Tetrahedron Letters Vol. 21, pp 5067 - 5070 0040-4039/80/1222-5067$02.00/0

SELECTIVE FLUORINATION ON TERTIARY CARBON-HYDROGEN SINGLE BONDS IN THE ALIPHATIC SERIES

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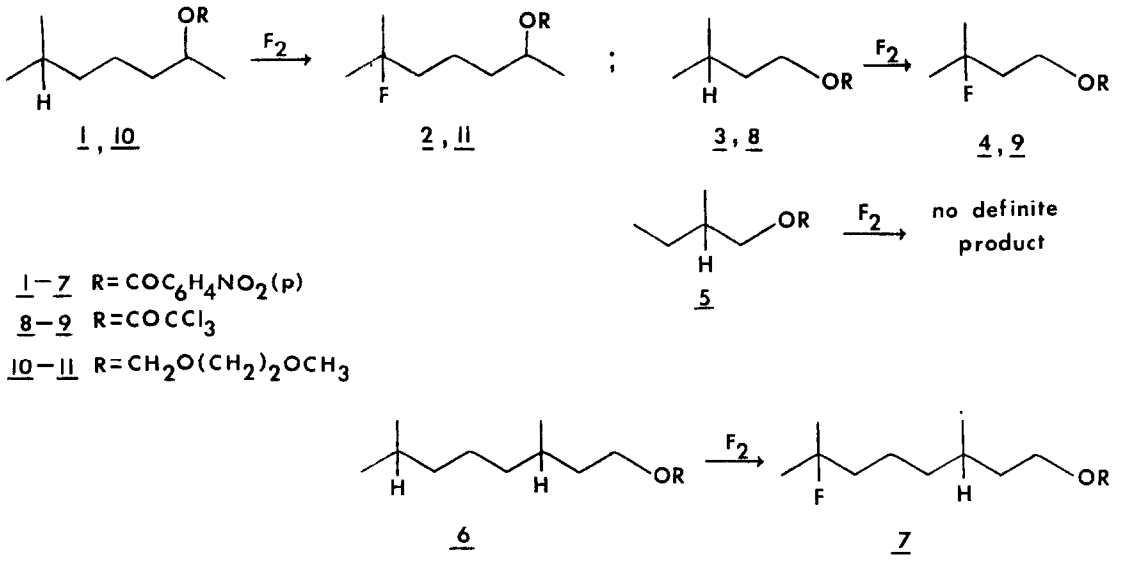
Abstract: Fluorine acts as an electrophile and, as such, reacts with remote and unactivated tertiary hydrogens in aliphatic alcohols and acids, resulting in the corresponding fluorine derivatives.

Executing chemical reactions around remote and unactivated tertiary hydrogens is quite a formidable task. Indeed, only a few examples of such chemistry are described, most of them in the steroidal field. There are two approaches for activating remote tertiary sites: a attacking the steroid skeleton by free radicals either by intra-[1] or intermolecular[2] process, b acting in an ionic mode with the powerful electrophile fluorinating reagents such as CF_3OF or even better, F_2, producing various fluorosteroids[3].

Recently we have described a way of activating tertiary positions in some cyclohexane derivatives using elemental fluorine[4]. It has been well established by now[3,4], that the fluorine molecule acts at low temperatures as an electrophile and is capable of interacting with the relatively high electron density tertiary C-H bonds. An oxygenated or other strong electron-withdrawing group should deactivate the nearby carbon-hydrogen bonds toward electrophilic attack, thus increasing the selectivity of the reaction. We wish now, for the first time, to describe this novel and unusual reaction for activating tertiary positions in the aliphatic field.

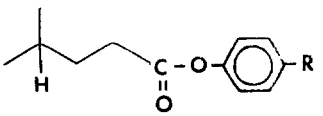
When 500 mg of 6-methyl-2-heptyl p-nitrobenzoate (1) were dissolved in 400 ml of a mixture of $CHCl_3$:$CFCl_3$ (1:1) and treated with nitrogen diluted fluorine (4-6% v/v) at -70°, a fluorinated product was obtained in 65% yield[5]. It was identified as 6-fluoro-6-methyl-2-heptyl p-nitrobenzoate (2) (m.p. = 43°)[6].



