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Elemental fluorine
Part 8. [1]Preparation of α-fluoroketones

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Abstract

The direct fluorination of enol derivatives of ketones—enol acetates, enol ethers, trimethylsilyl ethers and enamines—has been investigated at ambient temperatures. Of these the fluorination of enol acetates gives the highest yields of the desired α-fluoro ketones and thus provides a viable route to these valuable compounds. © 1998 Elsevier Science S.A. All rights reserved.

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1. Introduction

We have previously shown how elemental fluorine can be used to fluorinate 1,3-dicarbonyl compounds to give the corresponding 2- and 2,2-di-fluoro compounds in high yield [2,3]. In view of our continuing interest in the use of elemental fluorine in organic synthesis and the potential of fluoroketones in the synthesis of molecules having biological activity, we have now turned our attention to the synthesis of α-fluoroketones. Generally, α-fluoroketones cannot be prepared directly from the parent ketones, but by treating their enol derivatives—enol acetates, enol ethers, trimethylsilyl ethers and enamines—with fluorinating agents such as the 'N–F' reagents [4,5], xenon difluoride [6–8], caesium fluoroxysulphate [9,7], various hypofluorites [10–14], perchloryl fluoride [15–17], and tetrafluorohydrazine [18], good yields of the required α-fluoroketones can be obtained. Some of these fluorinating agents are difficult to prepare and handle, and since all require the use of elemental fluorine in their preparation it would be convenient if fluorine could be used directly in reaction with simple enol derivatives.

Early attempts at treating enol acetates with elemental fluorine gave a complicated mixture of products and no matter how mild the conditions, no α-fluoroketones were obtained [13]. Also, when trimethylsilyl ethers were first treated with elemental fluorine, the parent ketone was the only identifiable product [8], although, later it was found that when the fluorination was carried out at −78°C in trichlorofluoromethane (no longer available), good yields of fluoroketones could be obtained [19]. Our recent work on the direct fluorination of β-dicarbonyl compounds [2,3] and other substrates has encouraged us to re-examine the reaction of fluorine with enol acetates and trimethylsilyl ethers, and to investigate the reaction of fluorine with enol ethers and enamines.

2. Results and discussion

2.1. Reaction of fluorine with enol acetates

Because of the discouraging reports from previous work on this topic it was a surprise to find that enol acetates could indeed be converted into α-fluoroketones in good yields, simply by passing fluorine through solutions of these substrates at ca. 0°C (Table 1).

Initially, reactions were carried out in acetonitrile (Conditions 'a') but it was subsequently found that these esters were sufficiently stable to acid hydrolysis for fluorination to be accomplished in 98% formic acid, a solvent which we have found to be of particular value in the selective direct fluorination of various substrates [2,3,20] (Conditions 'b'). Fluorination was observed to be slower in formic acid than in acetonitrile but in most cases the yields in formic acid were similar or higher than in acetonitrile. Where the yield was lower in formic acid (entry 4), a significant amount of parent ketone was found in the product so it was concluded that these particular esters were less stable in the acid medium.

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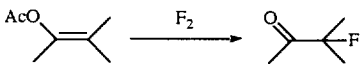
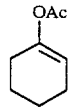
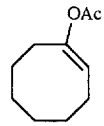
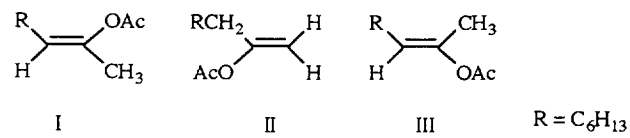
Table 1
Fluorination of enol acetates



	Substrate	Conversion[a] (%)	Yield[a] (%)	Conversion[b] (%)	Yield[b] (%)
1		>95	56	75	71
2		>95	66	>95	61
3	$C_4H_9C(OAc)=CHC_3H_7$	>95	61	64	71
4	$C_6H_{13}CH=C(OAc)CH_3$ (*cis* and *trans*) and $C_7H_{15}C(OAc)=CH_2$	>95	65[c]	>95	42[c]

Conditions: [a] 20 mmol enol acetate in 50 ml CH_3CN, 50 mmol F_2 (10% in N_2) in 110 min. [b] 20 mmol enol acetate in 50 ml HCOOH, 64 mmol F_2 (10% in N_2) in 240 min.
[c] These yields are the combined yields for all the isomers–see Section 3.



I II III $R = C_6H_{13}$

Fig. 1. Products from the acylation of 2-nonanone.

