Solvent dependence of the synthesis and reactions of acetyl hypofluorite

Shlomo Rozen*, Yifat Bareket and Moshe Kol
School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978 (Israel)

(Received March 12, 1992; accepted June 11, 1992)

Abstract

Acetyl hypofluorite (AcOF) has been previously prepared using $CFCl_3$ (CFC-11) as a solvent. It was found that acetonitrile can replace trichlorofluoromethane without sacrificing the efficiency and the regio- and stereo-selectivity of the addition of AcOF to olefins. Most other solvents tested proved to be inadequate for the synthesis of AcOF, despite the fact that fluorine does react with the dispersed sodium acetate present in the solvent.

Introduction

Since its first preparation 10 years ago [1], acetyl hypofluorite (AcOF) has become a very popular electrophilic fluorinating agent [2], as well as a tool for introducing the ^{18}F isotope used in positron-emitting transaxial tomography (PET) [3]. A third field of importance was found in general organic synthesis resulting eventually in fluorine-free products [4]. Up to now it has been prepared by passing F_2, diluted by an inert gas, through a cooled suspension of NaOAc in $CFCl_3$/AcOH [5]. However, Freon®-11 (F-11, $CFCl_3$) is a major ozone-depleting agent* and is becoming increasingly less available. This led us to investigate the possibility of using other more environmentally friendly solvents in the production of AcOF and its reactions with various types of organic molecules.

Results and discussion

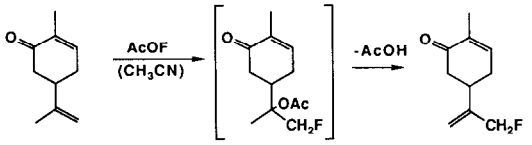
In general, the choice of a suitable solvent for working with fluorine is not very wide. Since AcOF results from the action of F_2 on suspended AcONa, the solvent has to be reasonably stable towards concentrations of 10–15% of it in an inert gas, and also able to dissolve the AcOF which is reasonably stable only at low temperatures. These requirements eliminate the possibility of using acetic acid with its high freezing point, since most of the acetyl hypofluorite decomposes thermally shortly after its creation. The behavior with other solvents is not so easy to explain. When a cold (-60 °C) suspension

*Small amounts of AcOF, mainly for production of $AcO^{18}F$, can also be produced by passing F_2 through a column of solid AcOM (M+Na, K) [6].

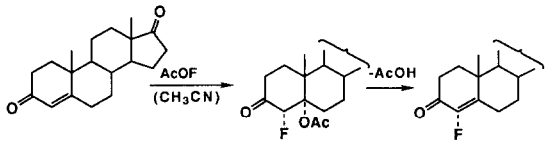
0022-1139/93/$6.00

of AcONa in $CHCl_3$/AcOH (10:1) was reacted with F_2, only a low concentration of AcOF (less than 5 mmolar) was obtained and this decomposed in a matter of minutes*. Replacing the chloroform with DMF completely inhibited any formation of AcOF and no oxidizing compound was detected.

Eventually, however, we found that acetonitrile can fully replace F-11 as a reaction medium. Thus, when a cold (−45 °C) suspension of AcONa in CH_3CN/AcOH (10:1) was treated with 15% F_2 in N_2, oxidizing solutions of up to 0.3 molar were obtained. To prove that the oxidizing material is indeed acetyl hypofluorite and to check its reaction course, we reacted it with several types of olefins. Carvone (**1**) is a good example, since it has two double bonds of different types. When it was treated with a threefold excess of AcOF, a reaction took place only at the isolated exocyclo double bond, while the enone system remained intact. The product was identified as the previously unknown 9-fluorocarvone (**2**), which obviously resulted from the addition of AcOF to the olefin followed by the elimination of the elements of AcOH. With more rigid enones such as androst-4-ene-3,17-dione (**3**), one can detect the adduct 5α-acetoxy-4α-fluoroandrostane-3,17-dione (**4**), but purification attempts again led to AcOH elimination forming the corresponding fluoroenone (**5**).