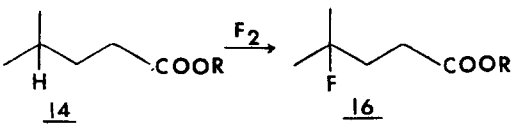
Bringing the tertiary position nearer to the ester group as in 3-methyl-1-butyl p-nitrobenzoate (3), slowed the reaction somewhat, but eventually the yield of the expected fluorinated product 4 (oil) was again around 60%. When however, the tertiary hydrogen was placed even closer to the strongly electronegative p-nitrobenzoate group as in 5, the consumption of the starting material was very slow, numerous products were formed as evidenced by TLC, but no definite compound was isolated and identified. The 3,7-dimethyl-1-octyl p-nitrobenzoate 6, represents an interesting case where two tertiary hydrogens can be potentially replaced by electrophilic fluorine. However, only one monofluoro product was isolated and it proved to be the 3,7-dimethyl-7-fluoro-1-octyl p-nitrobenzoate (7) (oil, 30% yield). This result emphasizes the strong influence of the electronegative elements of the protective group on the reactivity of the tertiary hydrogens toward an electrophilic attack.

The p-nitrobenzoate group was used in this work, mainly for decreasing the volatility of the low boiling alcohols we have used. If desired it can be replaced by the equally efficient and fluorine resisting trichloroacetate group as demonstrated by 8. This when reacted as above gave the fluorinated product 9 (oil) in 65% yield. When however the ester group was replaced by an ether function as in 10, the yield of the fluorinated product 11 (oil) was considerably lower - 20%. It seems that in ethers the selectivity of the electrophilic fluorination was reduced and among the other by-products we could detect also compounds with a carbonyl group[7].

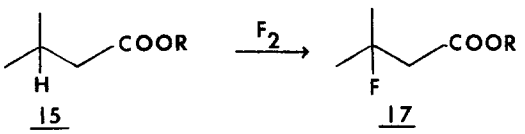
We have tried this novel fluorination also on aryl-esters of aliphatic acids. For example, when the phenyl 12, or the p-nitrophenyl ester 13 of isocaproic acid were used, the reaction was very messy and no definite product could be obtained. The proton NMR of the crude reaction mixture from 12 showed no aromatic protons, while the FMR spectrum showed many signals ranging from ϕ^* = 200 down to ϕ^* = -40ppm. Again when 13 was reacted, no aromatic protons could be seen, so obviously fluorine is responsible in a yet unknown mechanism, for breaking the aryl ester bond. Nevertheless we believe that the initial attack of the fluorine is on the aromatic ring which is a phenol derivative and as such is activated to some extent toward electrophilic attack even with the p-nitro group attached.



12 R=H 13 R=NO_2



14 16



15 17

14—17 R=CH_2CCl_3

This difficulty however, can easily be circumvented by using esters of 1,1,1-trichloroethanol. Thus when 1,1,1-trichloroethyl isocaproate (14) was treated with fluorine, 16 was isolated in 55% yield (oil). Moving the tertiary position even nearer toward the oxygens as in the isovaleric ester 15, slowed down the reaction considerably, but eventually the expected fluorinated product 17 (oil) was obtained, although in lower yield (25-30%) than for 16 (compare with 5).

References and Notes

1. R. Breslow, R.J. Concoran, B.B. Snider, R.J. Doll, P.L. Khanna and R. Kaleya, J. Am. Chem. Soc. 99, 905 (1977) and references therein.
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5. For a general description of the fluorination procedures see ref. 4 and ref. 6 there. It is also important to bear in mind that fluorine is a highly reactive and corrosive material and only experienced persons should handle it.

6. The identification of the fluorinated compound 2 can easily be deduced from its NMR spectrum: in the starting material 1 the isopropyl group resonates at 0.87ppm as a doublet (J = 6.8Hz). In the fluorinated compound the two methyls of this group are shifted downfield to 1.34ppm and are split into a doublet with J = 21Hz which is characteristic of the Me_2CF group. In the FMR spectrum a multiplet with 7 lines at ϕ^* = 138.8ppm (J = 21Hz) was observed, which is in excellent agreement with the proposed structure. All other recognizable signals in H' NMR which are in the vicinity of the ester group have practically the same chemical shifts in both reactant and product. These spectra are characteristic to all fluorine containing materials described in this work. As all these compounds are previously unknown, we have also confirmed their composition by microanalysis. Usually the course of the reaction was monitored by G.C. and was stopped when very little starting material (~5%) was left. If the reaction was continued beyond this stage, usually a slow deterioration took place, due to random radical fluorination (see ref. 4).

7. In the work of one of our group (S.R.) on the fluorination of steroids (Ref. 3), it was also found that in some cases the etherial group is not suitable for protection of alcohols, since it could be oxidized to the corresponding carbonyl compound.

(Received in UK 18 October 1980)