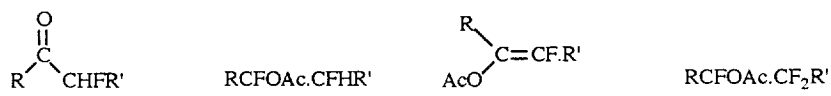
The enol acetates used in these studies were prepared by treating the parent ketone with isopropenyl acetate in the presence of *para*-toluene sulphonic acid [21]. Cyclohexanone, cyclooctanone and 5-nonanone each gave a single product but in the case of 2-nonanone, a mixture of enol acetates, in order of increasing retention time (GC) **I**, **II**, and **III** (Fig. 1) in the ratio 2:2:1, was obtained. This mixture was used as starting material in the fluorination reactions (Entry 4, Table 1).

While the individual isomeric products of fluorination could not be isolated, it was possible to obtain samples, highly enriched in each isomer by preparative GC and therefore to identify the main peaks in a chromatogram of the product mixture. In order of increasing retention time, these were $C_6H_{13}CH_2C(OH)=CHF$ (**IV**), $C_6H_{13}CHFCO\cdot CH_3$ (**V**) and $C_6H_{13}CH_2CO\cdot CH_2F$ (**VI**) in an approximate ratio of 1:3.4:2.1. It is interesting to note that the α-fluoroketone **VI** exists to a significant extent in its enol form **IV** (doublet in ^{19}F NMR at −127.4 ppm). Normally, a higher level of fluorination is necessary for enol forms of α-fluoro ketones to have significant stability [22].

As well as the α-fluoroketones, **VII**, the reaction products included minor components whose mass spectra (CI, NH_3) were consistent with difluoroketones and the fluoroesters **VIII**, **IX** and **X** (Fig. 2). The presence of these compounds suggests that α-fluoroketones are produced by the addition/elimination sequence outlined in Scheme 1.

2.2. Reaction of fluorine with trimethylsilyl ethers

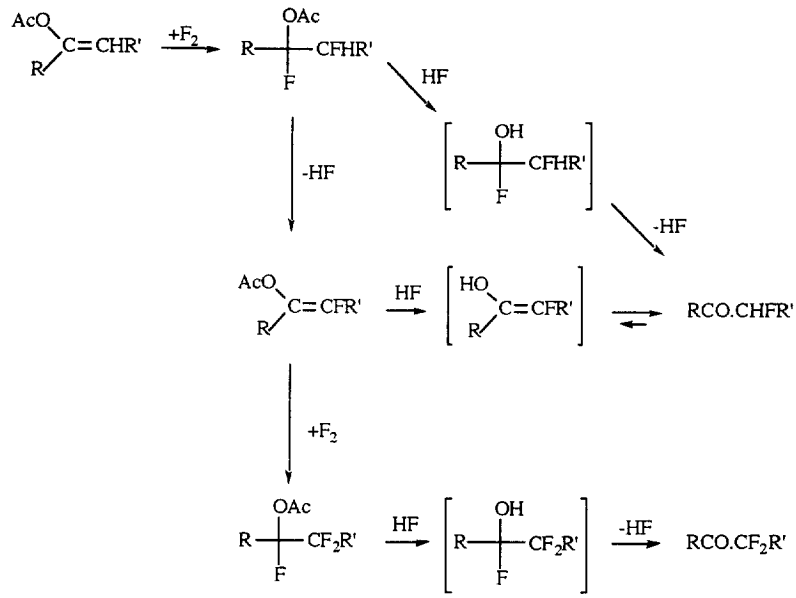
Direct fluorination of the trimethylsilyl ethers was less successful than the fluorination of enol acetates as a useful route to α-fluoroketones. Thus, the fluorination of the trimethylsilyl ethers of cyclohexanone, cyclooctanone and 5-nonanone in dry acetonitrile at ca. 0°C gave the corresponding monofluoroketones in yields of 30, 23 and 35%, respectively. Unlike the fluorination of enol acetates where the main product was the α-fluoroketone, the major product from the fluorination of trimethylsilyl ethers was the parent ketone reflecting the relatively low stability of these ethers to acid. From their mass spectra, the main by-products of these reactions appear to be difluorinated ketones and trimethylsilyl



VII VIII IX X

R,R' = -C_4H_8-; R,R' = -C_6H_{12}-; R = C_4H_9, R' = C_3H_7; R = C_7H_{15}, R' = H; R = C_6H_{13}, R' = CH_3

Fig. 2. Products of fluorination of enol acetates.



Scheme 1. Possible reaction pathway for the fluorination of enol acetates.

ethers with the general structure corresponding to **IX** which suggests an addition/elimination sequence for these fluorinations similar to that outlined above for the fluorination of enol acetates [23].

When 1-methoxy- and 1-morpholino-cyclohexene were fluorinated under similar conditions to those used for trimethysilyl ethers, they both gave poor yields of 2-fluorocyclohexanone with cyclohexanone, and small amounts of difluorocyclohexanone, being the only other recognisable products in complicated mixtures.