1 2

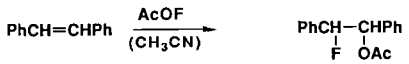


3 4 5

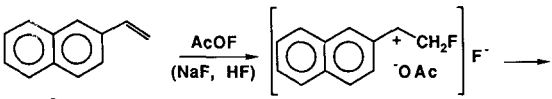
Since acetonitrile is more polar than $CFCl_3$, it was of interest to compare these solvents for the stereospecificity of the addition of AcOF to alkenes. *trans*-Stilbene (**6**) was chosen for this purpose and it was found that acetyl hypofluorite added across the double bond with remarkable similarity for both solvents. Such solvents encourage mainly a *syn*-mode addition resulting in *threo*-1-acetoxy-2-fluoro-1,2-diphenylethane (**7**) accompanied by only traces of the erythro isomer. Acetyl hypofluorite prepared in acetonitrile was also added across the double bond of 2-vinyl-naphthalene (**8**) to produce the novel 1-fluoro-2-acetoxy-2-naphthylethane (**9**) along with some 1,2-difluoro-2-naphthylethane (**10**). This somewhat unexpected derivative is apparently the result of the very stable naphthylic carbocation which enables the acetoxy

*The amount of AcOF was determined iodometrically after reacting an aliquot with KI. The nature of the oxidizing material was deduced from its reaction with *trans*-stilbene which resulted in *threo*-1-acetoxy-2-fluoro-1,2-diphenylethane [5].

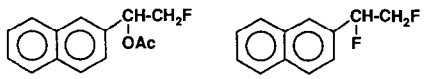
moiety to diffuse out of the tight ion-pair cage*, allowing fluoride ions, always present in the reaction mixture, to compete successfully with the acetate.



6 *(trans)* 7 *(threo)*

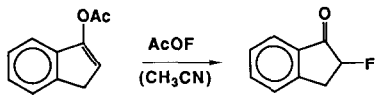


8

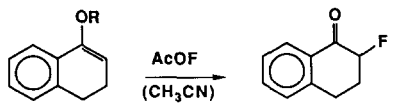


9 10

One of the most useful reactions of any electrophilic fluorinating agent in general, and of AcOF in particular, is the reaction with enol derivatives to form the corresponding α-fluorocarbonyls [5]. AcOF prepared in acetonitrile fulfills this requirement very well indeed. Thus 2-fluoro-1-indanone (**12**) was the sole product from the reaction between indanone enol acetate (**11**) and AcOF**. Very good results were also obtained from the reaction of tetralone enol acetate (**13**) and its silyl enol ether **14** with AcOF in CH_3CN, which in both cases resulted in 2-fluorotetralone (**15**). Similarly, the silylenol ether of acetophenone **16** produces α-fluoroacetophenone (**17**) along with some of the difluoro derivative **18**. The latter is formed apparently by the decomposition of the silyl group of the adduct by the fluoride ions, followed by water elimination and a subsequent fluorination of the resultant fluoro-enol acetate. This hypothesis is supported by the fact that, with acetophenone enol acetate (**19**), only the monofluoro ketone **17** was formed.



11 12

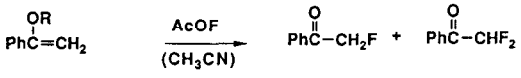


13 R = Ac 15

14 R = $SiMe_3$

*The formation of a tight ion pair is characteristic of an electrophilic fluorination process which produces the extremely unstable α-fluorocarbocation [7].

Compound **12 is described in the literature as one of five compounds formed in the reaction between indene and $FClO_3$ [8].



16 R = $SiMe_3$ 17 18

19 R = Ac

While acetonitrile proved to be a successful solvent for AcOF production and at least as efficient as Freon®-11, mixtures of solvents based on acetonitrile were not that efficient. We have already mentioned that AcOF could not be made in chloroform, but even 10% $CHCl_3$ in acetonitrile did not allow the formation of AcOF in concentrations higher than 10 mmolar, almost two orders of magnitude lower than the concentrations achieved in CH_3CN or $CFCl_3$. When mixtures of 10% or more DMF, sulfolane or DMSO in either acetonitrile or F-11 were used, the AcOF concentration dropped to 0–1 mmolar.

