Journal of Fluorine Chemistry, *30* (1985) 251–258

Received: April 25, 1985; accepted: July 1, 1985

THE FLUORINATION OF ORGANIC SUBSTRATES WITH TETRAPHENYL-PHOSPHONIUM HYDROGENDIFLUORIDE

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SUMMARY

Tetraphenylphosphonium hydrogendifluoride acts as a powerful source of F^- in various reactions with organic substrates to give fluorine containing-products.

INTRODUCTION

The most widely used reagents in organofluorinations are the alkali metal fluorides but their usefulness is severely limited by their poor solubility in aprotic solvents [1,2]. Very many attempts have been made to overcome this problem including the use of quaternary ammonium fluorides, a metal fluoride together with a phase transfer catalyst, and metal fluoride-crown ether systems. Unfortunately all F^- systems that have been developed so far suffer from poor solubility (e g. metal fluorides), low thermal stability usually coupled with high hygroscopicity (e g. quaternary ammonium fluorides) or strong ion-ion (e g. KF-18-crown-6, [3]) or ion-solvent (e g. KF-ethanoic acid [4]) interactions [5]. The considerable importance of the fluoride ion in organofluorine chemistry demands the continuing search for new sources of this anion.

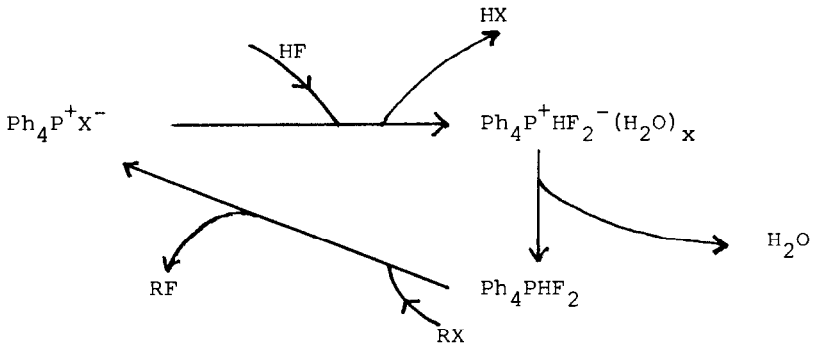
RESULTS AND DISCUSSION

Monofluorophosphoranes are very promising F^- reagents [6,7]. The delicate balance between four and five coordination at phosphorus seems to be especially fine when one fluorine is

0022-1139/85/$3.30

present and this results in the possibility of isolating more than one structural form of any monofluorophosphorane. We recently reported the preparation of at least three different forms of tetraphenylfluorophosphorane from tetraphenylphosphonium bromide via the hydrogendifluoride, $Ph_4P^+HF_2^-$ [8]. In its original form, the hydrogendifluoride showed spectroscopic properties consistent with the presence of a simple, undistorted HF_2^- anion [8,9]. In this form, the compound contains at least one water molecule of crystallisation. Exhaustive drying of the wet material results in significant changes in the i.r. spectrum of the compound and in particular the splitting of the characteristic HF_2^- vibrational band at 1208 cm^{-1}. Such an effect can be attributed to the distortion of the HF_2^- anion [9,10]. The dried form of the compound slowly reverts to the monohydrate on exposure to the atmosphere and the i.r. spectrum of the compound returns to its original form [8]. We interpret these observations in terms of the formation of an ion-paired form of the compound where the resulting $P^+-(F...HF)^-$ interaction is comparable but probably not as strong as that observed in $Ph_4P^+F^-$ [8].

The hydrogendifluoride ion is normally unreactive and is only expected to react with very powerful electrophiles [11]. The inertness of the anion can be attributed to its very strong hydrogen bond [9]. The weakening of this hydrogen bond (e.g. by interaction with another hydrogen bonding centre such as $R_3\overset{+}{N}H$ or a second HF molecule) is known to result in a marked loss in ion stability [9]. One consequence of this may be an increase in reagent nucleophilicity resulting from in-situ F^- formation. This possibility for our reagent is especially attractive for several reasons. The compound is easily prepared [8] and dried. It enjoys good thermal stability (no HF loss occurs below 130°C) and excellent solubility characteristics (it is very soluble in polar solvents such as CH_3CN and will also dissolve in many less polar solvents on warming). A further and perhaps most important advantage of the reagent is that typical inorganic side-products from fluorination reactions employing the reagent can be easily reconverted to Ph_4PHF_2 (see Experimental). The overall methodology is summarised below.



