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PREPARATION OF α-FLUOROALDEHYDES AND α-FLUOROKETONES USING DILUTE FLUORINE

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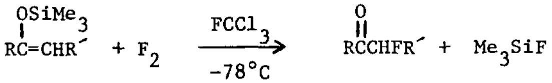
Abstract: Fluorination of silyl enol ethers with 5% F_2 in N_2 at -78°C in Freon 11 results in the formation of α-fluoroketones and α-fluoroaldehydes.

Organic molecules containing fluorine have found wide applications.[1] Although there are a number of methods for introducing fluorine alpha to a carbonyl group,[2] these all suffer from drawbacks. α-Fluoroketones result from reaction of CF_3OF with silyl enol ethers.[3] Although yields are good, both the reagent and its byproduct COF_2 are toxic gases. Similarly, enol acetates react with XeF_2[4] and enamines[5] or enol ethers[6] react with $FClO_3$ to give rise to α-fluoroketones.

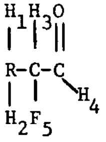
Since dilute fluorine gas reacts with 2-(trimethylsiloxy)pyridine to form 1-fluoro-2 pyridone,[7] the corresponding reaction with silyl enol ethers was undertaken. The silyl enol ether (0.01 mole),[8] was dissolved in $FCCl_3$ (30 mL) and cooled to -78°C. For 3.5 h the diluted fluorine[9] was passed through solid NaF, bubbled through the solution and then through two KI traps so that no unchanged fluorine escaped. An advantage of this fluorination system is that it utilizes glass vessels and tygon tubing. Bubbling of the gas mixture is continued until the first trap starts to turn dark. Trimethylsilyl fluoride, formed as an innocuous byproduct, is volatile and can be easily removed.



$$\mathrm{R\overset{OSiMe_3}{\overset{|}{C}}=CHR'} + F_2 \xrightarrow[-78^\circ C]{FCCl_3} \mathrm{R\overset{O}{\overset{\|}{C}}CHFR'} + Me_3SiF$$

The α-fluorocarbonyl product, obtained in nearly pure form by evaporation of the reaction mixture, was purified by eluting through a Florisil column with hexanes, (Table I). The α-fluoroaldehydes were unstable and decomposed on attempted distillation as well as on standing. The α-fluoroaldehydes and ketones were characterized by ^{1}H and ^{19}F NMR. The complex ^{19}F NMR spectra of 2-fluoroheptanal (10 lines) and of 2-fluoro-3-phenylpropanal (16 lines) were simulated using the RACCOON computer program,[12] (Table II). In a similar manner the six-line ^{19}F NMR

Table II. Coupling Constants for



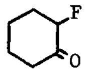
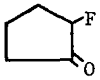
$$\underset{H_2}{\overset{H_1}{R}}-\underset{F_5}{\overset{H_3}{C}}-\overset{O}{\overset{\|}{C}}\diagdown H_4$$

R	1.2	1,3 and 2,3	3,4	1,5	2,5	3,5	4,5
$CH_3(CH_2)_3$	12.0	8.0	0	25.5	25.5	51.0	7.0
C_6H_5	12.0	8.0	0	23.0	27.0	53.0	6.0

spectrum of 2-fluoropropiophenone was simulated: $^{2}J_{HF} = 48.0$; $^{3}J_{HF} = 24.0$ and $^{3}J_{HF} = 8.0$. ^{19}F NMR analysis of products from the fluorination of trimethylsilyl enol ethers derived from methyl ketones revealed a mixture of mono-, di-, and trifluoromethyl ketones. The problem of overfluorination could be alleviated by purification of the silyl derivative prior to fluorination and by interrupting the reaction at the first sign of yellow in the iodide trap. Unchanged silyl enol ether could be detected under these circumstances.

In conclusion, direct fluorination of silyl enol ethers provides an easy entry to α-fluoroketones and aldehydes. Short reaction times make this method especially useful for the introduction of ^{18}F ($t_{1/2}$ = 110 min) in molecules to be studied by positron based imaging systems. Reaction of various silylated acid derivatives with fluorine is currently under investigation.

Table I. Formation of α-Fluorocarbonyl Compounds

Compound	Crude Yield	Pure Yield	bp°C/mm(mp°C)	Lit bp°C/mm(mp°C)	^{19}F NMR	$^{2}J_{HF}$
PhCHFCHO	81	72	46/2(dec)	35-6/1[a]	191(d,d)	49
$CH_3(CH_2)_4CHFCHO$	84	70	92/100(dec)	b,c	199(m)	d
$PhCF(CH_3)CHO$	89	52	e		161(q)	f
Ph_2CFCHO	81	57	e		152(d)	g
$PhCH_2CHFCHO$	96	70	e		197(q)	d
$PhCOCHFCH_3$	85	59	68-70/2	96/12[h]	182(m)	d
	89	78	56-8/3.8	46/28[a]	188(d,m)	51
	86	73	87-88/30	70/16[b]	194(d,m)	50
$PhCOCH_2F$	90	61	69-71/1.1	45-7/0.03[h]	232(t)	47
PhCHFCOPh	82	64	(49-51)	(50-51)	176(d)	49

a. Ref. 3. b. Ref. 10. c. No physical properties given. d. See text. e. Decomposes. f. $^{3}J_{HF}$= 6.24. g. $^{3}J_{HF}$= 7. h. Ref. 11.

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