We do not yet know why some solvents such as $CHCl_3$ or sulfolane are suitable for certain reactions of F_2 with organic substrates [9], but not for the formation of acetyl hypofluorite. What can be said, however, is that the sodium acetate in all the above-mentioned solvents does react readily with F_2. What is more, only *c.* 1 mol equiv.$^{-1}$ is needed for all the NaOAc to disappear, indicating that fluorine reacts with the salt faster than it reacts with the solvents. Mass balance and IR studies suggest that all the sodium acetate is converted to sodium fluoride, the usual byproduct in the preparation of AcOF. Since, however, it was found that these solvents do not affect the decomposition rate of already prepared AcOF, we have to conclude that they do not support the transition state which leads to the formation of this electrophilic fluorinating agent.

Experimental

^1H NMR spectra were recorded with a Bruker AM-360 WB instrument at 360 MHz with $CDCl_3$ as solvent and Me_4Si as internal standard. The ^{19}F NMR spectra were measured at 338.8 MHz and are reported in parts per million (ppm) as positive upfield from $CFCl_3$, which also served as internal standard. The proton broad-band-decoupled ^{13}C NMR spectra were recorded at 90.5 MHz and only the C–F couplings were observed. Here too $CDCl_3$ served as a solvent and TMS as internal standard. Mass spectra were measured with a DuPont 21-491B instrument and IR spectra were recorded on a Perkin-Elmer 177 spectrometer.

Preparation of AcOF and its reaction with olefins

A mixture of 15% F_2 in N_2 was bubbled into a cold (−45 °C) suspension of 8 g AcONa in 400 ml CH_3CN and 50 ml AcOH*. The amount of the AcOF

*Alternatively, 20 g AcONa·AcOH dispersed in 450 ml $CFCl_3$ can be used. The solvated salt can be made by leaving anhydrous AcONa over AcOH in a closed desiccator overnight.

TABLE 1

Compound	Yield (%) [m.p.(°C)]	^1H, ^{19}F and ^{13}C NMR spectra	IR (cm^{-1}) MS (m/e)
2	35 [oil][a]	^1H NMR δ: 6.76 (1H, m); 5.22 (1H, d, J=3.6 Hz); 5.09 (1H, s); 4.87 (2H, d, J=47 Hz); 2.61–2.33 (5H, m); 1.79 (3H, s) ppm. ^{19}F NMR δ: −214.6 (dt, J_1=47, J_2=3.6 Hz) ppm. ^{13}C NMR δ: 198.9; 145.9 (d, ^2J=13 Hz); 135.6; 114.2 (d, ^3J=10 Hz); 64.3 (d, ^1J=167.5 Hz); 42.69; 37.9; 31.1; 15.6	1675; MS: 168 (M^+)
5	65 [172][b]	For physical and spectral details of **3** and **5**, see ref. 6	
7	50 [60][c]	For physical and spectral details, see ref. 6	
9	30 [oil][d]	^1H NMR δ: 7.4–7.8 (7H, m); 6.19 (1H, ddd, J_1=16.3, J_2=7.1, J_3=3.7 Hz); 4.66 (2H, dm, J=47 Hz); 2.17 (3H, s) ppm. ^{19}F NMR δ: −222.6 (dt, J_1=47, J_2=16.3 Hz) ppm. ^{13}C NMR δ: 128.6–124.2 (C_{ar}); 64.0 (d, ^1J=169.3 Hz); 74.4 (d, ^2J=20.5 Hz); 21.6	1740; MS: 212 $(M-HF)^+$
10	18 [oil][e]	^1H NMR δ: 7.4–7.9 (7H, m); 5.86 (1H, dddd, J_1=48, J_2=16, J_3=7, J_4=3.4 Hz); 4.63 (2H, dm, J=47 Hz) ppm. ^{19}F NMR δ: −223.3 (1F, tt, J_1=47, J_2=16 Hz); −186.5 (1F, dm, J=48 Hz)	MS: 192 (M^+)
12	85 [60] [8]	^1H NMR δ: 7.4 (4H, m); 5.2 (1H, ddd, J_1=51, J_2=7.7, J_3=4.2 Hz); 3.6 (1H, m); 3.26 (1H, m) ppm. ^{19}F NMR δ: −194.3 (ddd, J_1=51, J_2=23, J_3=7.7 Hz)	1720
15	87 [38] [10]	For physical and spectral details, see ref. 10	1690
17	70 [26] [11]	For physical and spectral details, see ref. 11	1690
18	25 [oil] [11]	^{13}C NMR δ: 187.2 (d, ^1J=22 Hz); 134.9; 133.1; 129.6; 128.5; 128.2; 120.9 (C_{ar}); 111.1 (t, ^1J=252.6 Hz). For other spectral details, see ref. 11.	1690

