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DIRECT FLUORINATION OF BICYCLIC MOLECULES

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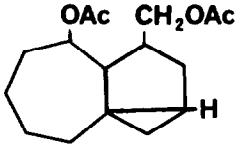
Summary: Elemental fluorine substitutes certain tertiary hydrogens of various bicyclo systems via the rare electrophilic pathway.

There is a substantial interest in fluorobicyclo compounds, not only from the synthetic point of view, up to now based mainly on the difficult total synthesis approach[1], but also from the theoretical and spectroscopic[2] one. The interest arises mainly from the fact that such systems are rigid and therefore various long range effects originating from the most electronegative fluorine atom, can be measured with a degree of certainty, without the complications arising from many possible conformers.

One of our main goals in chemistry is to introduce elemental fluorine into organic synthesis as a "legitimate" reagent. We would like to present here a new route for the preparation of various bicyclo derivatives, starting simply from the parent bicyclo compound and F_2.

When nitrogen diluted fluorine was reacted with organic substrates under conditions depressing radical reactions, but favoring ionic pathways, we found that it can substitute hydrogens with a full retention of configuration via the very rare electrophilic attack on a σ bond[3]. The most suitable hydrogens for such substitution will be of course the ones with the highest p-character. In this respect, the tertiary hydrogens are usually the best candidates in a given molecule. The p-contribution to the C-H bond depends mainly on its distance from an electronegative moiety and on the strain felt by the carbon in question. Bicyclic compounds usually possess several tertiary hydrogens and in many cases the deviation from the normal tetrahedron angle is considerable. When an attempt was made to react bicyclo compounds containing a three membered ring, such as the tricyclo derivative 1, or an i-steroid of type 2, with fluorine, no substitution of the low p-hybridized cyclopropyl hydrogens was observed and most of the starting material could be isolated even after prolonged treatment. The hybridization of the tertiary hydrogens in the bicyclo[3.1.1] systems such as cis-pinalol (3) have somewhat higher p-character. Running PRDDO calculations[4], with molecular coordinates obtained from Allinger's MM1[5] program, show however, that the hybridization of the two tertiary hydrogens is about $sp^{2.5}$, which is too low for a successful electrophilic fluorination. In such cases the only remaining pathway is indiscriminate radical fluorination resulting in tars.

$$R_3C-H + F_2 \longrightarrow R_3C-F$$



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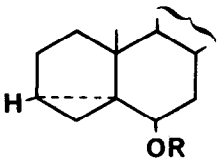

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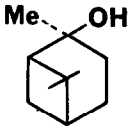

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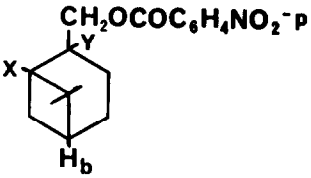
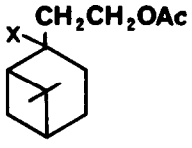
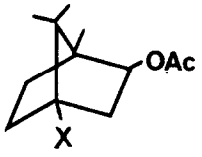


4 X = H_a ; Y = H_c
5 X = H ; Y = F
6 X = F ; Y = H

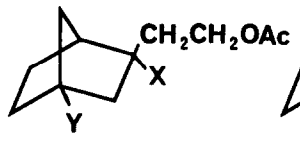
Moving the electronegative oxygen away from the rings, as in the case of cis-mirtanol-p-nitrobenzoate (4), does not much change the hybridization of the tertiary hydrogens on the bridges of the bicyclo system from $sp^{2.5}$, for both H_a and H_b, but the hybridization of the tertiary hydrogen H_c was calculated to be $sp^{3.0}$. The atomic charge on H_a however is higher than that on H_c because of the proximity of the electronegative oxygen to the latter. These facts are reflected in the results of the reaction, which produces cis-6,6-dimethyl-2-fluorobicyclo [3.1.1] heptyl methanol p-nitrobenzoate (5), m.p. = 65° in 15% yield, oil, ^{19}F NMR = -154 ppm, together with the 1-fluoro isomer 6, m.p. = 55°, 10% yield, oil, ^{19}F NMR = -148.7 ppm(bs)[6].



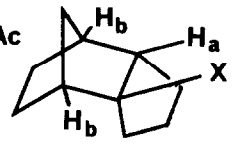
7 X = H
8 X = F



9 X = H
10 X = F



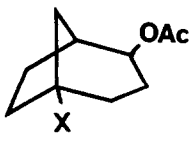
11 X = Y = H
12 X = F ; Y = H
13 X = H ; Y = F



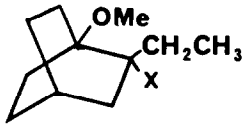
14 X = H_a
15 X = F

When conditions are more favorable for such electrophilic attack on a σ bond as in the case of nopyl acetate (7) the yield for selective monofluorination is raised to 40 % and 2-[6,6-dimethyl-2-fluoro-2-bicyclo[3.1.1]heptanyl]ethyl acetate (8) was formed as an oil, ^{19}F NMR = -179.3 ppm(dd, J_1=38, J_2= 15Hz). No substitution of the bridgehead hydrogens was observed, since their hybridization still remains low with respect to p : $sp^{2.5}$ vs. the $sp^{3.2}$ of the substituted hydrogen which also enjoys now higher atomic charge compared to the corresponding hydrogen in 4 because of its greater distance from the electronegative oxygen.

