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SELECTIVE ELECTROPHILIC MONOFLUORINATION ON RINGS OF VARIOUS SIZES USING ELEMENTAL FLUORINE

SHLOMO ROZEN* AND CHAVA GAL

Department of Chemistry, Tel-Aviv University, Tel-Aviv 69978 (Israel)

SUMMARY

Elemental fluorine substitutes tertiary unactivated hydrogens in an electrophilic mode. This unorthodox substitution depends on the atomic charge density, on the hydrogen atom and on the p-orbital contribution on the C-H bond. This is demonstrated by reacting F_2 with tertiary C-H bonds located on rings of various sizes, producing the corresponding tertiary fluorine derivatives.

Not long ago the common general belief among organic chemists was that fluorination by fluorine is unlikely to be used in normal organic synthesis [1]. In recent years, however, we have shown that this element can be converted <u>in situ</u> to some useful fluoroxy reagents [2], which have great potential as synthetic tools in organic and medicinal chemistry, as demonstrated for example by the use of AcOF in the exciting field of positron emitting tomography [3].

The direct use, however, of this most reactive element is still quite rare. There were some attempts to add F_2 to certain double bonds [4], or to use it as a fluorinating agent with some aromatic [5] or pyruvic acid [6] derivatives, but undoubtedly its

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most important and noticeable feature is its ability to substitute tertiary unactivated hydrogens in organic molecules [7,8]. Based on the retention of configuration which was observed in these substitutions, we have suggested that the reaction proceeds through a pentacoordinated fluorocarbocation intermediate \underline{A} .

$$-\overset{I}{C} - \overset{\delta}{F} - \overset{F}{F} - \overset{C}{F} \xrightarrow{CHCI_{3}} \left[\begin{array}{c} I \\ C & - \\ - C & - \\ H \end{array} \right] \xrightarrow{\bullet} -\overset{I}{C} - + HF$$

Apart from a polar solvent, which has several functions [8]*, this mechanism also calls for an attraction of the positive end of the F-F dipole to a hydrogen and a consecutive electrophilic attack on the electrons of the carbon hydrogen bond. Therefore, if the conditions encourage an ionic reaction, electrophilic attack will be facilitated by a high atomic charge density on a prospective hydrogen and by the highest possible p-orbital character for its bond with carbon. It was of interest, then, to compare the efficiency of the fluorination of tertiary C-H bonds situated on various rings, since the p contribution varies with the ring size.

Carbon hydrogen bonds in three-membered rings are known to have relatively very low p character which does not encourage electrophilic attack on them. Thus, when the pivalic ester of l-methylcyclopropanemethanol (I) was subjected even to a high concentration of fluorine (up to 20% F_2 in N_2) no electrophilic fluorination took place and only very slow deterioration of the

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^{*} Other polar solvents with acidic hydrogens, such as AcOH and $$^{\rm CH}_{\rm 3}\rm NO_2$, can also be used.$

starting material was observed. In contrast, electrophilic substitution with F_2 on the tertiary C-H bond at C-3 in <u>cis</u> methyl 2,2-dimethyl-3-ethylcyclobutaneacetate (II) produces <u>cis</u> methyl 2,2-dimethyl-3-ethyl-3-fluorocyclobutaneacetate (III) in 30% yield, ¹⁹F NMR: -165 ppm (quintet, J = 23 Hz).*



* As in all other cases which we have studied, [7,8] the retention of configuration is observed here too. While one of the geminal methyl groups in C-2, which is syn to the carbomethoxy moiety, was practically unaffected by the introduction of the fluorine (NMR: $\Delta \delta = -0.02$ ppm) the second methyl group, anti to the carbomethoxy, and positioned in the same direction as the halogen atom, is considerably deshielded by it $(\Delta \delta = +0.1 \text{ ppm})$. The reactions were carried out in glass vessels with 2-4 mmol of substrate dissolved in 450 ml of CHCl₃-CFCl₃ (1:1) at -75°C. Unless otherwise stated, 4-5% F₂ in N_2 were used after passing the mixture through a HF scavenger trap. The progress of the reaction was monitored by GC (SE-30, 20%). The reactions were stopped when about 90% of the starting material was consumed. The fluorinated compounds described here are all oils. Their spectral data (IR, 19 F and 1 H NMR and mass spectra) are in excellent agreement with the assigned structures. The $^{19}{
m F}$ NMR spectra were recorded with a Bruker WH-90 instrument at 84.67 MHz, CFCl, serving as internal standard.