Clearly, treating simple derivatives of ketones with elemental fluorine is a practically useful method for preparing α-fluoroketones and of the derivatives examined, enol acetates appear to afford the best yields. Thus we have again demonstrated that contrary to common perception, elemental fluorine can be used for practical site specific fluorination reactions.

3. Experimental

Generally, ^{19}F NMR spectra were recorded on a Bruker AC250 spectrometer operating at 250 MHz for hydrogen or 235 MHz for fluorine with tetramethylsilane and fluorotrichloromethane as internal references. Chemical shifts are recorded in ppm and coupling constants in Hz. ^{13}C NMR spectra were measured on a Varian Gemini 200 spectrometer. The spectra were recorded in $CDCl_3$. Except where stated otherwise, mass spectra were measured on a Fisons Trio 1000 mass spectrometer in the electron impact mode coupled to a Hewlett Packard 5890 II gas chromatograph fitted with a silicone elastomer coated column (SE 30; 25 m.; 0.2 mm. i.d.). Accurate mass measurements were determined at the EPSRC Mass Spectrometry Service Centre, Swansea.

Enol acetates and enol ethers were prepared by treating the parent ketones with isopropenyl acetate [21] and trimethyl orthoformate [24], respectively, in the presence of *para*-toluene sulphonic acid. Reaction of the parent ketone with chlorotrimethylsilane in the presence of base was used to prepare the trimethylsilyl ethers [25] and the enamine was a commercial sample.

3.1. Fluorination reactions—general procedure

Reactions were carried out under the conditions outlined in Table 1. An FEP reaction vessel, fitted with a stirrer, was charged with the substrate (20 mmol) in either acetonitrile or formic acid (50 ml), purged with nitrogen and cooled so that the internal temperature was maintained at 0–5°C. A metered flow of 50% fluorine in nitrogen, v/v, was diluted further with nitrogen to 10%, v/v, before being passed through the solution. Exit gases were led to a soda lime filled scrubbing tower. When reaction was complete, the vessel was purged with nitrogen, and the reaction mixture was poured into water and extracted with dichloromethane. The extracts were dried, solvent was removed and the residue distilled. Pure samples were generally obtained by preparative scale gas chromatography. Yields were calculated by taking an aliquot of the reaction mixture (before aqueous treatment except in the case of the enamine), adding a weighed amount of benzotrifluoride and examining the ^{19}F NMR spectrum of this solution. Conversions were calculated from a combination of the ^{19}F NMR and GC of the product.

Fluorination of enol acetates was carried out as indicated above and the results obtained are given in Table 1.

3.1.1. Fluorination of cyclohexenyl acetate

On work up, the main product was identified as 2-fluorocyclohexanone [14] (HRMS: Found, 116.0637. C_6H_9FO

requires 116.0637); δ_F −188.7 (d, $J_{H,F}$ 49); δ_H 1.7–2.6 (8H, m, CH_2), 4.9(1H, dm, $J_{H,F}$ 49, CHF); δ_C 22.7 (d, $^3J_{C,F}$ 9.6, C4), 26.9 (d, $^3J_{C,F}$ 1.2, C6), 34.1 (d, $^2J_{C,F}$ 18.3, C3), 40.2 (s, C5), 92.6 (d, $^1J_{C,F}$ 190.4, C2), 205.7 (d, $^2J_{C,F}$ 14.5, C1); *m/z* 116(M^+, 17%), 55 (100)). GC/MS (CI, NH_3) showed the presence of minor products with $(M+NH_4)^+$ 116 ($C_6H_{14}NO$), 176 ($C_8H_{15}FNO_2$), 214 ($C_8H_{15}F_3NO_2$), 196 ($C_8H_{16}F_2NO_2$).

3.1.2. Fluorination of cyclooctenyl acetate

The main product was identified as 2-fluorocyclooctanone [6] (HRMS; Found, 144.0950. $C_8H_{13}FO$ requires 144.0950); δ_F −191.6 (m); δ_H 1.36–2.7 (12H, m, CH_2), 4.9(1H, dm, $J_{H,F}$ 49.5, CHF); δ_C 20.5 (d, $^3J_{C,F}$ 3.6, C4), 24.6 (d, $^3J_{C,F}$ 3.7, C8), 24.7 (s, CH_2), 27.2 (s, CH_2), 32.7 (d, $^2J_{C,F}$ 21, C3), 39.6 (s, CH_2), 91.5 (d, $^1J_{C,F}$ 184.7 C2), 213.9 (d, $^2J_{C,F}$ 20.9, C1); *m/z* 144(M^+, 3%), 55 (100)). GC/MS (CI, NH_3) showed the presence of minor products with $(M+NH_4)^+$ 144 ($C_8H_{18}NO$), 180 ($C_8H_{16}F_2NO$), 224 ($C_{10}H_{20}F_2NO_2$), 242 ($C_{10}H_{19}F_3NO_2$), 202 ($C_{10}H_{19}FNO_2$).

