



S0040-4039(96)00475-3

Fluorination or Hydroxylation of non Activated C-H Bonds in Amides and Ketones using CCl_4 or NBS in Superacids

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Abstract : *Amides and ketones are fluorinated or hydroxylated in HF-SbF_5 in the presence of 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 σ 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.¹ 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 HF-SbF_5 with various amides and ketones in presence of 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 HF-SbF_5 alone, no protolytic activation was observed in the same experimental conditions.

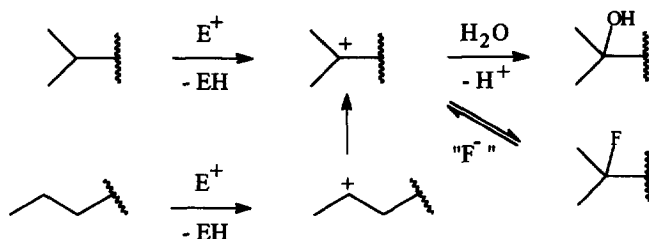
The results observed with CCl_4 are collected in Tables I and II and use of NBS led to similar yields. Products were obtained after usual work-up, flash-chromatography over silica gel, and identified by NMR spectroscopy.

In superacid amides² and ketones³ 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 CCl_4 or NBS must be due to the intermediacy of electrophilic species trichloromethyl cation CCl_3^+ and halogen cation "Br⁺" (or its equivalent)⁴ respectively, which are more reactive towards C-H than the poorly solvated proton. Cation CCl_3^+ , previously observed by Olah⁵ using NMR has been shown by Sommer⁶ to ionize rapidly propane (the reaction is extremely slow in absence of CCl_4) and cyclohexane even at 150K in SbF_5 matrix.⁷ In order to explain this unusual hydride abstraction power, Olah assumes "superelectrophilic" activation of trichloromethyl cation by protosolvation in superacidic media.⁸ 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.

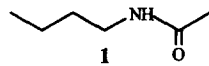
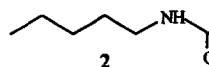
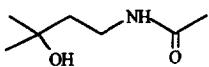
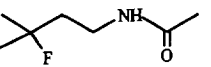
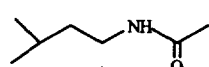

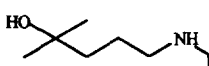
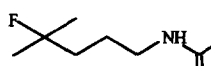
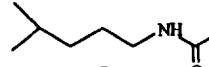
Table I shows that reaction does not involve cleavage of C-C bonds but that skeletal isomerization is operative with straight chain substrates. Hydride abstraction by electrophile occurs at the more reactive C-H bonds, far located from the protonated functional group. This explains why amide 1 is too 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 (ω -1) position yields a secondary ion which isomerizes. Trapping by water or fluoride ion accounts for the formation of hydroxyderivatives 6 and 8 and fluoroderivatives 7 and 9, respectively.



Compounds 7 and 9 placed again in the reaction conditions yielding the corresponding hydroxy and fluoroderivatives, this implies that fluorides and tertiary carbenium ions are in equilibrium in the medium. Consequently yield of fluoroderivatives 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-SbF₅-CCl₄^a at -30°C

Substrate	Time (min)	Quenching conditions ^b	Products (yield %)	
	30	A	No reaction	
	20	A		
	20	A	6 (55)	7 (10)
	5	A		
	5	B		9 (76)
	5	B		9 (80)

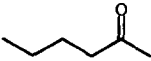
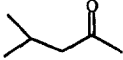
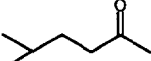

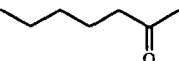
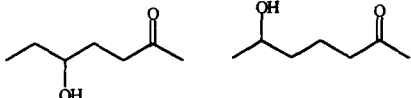
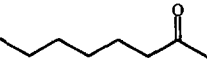
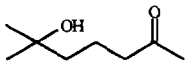
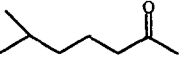
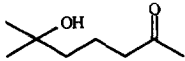
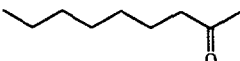
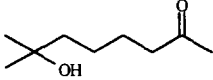
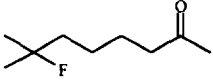
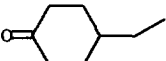
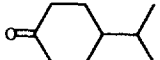
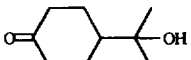
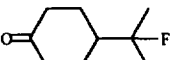
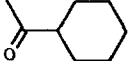
a) HF/SbF₅/Substrate molar ratio : 20/1/0.05

b) A : Na₂CO₃/Ice/H₂O; B : 1) excess PPHF (HF/Pyridine molar ratio 70/30) at -30°C for 2 minutes

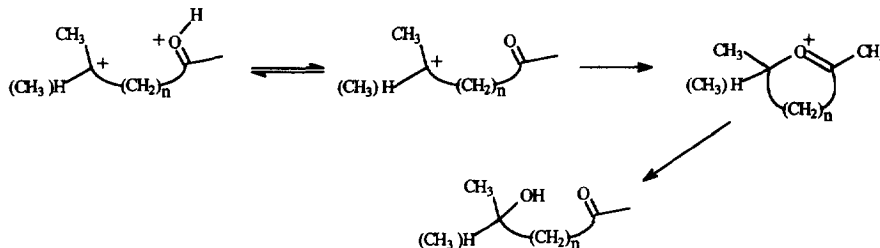
2) Na₂CO₃/Ice/H₂O

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

Table II - Reaction of ketones with HF-SbF₅-CCl₄^a at -30°C (a and b : see Table I)

Substrate	Time (min)	Quenching conditions ^b	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)
		B	 (12) (20)
 17	45	A	No reaction
 18	2	A	 (20)
	2	B	 (60) (75)
 19	30	A	No reaction

Ketones **10** and **11** are as expected unreactive, the alkyl group with four carbon atoms being too deactivated. With ketones **12** - **15** only hydroxyderivatives are formed, whatever the quenching conditions are (A or B). This implies participation of the carbonyl group to give a five or six-membered cyclic carboxonium preventing the substrate from fluorination.^{9,10}



With ketone **16** formation of a seven membered ring carboxonium ion is more difficult, favoring an equilibrium with the opened diprotonated species. Treatment of the reaction medium with PPHF improves only slightly the yield of fluoroderivative.

Cyclohexanones **17** and **19** do not react in the reaction conditions, γ and δ positions (in **17**) and δ position (in **19**) being probably deactivated by the cumulative effect of the ring arms.

On the other hand, results observed with ketone **18** show that the tertiary cation is in equilibrium with the fluoroderivative which is the sole product obtained when trapping the medium with PPHF.

To conclude, electrophilic (superelectrophilic) halogen cation are efficient promoters for ionization and functionalization of non activated C-H bonds in superacids. Amides and ketones being protonated in the reaction conditions, electrophilic attack occurs at a carbon far located from the functional group.

Extension of this reaction to polyfunctional natural products is currently under progress and will be reported in a future paper.

We wish to thank the CNRS for financial support.

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(Received in France 14 February 1996; accepted 6 March 1996)