Reactions employing Ph_4PHF_2 were generally very successful (TABLE) giving F-incorporation into the organic substrate at reaction rates at least comparable to those reported for reactions employing other F^- reagents. Thus $PhCH_2Br$ can be completely converted to $PhCH_2F$ after 2·5 h at 52°C using Ph_4PHF_2 in CH_3CN. When the same reaction was attempted using KF-18-crown-6 at the same F^- concentration (0.13M) and higher reaction temperature (83°C), the reaction rate was barely one thirtieth of that observed with Ph_4PHF_2. Not surprisingly, water has a significant effect on reaction rates so that use of $Ph_4^+HF_2^-(H_2O)$ in the above reaction resulted in a reduction of rate to about one third of that observed in the reaction employing the anhydrous material.

The stoichiometry of the non-catalytic reactions attempted proved to be less than straightforward. Quantitative fluorination of the organic substrate generally required two mole equivalents of Ph_4PHF_2. This appears to be the result of the formation of an unreactive and surprisingly stable poly-fluoride $Ph_4P^+F(HF)_2^-$ resulting from the scavenging of a molecule of HF from one hydrogendifluoride molecule by another. This rather surprising aspect of the reaction chemistry is the subject of a current programme of research but it is worth noting at this stage that this side-product is easily reconverted to its parent hydrogendifluoride (see Experimental).

Fluorodenitration reactions as well as halogen exchange reactions occur readily with Ph_4PHF_2 as the source of fluorine. The replacement of an activated nitro group by fluoride is a quite useful yet surprisingly little exploited route to

TABLE

Fluorinations with Ph_4PHF_2

Substrate	Solvent	T/°C	Time/h	Product	Yield[a] %
$PhCH_2Br$	CH_3CN	52°C	2.5	$PhCH_2F$	100
$CH_3(CH_2)_6I$	CH_3CN	80°C	2	$CH_3(CH_2)_6F$	46[b]
$CH_3(CH_2)_9Br$	Sulpholane	130°C	2	$CH_3(CH_2)_9F$	70[b]
$2,4\text{-}(NO_2)_2C_6H_3Cl$	CH_3CN	80°C	2	$2,4\text{-}(NO_2)_2C_6H_3F$	100
$3,4,5\text{-}Cl_3C_6H_2CF_3$	-	reflux	2	$3,5\text{-}Cl_2\text{-}4\text{-}F\text{-}C_6H_2CF_3$[c]	82
$3,4\text{-}Cl_2C_6H_3CF_3$	-	reflux	2	$3,4\text{-}F,Cl\text{-}C_6H_3CF_3$[d]	32
$2\text{-}Cl\text{-}6\text{-}NO_2C_6H_3CN$	DMSO	25°C	2	$2\text{-}Cl\text{-}6\text{-}FC_6H_3CN$	100
$1,2\text{-}(NO_2)_2C_6H_4$	Sulpholane	100°C	2	$2\text{-}F\text{-}C_6H_4NO_2$	70
C_3F_6	CH_3CN	25°C	-	C_6F_{12}[d]	-
C_3F_6	DMF	25°C	-	$C_6F_{12}+C_9F_{18}$[d,e]	-

[a]G.l.c. yields assuming a 2:1 stoichiometry. [b]Along with <10% of the dehydrohalogenation(alkene) product. [c]Along with small quantities of other mono-fluoro isomers and difluoro products. [d]Mixture of isomers. [e]The ratio of dimers to trimers produced was 1:1.6.

fluoroaromatics [12-16]. The nitro group is an excellent leaving group when itself activated and/or twisted out of the plane of the aromatic ring by neighbouring bulky groups. 2-Chloro-6-nitrobenzonitrile is a particularly interesting substrate as both the chlorine (-M activation by CN and -I activation by CN and NO_2) and the nitro (-M activation by CN, -I activation by CN and Cl and steric effects from CN) groups are potentially labile to substitution. Reaction with RbF at 150°C in dimethylsulphoxide has been reported as giving both 2-fluoro-6-nitrobenzonitrile and 2-chloro-6-fluorobenzonitrile in the mole ratio ca. 1:3 [16]. Reaction of this substrate with two mole equivalents of Ph_4PHF_2 in dimethylsulphoxide at room temperature gave the product, 2-chloro-6-fluorobenzonitrile, from fluorodenitration exclusively. We were not able to tell if this excellent regiospecificity is a result of some feature of the reaction chemistry of our reagent or of the mild conditions under which we were able to carry out the reaction but the potential usefulness of this type of chemistry is clear and is the subject of current research in our laboratory.