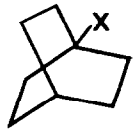
The bicyclo[2.2.1] system behaves similarly and the agreement between the predicted reaction site and the actual one is quite good. There is only one tertiary hydrogen in bornyl acetate (9) with hybridization only slightly higher, $sp^{2.6}$, compared to the bridgehead hydrogens in 4 or 7. Reacting 9 with F_2 thus leads to 4-fluorobornyl acetate (10), again in about 20 % yield, oil, ^{19}F NMR = -158.4 ppm. Creating another tertiary center in the [2.2.1]bicyclic system as in the case of 2-norbornyl ethyl acetate (11), directs the fluorination mainly to the unbridged tertiary hydrogen with $sp^{2.8}$ hybridization, producing 12 in 25 % yield, oil, ^{19}F NMR = -162.6 ppm (d quintet, J_1 = 30.5, J_2 = 9 Hz). At the same time the bridge hydrogen at C-4 ($sp^{2.6}$) was substituted by fluorine to produce 13 in 15 % yield, oil, ^{19}F NMR = -159.6 ppm (heptet J = 23 Hz). Another system which resembles 9 and 11 is the tricyclo[5.2.1.$0^{2.6}$]decane (14) which was obtained by hydrogenation of dicyclopentadiene. Two different sets of tertiary hydrogens are present H_a,$sp^{2.8}$ on the shorter bridge and H_b,$sp^{2.7}$, on the larger one. Since there are no further influences by any other heteroatom the electrophilic substitution proceeds smoothly and the product 2-fluorotricyclo[5.2.1.$0^{2.6}$]decane (15) was isolated in 75 % yield, oil, ^{19}F NMR = -126.8 ppm (m,W ½h = 75 Hz). Two tertiary hydrogens are present also in the different bicyclic system: 2-bicyclo[3.2.1]octyl acetate (16). In agreement with common intuition, calculations show that the hybridization at H-5 is somewhat higher in p than that of H-1,2.8 vs. 2.7, thus only 5-fluoro-2-bicyclo[3.2.1]octyl acetate (17), was formed in 20 % yield, oil, ^{19}F NMR = -162.7 ppm (m,W ½h = 110 Hz), while the rest of the starting material suffered extensive fragmentation originating in the undiscriminating radical fluorination.



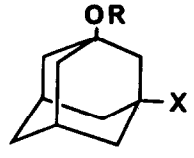
16 X=H
17 X=F



18 X=H
19 X=F



20 X=H
21 X=F



22 R=$COC_6H_4NO_2$; X=H
23 R=$COC_6H_4NO_2$; X=F
24 R=X=H
25 R=H; X=F

The next system which we have examined is the bicyclo[2.2.2]octan family. As with the other systems, e.g. 7 and 11, when an unbridged tertiary hydrogen is present this is the one which will preferably be substituted. This is demonstrated in the case of 1-methoxy-2-ethyl bicyclo[2.2.2]octane (18) which yields 1-methoxy-2-ethyl-2-fluoro bicyclo[2.2.2]octane (19) in 20% yield, oil, ^{19}F NMR= -146.1 (q, J = 32 Hz). This regio selectivity is again in accordance with the calculated hybridization of H-2: $sp^{3.1}$ vs. $sp^{2.9}$ for H-4, while the electronegative

oxygen situated near the reactive center is the main cause for the moderate yield. When fluorine was applied to the parent compound 20, which this time is not deactivated by any electronegative atom, an about 50 % yield of the 1-fluorobicyclo[2.2.2]octane (21), m.p. = 174° was produced[7]. With 1-Adamantanol p-nitrobenzoate (22) all the conditions are favorable for electrophilic reaction on the three equivalent tertiary hydrogens far away from the oxygen. Consequently, 3-fluoro-1-adamantanol-p-nitrobenzoate (23) was obtained in higher than 90 % yield, m.p. - 179°, ^{19}F NMR = -133.5 ppm. It is of interest to note that 1-adamantanol (24) itself can be successfully fluorinated as well to produce 3-fluoro-1-adamantanol (25) in 70 % yield m.p. = 174° (sealed tube) (lit. 174°, sealed tube)[8] showing that tertiary hydroxyls are not affected by F_2.

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References and Notes

1. See for example a) Della, E.W.; Cotsaris, E.; Hine, P.T., J. Am. Chem. Soc., 1981, 103, 4131. b) Adcock, W.; Abeywickrema, A.N., J. Org. Chem., 1982, 47, 2951.
2. See for exmaple a) Barfield, M.; Della, E.W.; Pigou, P.E.; Walter, S.R., J. Am. Chem. Soc. 1982, 104, 3549. b) Adcock, W.; Abeywickrema, A.N., Tetrahedron Letters, 1979, 1809.
3. Gal, C.; Rozen, S., Tetrahedron Letters, 1984, 25, 449 and references therein.
4. Dixon, D.A.; Kleier, D.A.; Lipscomb, W.N., J. Am. Chem. Soc., 1978, 100, 5681 and references therein.
5. Allinger, N.L., Adv. Phys. Org. Chem., 1976, 13, 1.
6. A description of the fluorination set-up for using elemental fluorine can be found in Rozen, S.; Lerman, O., J. Org. Chem., 1980, 45, 672. In a typical experiment, a stream of 4-5% F_2 in N_2 was passed through a solution of about 1 gr of substrate in 450 ml of $CFCl_3/CHCl_3$ (1:1) at -75° C. The reactions were usually monitored by GC or tlc and stopped at a conversion of about 95%. Analytical data of the new fluorinated compounds described here, including micro analyses, mass spectra and ^{13}C NMR are in excellent agreement with the assigned structures. The ^{19}F NMR spectra were recorded with a Bruker WH-90 instrument at 84.67 MHz, $CFCl_3$ serving as an internal reference.
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