VI R=H $\frac{F_2/N_2}{N_2}$ VIIR=F

VIIIR=H F2/N2 IX R=F

The squares of the bond orders (B.O.) ls-2s and ls-2p derived from semiempirical MO calculations can serve as indicators of the amount of s and p orbitals contributions to a C-H bond and are related to the hybridization. The higher the ratio of the $B \cdot O \cdot \frac{2}{1s-2p}/B \cdot O \cdot \frac{2}{1s-2s}$, the higher is the p orbital character of the bond [9].* This ratio for the reacting tertiary C-H bond in <u>II</u> is 3.3, a much higher p contribution than in the case of the cyclopropane derivative <u>I</u>. It bears also the highest atomic charge density in this molecule (1.0190) and is thus the best candidate for electrophilic substitution. The tertiary C-H bond in 3-cyclopentanepropyl acetate (<u>IV</u>) has again the highest atomic charge density 1.0190 and the highest p character ($B \cdot O \cdot \frac{2}{1s-2p}/B \cdot O \cdot \frac{2}{1s-2s} = 3.8$) of all the rest of the C-H bonds in this molecule. It is thus clear that this hydrogen is the most suitable for substitution by the electrophilic fluorine and,

* We used Allinger's MMl program for force-field calculation [10], coupled with the CNDO/2 program in order to derive the hydrogen atomic charge densities and the bond orders of all the C-H bonds. The results clearly show that the tertiary hydrogens and the ones on the carbon α to the oxygen atom bear the highest atomic charges. However, the ratio of the B.O.²_{1s-2p}/B.O.²_{1s-2s} for the etheric C-H bonds is very low. On the other hand, tertiary hydrogens far away from any electronegative atoms have high atomic charge densities and highest B.O.²_{1s-2p}/B.O.²_{1s-2s}, ratio compared to all other C-H bonds in the molecule, thus encouraging ionic electrophilic reactions.

indeed, the 3-cyclopentane-3-fluoropropyl acetate (V) was obtained in 40% yield, ¹⁹F NMR: -144.3 ppm (m). The differences in the p-orbital contribution of the 4- and 5-membered rings was demonstrated not only by the slight increase in the yield, but also in the reaction of an equimolar mixture of II and IV with F₂. The cyclopentane derivative reacted considerably faster than the cyclobutane one, despite the fact that the electronegative oxygen in IV is nearer to the tertiary hydrogen than in II, a situation which usually results in decreasing the reactivity toward electrophilic fluorination. A tertiary C-H bond on a six-membered ring has higher p character than all the smaller rings, with a ratio of the respective square bond orders of about 4.0. Thus, although the tertiary hydrogen in trichloroethyl 2-cyclohexylpropionate VI is quite near the electronegative group, the reaction with F_2 proceeds quite well and a 60% yield of trichloroethyl 3-cyclohexyl-3-fluoropropionate (VII) was obtained, ¹⁹F NMR: -149.5 ppm (m).

Even when the conditions favor electrophilic reaction, we are unable to entirely suppress radical fluorinations. It seems that fluorine radicals are always present, although in low concentration. When substrates which are not suitable for electrophilic fluorination are present, like small rings these highly reactive radicals eventually destroy the starting material. This can also happen with mono fluoro derivatives, which are more deactivated toward further electrophilic attack than their parent compounds, so the reaction should be monitored and stopped shortly before completion. Radical fluorination is conspicuous with methylcyclododecane (VIII) which produces l-fluoro-l-methylcyclododecane (IX) in 30% yield, ¹⁹F NMR: -139.5 ppm (m). This time the low yield does not result from electronic considerations, but from the very low ratio of tertiary to primary and secondary hydrogens (1:25), diminishing the prospects of fruitful electrophilic fluorination, compared to random-radical attacks. Indeed, looking at the ¹⁹F NMR spectrum of the crude reaction mixture, one can see that, apart from the dominant IX, there are many fluorine signals arising from various CHF, CF_2 and CF_3 moieties.

In conclusion, this work demonstrates that F_2 can perform selective monofluorinations through electrophilic substitution. Apart from the necessary environmental conditions, including solvent, dilution and temperature, favoring the ionic mode of reaction, the substrate should have hydrogens with high atomic charge densities, so as to attract the positive end of the F-F dipole, high p-orbital content in their bond with the carbon, and a reasonable ratio of suitable to unsuitable hydrogens for such an attack.

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