characterization for compound **14**, and GC data for reactions of **1b**,**c** and **1f**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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