Tetrahedron Letters No. 8, pp 725 - 728.
© Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0215-0725$02.00/0

A NOVEL FLUORINATING METHOD FOR THE SYNTHESIS OF α-FLUOROKETONES

S. ROZEN and Y. MENAHEM
Department of Chemistry - Tel-Aviv University - Israel.

The conventional method for the synthesis of α-fluoroketones was the action of perchloryl fluoride on ketone enamines. Though this reagent has been successful, mainly with steroidal ketones,1) it has well-known and serious limitations. Thus the reagent can be used only with very electron-rich olefins. Enol acetates for instance hardly react. Often chlorinated or oxygenated compounds are obtained rather than the required fluoroketones.2) Moreover, the attractiveness of this reagent is reduced by the tendency for its reactions to be accompanied by violent explosions.

A new method for fluorinating electron rich double bonds was developed with the introduction of fluoroxytrifluoromethane CF_3OF.3) In addition to this reagent, which is expensive and of limited availability, F_2 can in particular circumstances act as a source of electronegative fluorine.4) However, in our attempts to react F_2 with enol acetates, no α-fluoroketones could be isolated from the complicated reaction mixture.

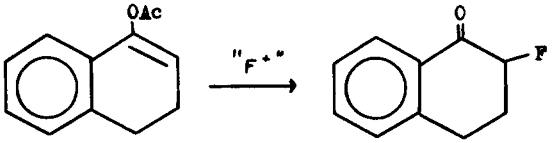
We have found that an oxidative solution results when elemental fluorine is passed into a suspension of CF_3COONa in freon at -75°, and a considerable portion of the oxidising ability of this solution is due to the presence of fluoroxypentafluoroethane CF_3CF_2OF (1).5,6) The presence of 1 is proved by its reaction, in situ, with various olefins. Thus from trans stilbene, DL-threo-2-fluoro-3-pentafluoroethoxybibenzyl (2) (m.p. 87°),6) the product of the cis addition of the elements of CF_3CF_2OF was isolated.

CF_3CF_2OF
1

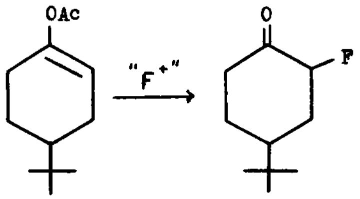
$PhCHF{-}CH(OCF_2CF_3)Ph$ (DL-threo)
2

Nevertheless, from experiments with several olefins, it was concluded that the fluoroxy compound 1 does not constitute more than 50% of the mixture of oxidising compounds formed in the reaction between F_2 and CF_3COONa. However, it seems reasonable to assume that the other oxidising compounds present are also of the perfluoroxyfluoride type.[7] All such compounds, including CF_3OF, are similar in that they contain electrophilic fluorine attached to a good leaving group $-OR_f^-$. In cases where the action of electrophilic fluorine is of main interest, and that of the conjugate anion OR_f^- is not critical, the oxidising mixture may effectively act as a homogeneous reagent and high yields can be expected. A typical reaction of this type would be the action of electrophilic fluorine on enol acetates, giving α-fluoroketones.

The enol acetate 3 was obtained from α-tetralone, using isopropenyl acetate. This derivative (1.5 mmole) was dissolved in a small amount of methylene chloride, the solution was cooled and added to 2.5 mmole of the oxidising solution at -75°.[8] After one minute the reaction mixture was poured into an aqueous thiosulphate solution and the isolated crude product then kept overnight in a methanolic solution of NaOH.[9] The required 2-fluoro-α-tetralone (4) (m.p. 38°) was isolated in 85% yield.