3.1.3. Fluorination of 4-nonenyl-5-acetate

The main product was identified as 4-fluoro-5-nonanone [26] (HRMS; Found, 160.1263; $C_9H_{17}FO$ requires 160.1263); δ_F −193 (m); δ_H 0.94 (6H, m), 1.2–1.9 (m, 8H), 4.7(1H, ddd, $J_{H,F}$ 49.5, $J_{H,F}$ 6, $J_{H,F}$ 6, CHF); δ_C 13.6 (s, CH_3), 13.8 (s, CH_3), 17.9 (s, CH_2), 22.3 (s, CH_2), 24.7 (s, CH_2), 34 (d, $^2J_{C,F}$ 20.5, CHF·CH_2), 37.7 (s, CH_2CO), 95.9 (d, $^1J_{C,F}$ 182.5, CHF), 210.5 (d, $^2J_{C,F}$ 24.1, CO). *m/z* 160(M^+, 6%), 57 (100). GC/MS (CI, NH_3) showed the presence of minor products with $(M+NH_4)^+$ 160 ($C_9H_{22}NO$), 202 ($C_{11}H_{24}NO_2$), 258 ($C_{11}H_{23}F_3NO_2$), 220 ($C_{11}H_{23}FNO_2$).

3.1.4. Fluorination of 1-nonenyl-2-acetate

The main products were identified as: *1-fluoro-2-hydroxy-1-nonene* (**IV**); δ_F −127.4 (d, $J_{H,F}$ 54). *m/z* 160; *3-fluoro-2-nonanone* (**V**) (HRMS; Found, 160.1263; $C_9H_{17}FO$ requires 160.1263); δ_F −190 (m); δ_C 14.0 (s, CH_3), 22.5 (s, CH_2), 24.4 (d, $^3J_{C,F}$ 3.1, CH_2CH_2·CHFCO.), 25.9 (s, CH_3CO.), 28.8 (s, CH_2), 31.5 (s, CH_2), 31.8 (d, $^2J_{C,F}$ 20.7, CH_2CHFCO), 96 (d, $^1J_{C,F}$ 182.6, CHF), 208.5 (d, $^2J_{C,F}$ 25.6, CO). *m/z* 160(M^+, 6%), 57 (100); *1-fluoro-2-nonanone* (**VI**) δ_F −227.9 (t, J_{HF} 50); δ_C 14.1 (s, CH_3), 22.6 (s, CH_2), 22.7 (s, CH_2), 22.8 (s, CH_2), 29.0 (d, $^3J_{C,F}$ 5.0, CH_2CO·CH_2F), 31.6 (s, CH_2), 38.3 (s, CH_2), 85 (d, $^1J_{C,F}$ 183.9, $COCH_2F$), 207.2 (d, $^2J_{C,F}$ 19.1, CO). ms (CI, NH_3) $(M+NH_4)^+$ 178. GC/MS (CI, NH_3) showed the presence of minor products with $(M+NH_4)^+$ 196 ($C_9H_{20}F_2NO$, a difluorononanone), 240 ($C_{11}H_{24}F_2NO_2$), 220 ($C_{11}H_{23}FNO_2$), 258 ($C_{11}H_{23}F_3NO_2$).

Trimethylsilyl ethers were fluorinated by passing 50 mmol fluorine, diluted to 10% in nitrogen, over 110 min through a solution of 20 mmol substrate in 50 ml dry acetonitrile at about 0°C. Work up was as indicated above and the main products were identified by comparing their mass spectra, retention times and, where appropriate, their ^{19}F NMR spectra with authentic samples.

3.1.5. Fluorination of 1-(trimethylsiloxy)-cyclohexene

The main products were cyclohexanone and 2-fluorocyclohexanone (30% yield) while the most significant minor product had $(M+NH_4)^+$ 206 ($C_9H_{21}FNOSi$).

3.1.6. Fluorination of 1-(trimethylsiloxy)-cyclooctene

The main products were cyclooctanone and 2-fluorocyclooctanone (23% yield) while the most significant minor products had $(M+NH_4)^+$ 180 ($C_8H_{16}F_2NO$, a difluorocyclooctanone), and 234 ($C_{11}H_{25}FNOSi$).

3.1.7. Fluorination of 5-(trimethylsiloxy)-4-nonene

The main products were 5-nonanone and 4-fluoro-5-nonanone (35% yield) while the most significant minor products had $(M+NH_4)^+$ 196 ($C_9H_{20}F_2NO$, a difluorononanone), and 250 ($C_{12}H_{29}FNOSi$).

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