We were also able to use Ph_4PHF_2 as an efficient catalyst for the oligomerisation of hexafluoropropene [17]. After a short induction period, reaction occurred rapidly and exothermically in acetonitrile or dimethylformamide as solvents. The rapid reaction in dimethylformamide was especially notable although both dimers and trimers were obtained from this reaction - a result of the good solubility of the dimer in dimethylformamide rather than a feature of the reactivity of the reagent. Surprisingly, we were unable to obtain any appreciable oligomerisation of tetrafluoroethylene using Ph_4PHF_2 in a variety of solvents even at high temperatures and pressures. Although this substrate is appreciably less reactive than C_3F_6, [17], we would have expected such a reactive F^- reagent to catalyse its oligomerisation. It may well be that the catalytic activity of our reagent is extremely sensitive to the presence of water and that more stringent drying procedures will be required for such a reaction. We have observed that as little as 0.6 mole equivalents of water completely stops the oligomerisation of C_3F_6.

Finally, it is worth noting that the excellent solubility characteristics and thermal stability of Ph_4PHF_2 opens the door to reactions being achieved in the absence of a solvent. Thus the fluorinations of chlorobenzotrifluorides were carried out in the neat substrates at reflux temperatures. Any decomposition of the reagent at these temperatures is only likely to give $Ph_4P^+F^-$ which itself should behave as an F^- source. Our preliminary experiments with $Ph_4P^+F^-$ in organo-fluorinations have been encouraging but have been hampered by the lower solubility and greater difficulty in drying of this reagent compared to Ph_4PHF_2. As yet, we are unable to confirm the hypothesis that the latter reagent operates as an in-situ source of F^- and while this would seem to be the most probable mechanism of reaction, alternative mechanisms cannot be ruled out.

EXPERIMENTAL

Tetraphenylphosphonium hydrogendifluoride was prepared by passing an acetonitrile solution of the bromide through a column of Anberlite IRA 410 resin in its HF_2^- form. The resin activation was achieved by passing a 0.5M solution of NH_4HF_2 through the column until no further precipitate was obtained with $AgNO_3$, followed by column washing with water and then acetonitrile. The solution of Ph_4PHF_2 in acetonitrile was evaporated to dryness on a rotary evaporator and the resulting solid dried at *ca.* 60°C and 0.1 mmHg for 24 h. Reaction solvents were dried before use but all substrates were commercial materials used without further treatment.

The Ph_4PHF_2 was analysed by infrared spectroscopy (see RESULTS AND DISCUSSION) using a Perkin Elmer 683 spectrophotometer interfaced to a 64K microcomputer and by volumetric analysis. Products were generally analysed by comparison with authentic materials using g.l.c., ^1H and ^{19}F n.m.r. spectroscopy and g.l.c.-mass spectrometry.

The halogen exchange and fluorodenitration reactions were generally carried out in the same way. In a typical reaction, tetraphenylphosphonium hydrogendifluoride (1.88 g, 0.05 mole) was dissolved in dried CH_3CN (20 g) and the solution was heated with stirring, to 52°C. The substrate, benzyl bromide (0.43 g, 0.025 mole), was added to the warm solution and the reaction was monitored by g.l.c. until no peak due to the starting material was evident. Addition of dry diethyl ether (100 g) at this stage resulted in precipitation of all of the inorganics. Filtration of this solution followed by evaporation to dryness gave spectroscopically pure benzyl fluoride (0.25 g, 0.044 mole, 88%). The inorganic products mixture could be reactivated by passing an aqueous mixture of these products through an ion exchange resin in the HF_2^- form as described earlier. Use of the resulting regenerated Ph_4PHF_2 in the fluorination of benzyl bromide under the same conditions as described above gave about the same reaction rate and a final product yield within $\pm$ 5% of that obtained earlier.

The oligomerisation of hexafluoropropene was carried out by gently bubbling the fluorocarbon through a solution of Ph_4PHF_2 (1.02 g, 2.7 mmol) in either CH_3CN or DMF (15 cm^3). After an induction period of 1 or 2 minutes, the solution became orange coloured and a heavy layer of fluorocarbons became evident. After 1 hour, the reaction was stopped, the mixture separated and the fluorocarbon layer fractionally distilled. One fraction was obtained for the CH_3CN reaction and two fractions were obtained for the DMF reaction. The resulting products were analysed by ^{19}F n.m.r. spectroscopy.

ACKNOWLEDGEMENT

We thank the SERC and ICI for their support. We are especially indebted to Drs. R.D. Powell and D. Bonniface for their advice and for providing facilities for some of the reactions described. The assistance of Miss C. Streich and other members of the York fluorine group is gratefully acknowledged.

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