Tetrahedron Letters,Vol.26,No.18,pp 2233-2236,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

FLUORODENITRATIONS USING TETRABUTYLAMMONIUM FLUORIDE

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Fluoroaromatics are prepared in good yield under mild conditions using the tetrabutylammonium fluoride promoted fluorodenitration of nitroaromatics.

The great demand for fluoroaromatics as building blocks in the synthesis of pharmaceuticals and pesticides has led to the search for attractive preparative routes.[1,2] The most important of these routes is the nucleophilic displacement of an activated leaving group by fluoride ion.[2] While the halogen exchange version of this type of reaction is now well established, little is known of the displacement of groups other than halogen by fluoride.

Numerous examples of nucleophilic substitution of activated nitro groups by groups such as CH_3O^-, CN^-, RS^-, etc., have been reported.[3] Examples of fluorodenitration are however, rare and usually involve very harsh conditions which can lead to a multiplicity of products.[3-6] Very recent work on the fluorodenitration of highly activated nitroaromatics has been more encouraging,[7,8] and has led us to consider the possible use of this reaction as a viable route to fluoroaromatics. We report here our preliminary results from experiments based on the use of the new and very powerful fluoride ion sources "anhydrous tetrabutylammonium fluoride"[9,10] as a reagent for the preparation of fluoroaromatics via fluorodenitration, under mild conditions.

The commercially available tetrabutylammonium fluoride trihydrate, TBAF.$3H_2O$, can be converted to a highly reactive oil containing less than one mole equivalent of water (and <10 mole % decomposition products) by evaporation at 50-60°C and <1 mmHg for 18-24 hours. The resulting reagent is highly reactive in the fluorodenitration of activated nitroaromatics. Thus 1,2-dinitrobenzene is rapidly and quantitatively converted into 2-fluoronitrobenzene by using an excess of the "anhydrous" tetrabutylammonium fluoride reagent (TBAF) in the absence of solvent or in tetrahydrofuran at room temperature. This can be compared to the same reaction using rubidium fluoride in dimethylsulphoxide as the fluorine source, which yields only 58% 2-fluoronitrobenzene after reaction for 20 minutes at 150°C.[7]

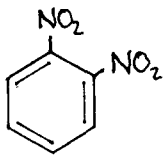
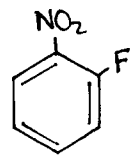
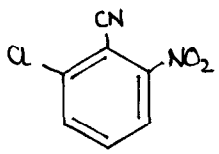
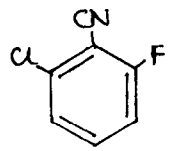
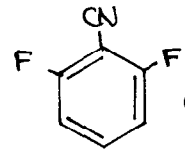
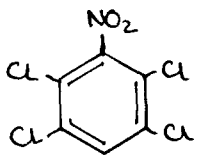
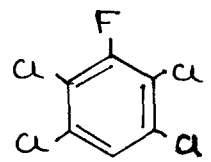
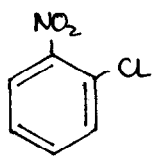
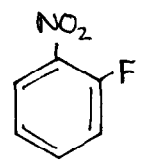
2-Chloro-6-nitrobenzonitrile also undergoes fluorodenitration on treatment with an excess of TBAF at room temperature although the reaction is complicated by competing halogen exchange reactions (Table). A mixture of 2-chloro-6-

fluorobenzonitrile and 2,6-difluorobenzonitrile is obtained after reaction for 1.5 hours in tetrahydrofuran. We were not able to detect any 2-fluoro-6-nitrobenzonitrile at any stage in the reaction suggesting that under these conditions fluorodenitration is significantly faster than halogen exchange. This can be contrasted to the reaction of the same substrate with rubidium fluoride in dimethylsulphoxide which gives a mixture of 2-chloro-6-fluorobenzonitrile and 2-fluoro-6-nitrobenzonitrile.[7] Little if any, difluorination is observed in the heterogeneous reaction even with an excess of the fluoride suggesting that the inorganic products resulting from the fluorodenitration reaction (presumably the metal nitrite, nitrate, or oxide) may poison the solid fluoride reagent.

2,3,5,6-Tetrachloronitrobenzene also undergoes fluorodenitration (to yield 2,3,5,6-tetrachlorofluorobenzene) on reaction for 1.5 hours with TBAF in tetrahydrofuran at room temperature. (Table). This can be compared to the same reaction using KF/DMF whichgives a yield of 37% of the monofluorinated product after 4.5 hours at 147°C.[4] In this case, fluorodenitration is presumably primarily a result of steric effects rather than electronic effects. Two ortho chlorines may well be sufficient to distort the nitro group out of the plane of the ring and thus increase its leaving group ability. This is supported by studies on the ability of various aromatics to form Meisenheimer-type complexes with F^-.[9,11] Thus a solution of 2,3,5,6-tetrachloronitrobenzene in tetrahydrofuran immediately turns orange/red on treatment with TBAF and the observed band in the visible spectrum is at a position (λ_{max} = 415 nm) characteristic of an F^--aromatic σ-complex.[9] The intensity of the band is, however, more comparable to that observed for an F^--pentachlorobenzene complex (λ_{max} = 425 nm) than to the much more intense bands observed for an F^--4-chloronitrobenzene complex under the same conditions.[11] Thus the nitro group which would normally play the major role in stabilising σ-complexes of this type, appears to be much less capable of stabilising anionic complexes of 2,3,5,6-tetrachloronitrobenzene. This inhibition of resonance delocalisation of charge is most reasonably explained by a loss in ring-nitro group coplanarity. The use of steric effects rather than or in addition to electronic effects to activate leaving groups in nucleophilic fluorine-transfer reactions may well open the door to a number of interesting and useful fluoroaromatics.

2-Chloronitrobenzene provides a useful contrast with the other substrates studied in terms of its reaction behaviour with F^-. This substrate has relatively little electronic or steric activation of the nitro group while the chlorine is electronically activated to nucleophilic exchange. Reaction of this substrate with TBAF under the same conditions as employed in the other reactions, gives 2-fluoronitrobenzene only. The reaction is very slow and only 25% halogen exchange is observed after 24 hours. The remarkable difference in reaction rates between this 'conventional' halogen exchange reaction and the fluorodenitration reactions is a good illustration of the potentially excellent leaving group ability of the nitro group when suitably activated by other groups.

TABLE Reactions of Nitroaromatics with Tetrabutylammonium Fluoride[a]

Starting Material	Products (% yield by g.l.c.)
	 (100)
	 (75)  (25)
	 (70)
	 (<5)

[a]All reactions were carried out by stirring a mixture of tetrabutylammonium fluoride (5 mol. equivs; prepared from the trihydrate by evaporation at 50-60°C and ca. 1 mmHg for 24 h) and the substrate in dried tetrahydrofuran for 1.5 h at room temperature. The mixture was then quenched with water and the products extracted into ether. The products were analysed by g.l.c. and g.l.c.-mass spectrometry.

We believe that our observations not only illustrate the usefulness of the fluorodenitration method as a route to fluoroaromatics but also illustrate the potency of the 'dried' form of TBAF as a source of fluorine for nucleophilic substitution reactions.

We are indebted to Shell International Chemie Maatschappij for their generous support of this work and to other members of the York fluorine group for their advice and assistance.

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(Received in UK 22 February 1985)