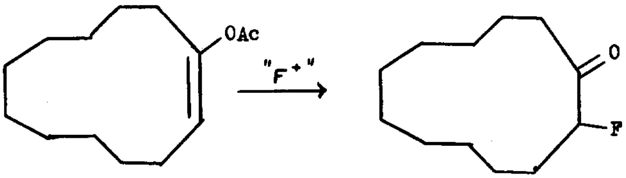
3 4



5

6 α-$F_{(ax)}$ -trans

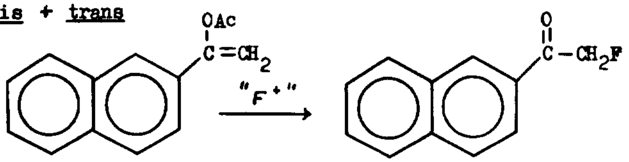
7 β-$F_{(eq)}$ -cis



8

cis + trans

9



10 11

Similarly, a mixture of two ketones was obtained from the enol acetate of 4-t-butylcyclohexanone (5). This was separated chromatographically into trans (6) and cis (7) 2-fluoro-4-t butylcyclohexanone in the ratio 4:3 (72% combined yield). In previous preparations of this mixture of ketones the isomeric ratio has been overwhelmingly in favour of the thermodynamically more stable cis isomer. Apparently the mixture of fluoroxy-compounds resembles CF_3OF 3) in showing mainly cis addition to double bonds, ensuring that the trans isomer 6 be the main product.

Large ring ketones are not basically different in this reaction. The action of isopropenyl acetate on cyclododecanone gave a mixture of cis and trans enol acetates 8. This mixture when reacted with the solution of perfluorofluoroxy compounds gave, after basic treatment, 2-fluorocyclododecanone (9) as the only product (87% yield, m.p. 54°).

In a reaction similar to the above, α-fluoromethylnaphthyl ketone (11) (45% yield, m.p. 80°) resulted from methylnaphthyl ketone enol acetate (10). The relatively low yield in this case is possibly due to some degree of electrophilic fluorination on the aromatic portion of 10.

In comparison to the use of other fluorinating reagents such as $FClO_3$ or CF_3OF (whose disadvantages and limitations have been detailed above) or the exotic reagent N_2F_2, 11) the above-described method opens up a new, easy and most effective route to the synthesis of α-fluoro ketonic compounds.

This is, to our knowledge, the first time that the extremely oxidising nature of elemental fluorine has been tamed by preparing from it, in one step, an intermediate reagent which can be used in situ for fluorination.

Notes and References

1) See for instance: J. W. Chamberlin, Steroid Reactions, C. Djerassi, ed. Holden-Day Inc. San Francisco, 1963 p. 155.

2) See for instance: Y. Osawa and N. Neeman, J. Org. Chem. 32 3055 (1967); W. A. Sheppard, Tetrahedron Lett., 83 (1969).

3) For an excellent review of the chemistry of the reactions of CF_3OF with olefins, see R. H. Hesse, Israel J. Chem. 17 60 (1978).

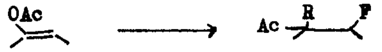
4) D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet and S. Rozen, J. Am. Chem. Soc., 98 3036 (1976).

5) CF_3CF_2OF along with some other oxyfluoro compounds are known compounds. However, because of the difficulties of its original synthesis, the tedious procedure and the low yields, it has practically never been employed in any organic synthesis.

6) A more detailed description of this reaction, as well as its mechanism, will appear elsewhere.

7) J. H. Prager and P. G. Thompson, J. Am. Chem. Soc., 87 230 (1965); P. G. Thompson and J. H. Prager, ibid 89 2263 (1967).

8) The oxidation power of the reaction mixture can be determined by titration of the iodine liberated from aqueous KI solution.

9) Along with the desired α-fluoroketone it seems that additional adducts such as  (R = OR_f or F) can be formed. A basic treatment can convert all these adducts to the desired α-fluoroketones - see ref. 3. Apart from this, the basic treatment destroys minute potential sources of HF which in their turn can decompose the α-fluoroketones by an autocatalytic reaction.

10) N. L. Allinger and H. M. Blatter, J. Org. Chem., 1523 (1962); P. Moreau, A. Casadevall and E. Casadevall, Bull. Soc. Chim. Fr., 2013 (1969).

11) J.Bensoam and F. Mathey, Tet. Lett. 2797 (1977).

12) All new fluorine-containing compounds had the correct composition established by microanalysis. Their spectral data (IR, NMR and mass spectra) are in excellent agreement with the assigned structures and stereochemistry.

(Received in UK 6 December 1978)