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## Fluorination or Hydroxylation of non Activated C-H Bonds in Amides and Ketones using $\text{CCl}_4$ or NBS in Superacids

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**Abstract :** *Amides and ketones are fluorinated or hydroxylated in  $\text{HF-SbF}_5$  in the presence of  $\text{CCl}_4$  or NBS, reaction occurring at a carbon far located from the functional group.* Copyright © 1996 Published by Elsevier Science Ltd

In the late sixties Olah developed the concept of  $\sigma$  basicity of alkanes in superacids, the single C-C or C-H bond sharing its electron pair with an electrophile through a two-electron-three-center bonded intermediate or transition state.<sup>1</sup> This concept was found to be promising, accounting for protolysis, alkylolysis and electrophilic substitution of alkanes.

We wish to report here the hydroxylation or the fluorination observed in  $\text{HF-SbF}_5$  with various amides and ketones in presence of  $\text{CCl}_4$  (see Tables I and II).

Tables show that most substrates are ionized within a few minutes to yield after quenching hydroxy and / or fluoroderivatives. In  $\text{HF-SbF}_5$  alone, no protolytic activation was observed in the same experimental conditions.

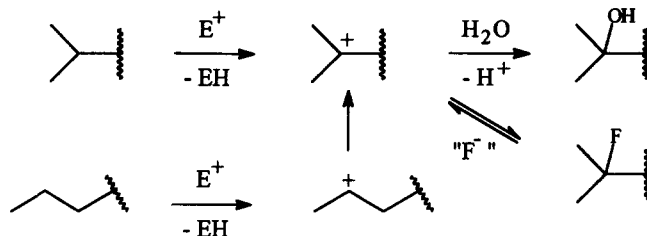
The results observed with  $\text{CCl}_4$  are collected in Tables I and II and use of NBS led to similar yields. Products were obtained after usual work-up, flash-chromatography over silica gel, and identified by NMR spectroscopy.

In superacid amides<sup>2</sup> and ketones<sup>3</sup> are protonated on the oxygen atom. As a result the strong electron-withdrawing effect of the protonated group is sufficient to inhibit protolysis of the C-H bonds in the reaction conditions.

The increased reactivity of the substrates observed by addition of  $\text{CCl}_4$  or NBS must be due to the intermediacy of electrophilic species trichloromethyl cation  $\text{CCl}_3^+$  and halogen cation "Br<sup>+</sup>" (or its equivalent)<sup>4</sup> respectively, which are more reactive towards C-H than the poorly solvated proton. Cation  $\text{CCl}_3^+$ , previously observed by Olah<sup>5</sup> using NMR has been shown by Sommer<sup>6</sup> to ionize rapidly propane (the reaction is extremely slow in absence of  $\text{CCl}_4$ ) and cyclohexane even at 150K in  $\text{SbF}_5$  matrix.<sup>7</sup> In order to explain this unusual hydride abstraction power, Olah assumes "superelectrophilic" activation of trichloromethyl cation by protosolvation in superacidic media.<sup>8</sup> After hydride abstraction the resulting chloroform can follow a similar reaction path but is less reactive than carbon tetrachloride. The same reactivity order was observed in this work, methylene chloride being completely unreactive.

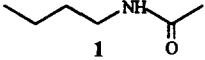
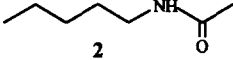
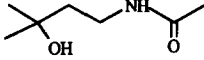
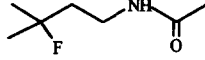
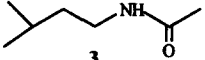
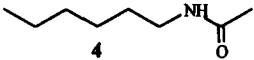
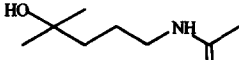
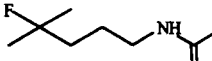
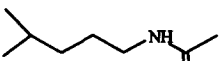
Table I shows that reaction does not involve cleavage of C-C bonds but that skeletal isomerization is operative with straight chain substrates. Hydride abstraction by electrophile occurs at the more reactive C-H bonds, far located from the protonated functional group. This explains why amide 1 is too deactivated to react and amides 2 and 3 are less reactive than 4 and 5. Tertiary C-H bonds in compounds 3 and 5 ionize to give directly the corresponding carbenium ion whereas for

compounds 2 and 4 with a straight chain, hydride abstraction at the ( $\omega$ -1) position yields a secondary ion which isomerizes. Trapping by water or fluoride ion accounts for the formation of hydroxyderivatives 6 and 8 and fluoro derivatives 7 and 9, respectively.



Compounds 7 and 9 placed again in the reaction conditions yielding the corresponding hydroxy and fluoro derivatives, this implies that fluorides and tertiary carbenium ions are in equilibrium in the medium. Consequently yield of fluoro derivatives has been improved by trapping the reaction mixture with pyridinium polyhydrogen fluoride (PPHF), a good source of fluoride ion.

Table I - Reactions of amides with  $HF-SbF_5-CCl_4^a$  at  $-30^\circ C$

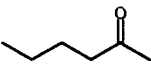
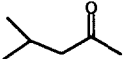
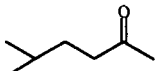

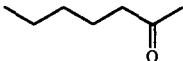
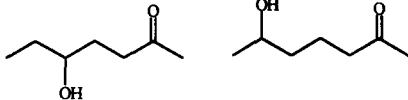
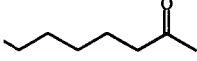
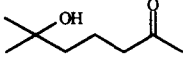
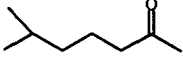
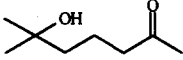
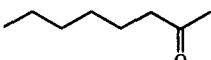
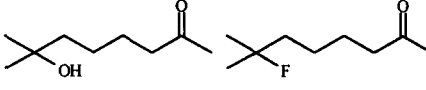

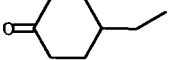

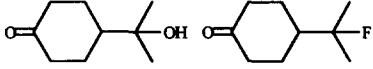
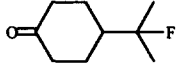
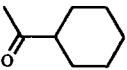
Substrate	Time (min)	Quenching conditions <sup>b</sup>	Products (yield %)	
	30	A	No reaction	
	20	A	 6 (55)	 7 (10)
	20	A	6 (55)	7 (10)
	5	A	 8 (31)	 9 (26)
	5	B		9 (76)
	5	B		9 (80)

a)  $HF/SbF_5$ /Substrate molar ratio : 20/1/0.05

b) A :  $Na_2CO_3/Ice/H_2O$ ; B : 1) excess PPHF ( $HF/Pyridine$  molar ratio 70/30) at  $-30^\circ C$  for 2 minutes  
2)  $Na_2CO_3/Ice/H_2O$

Ketones react similarly, hydride abstraction occurring at the tertiary C-H bond or at the ( $\omega$ -1) methylene group of straight chain alkyl group, as far as possible from the protonated carbonyl group.

Table II - Reaction of ketones with HF-SbF<sub>5</sub>-CCl<sub>4</sub><sup>a</sup> at -30°C (a and b : see Table I)

Substrate	Time (min)	Quenching conditions <sup>b</sup>	Products (yield %)
 10	30	A or B	No reaction
 11	20	A or B	No reaction
 12	10	A or B	 (82) (3/1 ratio)
 13	5	A or B	 (67) (3/1 ratio)
 14	5	A or B	 (80)
 15	5	A or B	 (92)
 16	3	A	 (50) (12)
		B	 (32) (20)
 17	45	A	No reaction
 18	2	A	 (20) (60)
	2	B	 (75) (60)
 19	30	A	No reaction

