

Solvent dependence of the synthesis and reactions of acetyl hypofluorite

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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 $\text{CFCl}_3/\text{AcOH}$ [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.

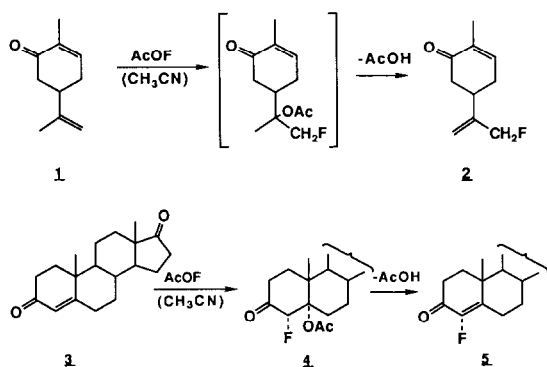
Results and discussion

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 ($-60\text{ }^\circ\text{C}$) 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].

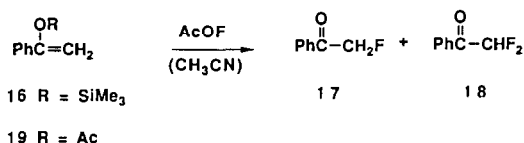
of AcONa in $\text{CHCl}_3/\text{AcOH}$ (10:1) was reacted with F_2 , only a low concentration of AcOF (less than 5 mmolar) was obtained and this decomposed in a matter of minutes*. Replacing the chloroform with DMF completely inhibited any formation of AcOF and no oxidizing compound was detected.

Eventually, however, we found that acetonitrile can fully replace F_2 as a reaction medium. Thus, when a cold (-45°C) suspension of AcONa in $\text{CH}_3\text{CN}/\text{AcOH}$ (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 exocyclic 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 5 α -acetoxy-4 α -fluoroandrostane-3,17-dione (**4**), but purification attempts again led to AcOH elimination forming the corresponding fluoroenone (**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 naphthyl cation 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].



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% CHCl₃ 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 CH₃CN or CFCl₃. 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 CHCl₃ or sulfolane are suitable for certain reactions of F₂ 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 F₂. 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 CDCl₃ as solvent and Me₄Si as internal standard. The ¹⁹F NMR spectra were measured at 338.8 MHz and are reported in parts per million (ppm) as positive upfield from CFCl₃, which also served as internal standard. The proton broad-band-decoupled ¹³C NMR spectra were recorded at 90.5 MHz and only the C–F couplings were observed. Here too CDCl₃ 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% F₂ in N₂ was bubbled into a cold (–45 °C) suspension of 8 g AcONa in 400 ml CH₃CN and 50 ml AcOH*. The amount of the AcOF

*Alternatively, 20 g AcONa·AcOH dispersed in 450 ml CFCl₃ 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)]	¹ H, ¹⁹ F and ¹³ C NMR spectra	IR (cm ⁻¹) MS (m/e)
2	35 [oil] ^a	¹ H NMR δ: 6.76 (1H, m); 5.22 (1H, d, <i>J</i> = 3.6 Hz); 5.09 (1H, s); 4.87 (2H, d, <i>J</i> = 47 Hz); 2.61–2.33 (5H, m); 1.79 (3H, s) ppm. ¹⁹ F NMR δ: -214.6 (dt, <i>J</i> ₁ = 47, <i>J</i> ₂ = 3.6 Hz) ppm. ¹³ C NMR δ: 198.9; 145.9 (d, ² <i>J</i> = 13 Hz); 135.6; 114.2 (d, ³ <i>J</i> = 10 Hz); 64.3 (d, ¹ <i>J</i> = 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	¹ H NMR δ: 7.4–7.8 (7H, m); 6.19 (1H, ddd, <i>J</i> ₁ = 16.3, <i>J</i> ₂ = 7.1, <i>J</i> ₃ = 3.7 Hz); 4.66 (2H, dm, <i>J</i> = 47 Hz); 2.17 (3H, s) ppm. ¹⁹ F NMR δ: -222.6 (dt, <i>J</i> ₁ = 47, <i>J</i> ₂ = 16.3 Hz) ppm. ¹³ C NMR δ: 128.6–124.2 (C _{ar}); 64.0 (d, ¹ <i>J</i> = 169.3 Hz); 74.4 (d, ² <i>J</i> = 20.5 Hz); 21.6	1740; MS: 212 (M - HF) ⁺
10	18 [oil] ^e	¹ H NMR δ: 7.4–7.9 (7H, m); 5.86 (1H, dddd, <i>J</i> ₁ = 48, <i>J</i> ₂ = 16, <i>J</i> ₃ = 7, <i>J</i> ₄ = 3.4 Hz); 4.63 (2H, dm, <i>J</i> = 47 Hz) ppm. ¹⁹ F NMR δ: -223.3 (1F, tt, <i>J</i> ₁ = 47, <i>J</i> ₂ = 16 Hz); -186.5 (1F, dm, <i>J</i> = 48 Hz)	MS: 192 (M ⁺)
12	85 [60] [8]	¹ H NMR δ: 7.4 (4H, m); 5.2 (1H, ddd, <i>J</i> ₁ = 51, <i>J</i> ₂ = 7.7, <i>J</i> ₃ = 4.2 Hz); 3.6 (1H, m); 3.26 (1H, m) ppm. ¹⁹ F NMR δ: -194.3 (ddd, <i>J</i> ₁ = 51, <i>J</i> ₂ = 23, <i>J</i> 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, ¹ <i>J</i> = 22 Hz); 134.9; 133.1; 129.6; 128.5; 128.2; 120.9 (C _{ar}); 111.1 (t, ¹ <i>J</i> = 252.6 Hz). For other spectral details, see ref. 11.	1690

^aAnal.: Calcd. for C₁₀H₁₃FO: C, 71.43; H, 7.74%. Found: C, 70.91; H, 7.66%. ^bFrom MeOH. ^cFrom cyclohexane. ^dAnal.: Calcd. for C₁₄H₁₉FO₂: C, 72.41; H, 5.60%. Found: C, 72.75; H, 6.06%. ^eAnal.: Calcd. for C₁₂H₁₆F₂: 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 NaHCO₃ solution followed by water until neutral, drying the organic layer over MgSO₄ 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.

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