[a]Anal.: Calcd. for $C_{10}H_{13}FO$: C, 71.43; H, 7.74%. Found: C, 70.91; H, 7.66%. [b]From MeOH. [c]From cyclohexane. [d]Anal.: Calcd. for $C_{14}H_{13}FO_2$: C, 72.41; H, 5.60%. Found: C, 72.75; H, 6.06%. [e]Anal.: Calcd. for $C_{12}H_{10}F_2$: C, 75.00; H, 5.21%. Found: C, 74.16; H, 5.33%.

thus obtained could be easily determined by reacting aliquots of the reaction mixture with aqueous KI solution and titrating the liberated iodine. After the desired concentration of AcOF had been achieved – usually *c.* 0.2 molar – 30–40 mmol of an alkene dissolved in *c.* 50 ml cold chloroform was added to the reaction mixture. The reactions were usually monitored by GC, TLC or NMR methods and in most cases were complete within a few minutes. The reaction was terminated by pouring into 500 ml thiosulfate solution, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$ and finally evaporating the solvent. The crude reaction mixture was usually subjected to vacuum flash chromatography using Silicagel 60-H (Merck) with mixtures of EtOAc in P.E. serving as eluent. Some of the compounds are not well characterized in the literature so their physical data along with the appropriate references and yields are given in Table 1.

Acknowledgment

This research was supported by Grant No. 89-00079 from the USA–Israel Binational Science Foundation (BSF), Jerusalem, Israel.

References

1 S. Rozen, O. Lerman and M. Kol, *J. Chem. Soc., Chem. Commun.*, (1981) 443.
2 See for example: D. Hebel, K. L. Kirk, L. A. Cohen and V. M. Labroo, *Tetrahedron Lett.*, *31* (1990) 619; S. Rozen, *Acc. Chem. Res.*, *21* (1988) 307; A. Luxen and J. R. Barrio, *Tetrahedron Lett.*, *29* (1988) 1501; K. Dax, B. I. Glanzer, G. Schulz and H. Vyplel, *Carbohydr. Res.*, *162* (1987) 13; G. W. M. Visser, C. N. M. Bakker, B. W. v. Halteren, J. D. M. Herscheid, G. A. Brinkman and A. Hoekstra, *J. Org. Chem.*, *51* (1986) 1886.
3 See for example: R. Chirakal, E. S. Garnett, G. J. Schrobilgen, C. Nahmias and G. Firnau, *Chem. Br.*, (1991) 47; M. Tada, T. Matsuzawa, K. Yamaguchi, Y. Abe, H. Fukuda, M. Itoh, H. Sugiyama, T. Ido and T. Takahashi, *Carbohydr. Res.*, *161* (1987) 314; C. Y. Shiue and A. P. Wolf, *J. Fluorine Chem.*, *31* (1986) 255.
4 D. Hebel and S. Rozen, *J. Org. Chem.*, *56* (1991) 6298.
5 S. Rozen, O. Lerman, M. Kol and D. Hebel, *J. Org. Chem.*, *50* (1985) 4753.
6 D. M. Jewett, J. F. Potocki and R. E. Ehrenkaufer, *Synth. Commun.*, *14* (1984) 45; D. M. Jewett, J. F. Potocki and R. E. Ehrenkaufer, *J. Fluorine Chem.*, *24* (1984) 477.
7 S. Rozen and O. Lerman, *J. Org. Chem.*, *45* (1980) 672, and references therein.
8 M. Neeman and Y. Osawa, *J. Am. Chem. Soc.*, *85* (1963) 232.
9 See for example: S. Rozen and C. Gal, *J. Org. Chem.*, *52* (1987) 2769.
10 S. Rozen and M. Brand, *Synthesis*, (1985) 665.
11 S. Stavber and M. Zupan, *J. Org. Chem.*, *52* (1987) 5022.