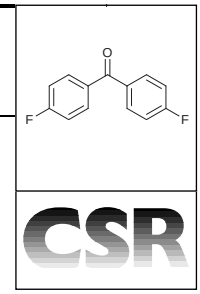
Nucleophilic routes to selectively fluorinated aromatics



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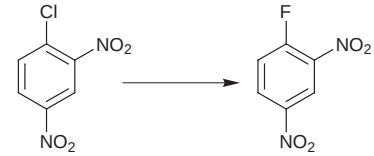
Selectively fluorinated aromatic compounds are of interest in many sectors. Of the methodologies used for their formation, halogen exchange is the only industrial rival to the diazonium based routes. Although many compounds can be formed by halogen exchange, the formation of *meta*-fluorinated species by this route is difficult. One possible method for overcoming this is fluorodenitration. Although traditionally plagued by side reactions, recent reports suggest that, with careful control of the reaction conditions, fluorodenitration could well provide a viable industrial alternative for the formation of selectively fluorinated aromatic compounds.

1 Introduction: Selective fluorination and its commercial importance

Selectively fluorinated compounds are used in many areas, including the pharmaceutical, agrochemical and dye industries. Such compounds have applications as herbicides and fungicides as well as being used in the treatment of cancer. Interest in selectively fluorinated aromatic compounds arises from the unique properties of the C–F bond and the effect of the incorporation of fluorine on the physical and chemical properties of organic molecules.[1,2] The high strength of the C–F bond can result in the inhibition of metabolism when fluorine is incorporated at or near a reactive site. Fluorine is also one of the smallest available substituents which can be significant for molecules in which molecular conformation is important. Thirdly, the electron-withdrawing effect of fluorine can have profound effects on the reactivity of other functional groups in the molecule. While organofluorine compounds are rare in nature, the interest in such compounds is demonstrated by the vast numbers of synthetic products which are now available.

Selectively fluorinated compounds can be formed by a number of methods.[1,2] Of the nucleophilic methodologies available, Balz–Schiemann, HF-diazotisation and halogen exchange are well established routes to such compounds. Both Balz–Schiemann and HF-diazotisation are based around the conversion of a diazonium salt to a fluoroaromatic, with hazardous and toxic reagents being required. In halogen exchange reactions, a chloro group is displaced by a fluoride ion to yield the corresponding fluoroaromatic, Scheme 1. First



Scheme 1 The halogen exchange of 2,4-dinitrochlorobenzene.

discovered in 1936 by Gottlieb[3] for the conversion of 2,4-dinitrochlorobenzene to 2,4-dinitrofluorobenzene (Sanger's reagent, used for the labelling of peptides and terminal amino acid groups in proteins), it is now routinely used on an industrial scale to make a wide range of compounds. While the chloro moiety is a good leaving group, it is known that aromatic nitro groups are much more labile.[4] Indeed, in a few cases, the nitro group has been shown to be more labile than fluorine. There are many reports of the displacement of a nitro group as a means of synthesising substituted aromatics.[4] This, coupled with the ready availability and relatively low cost of many nitroaromatics, makes these compounds attractive starting materials for the synthesis of fluoroaromatics *via* fluorodenitration. Finger and Kruse were the first to report fluorodenitration, initially as an unwanted side reaction.[5] In 1956, whilst attempting to fluorodechlorinate 2,4-dinitrochlorobenzene using KF at 150 °C, brown fumes, presumably due to the liberation of NO_2, were observed and low boiling products were detected on work-

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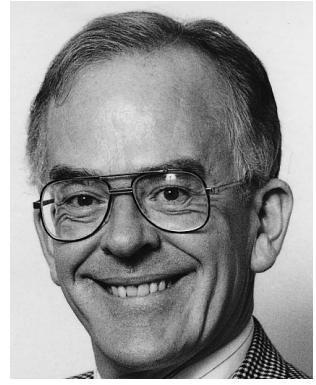

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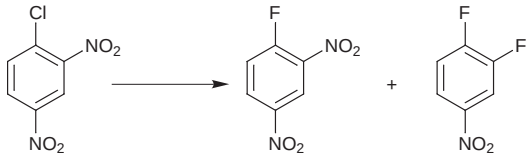
up. Further investigation revealed the presence of 1,2-difluoro-4-nitrobenzene, indicating that displacement of a nitro group was also possible under these conditions, Scheme 2. Although



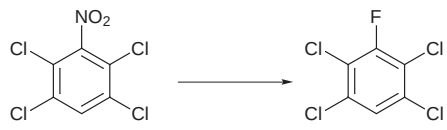
Scheme 2 First observation of fluorodenitration.

fluorodenitration is currently not widely used for the formation of fluoroaromatics, recent reports indicate that it should be possible to exploit this methodology to complement the currently available routes.

2 Applications and importance

Halogen exchange is an important procedure and represents the only real industrial rival to the diazonium-based methods for the synthesis of selectively fluorinated aromatic compounds. Starting materials are generally readily available and there is a major advantage in avoiding the use of hydrogen fluoride. Activation of the chloro group by other moieties on the ring is necessary for substitution to occur. This can be achieved through the presence of inductively activating −I groups on the ring or mesomerically activating groups *ortho*- and *para*- to the group to be displaced. Generally, cost restricts this to the use of nitro groups, although CF_3, CN, CHO and COOMe have also been used. A wide range of fluorinated compounds can be formed by halogen exchange. However, there are areas where halogen exchange is generally inappropriate or inefficient. One of the limitations of halogen exchange reactions is that, while good yields can be obtained from compounds with chlorine *ortho*- or *para*- to an electron-withdrawing group, *meta*-chloro compounds without any other activating groups generally give poor yields. A rare example of good yields of *meta*-fluoroaromatic products being achieved by halogen exchange is the formation of 3,4-difluorobenzonitrile from the corresponding dichlorobenzonitrile in 65% yield, but, even in this case, the reaction had to be carried out in 1,3-dimethylimidazolidin-2-one at 290 °C in a pressure reactor.[6]

Fluorodenitration could provide a useful alternative route to *meta*-fluorinated aromatic compounds. Activation by other groups is still necessary for substitution to occur but, in addition to inductive and mesomeric activation, bulky *ortho*-groups are thought to assist by twisting the nitro group out of the plane of the molecule, aiding fluorodenitration.[7] So, just as nitro groups were used to activate the chlorine towards displacement in 2,4-dinitrochlorobenzene, the nitro group was found to be activated by the inductive effects of the chlorine substituents as well as by steric congestion enabling the quite facile fluorodenitration of 2,3,5,6-tetrachloronitrobenzene, Scheme 3.[7] How-



Scheme 3 The fluorodenitration of 2,3,5,6-tetrachloronitrobenzene.

ever, the greater inductive effect of the nitro group compared to that of a chlorine atom makes its displacement more favourable under the same activation. For example, fluorination of 1-chloro-3-nitrobenzene only gives a low yield of 1-fluoro-3-nitrobenzene, but the fluorodenitration of 1,3-dinitrobenzene to produce this product in yields above 80% is well-documented.[8] Similarly, Maggini *et al.*[9] describe how 1,2-difluoro-4-(trifluoromethyl)benzene, an industrial intermediate, could not be formed *via* the fluorination of the 1,2-dichloro analogue under any reaction conditions. However, it was found that the required product could be formed by halogen exchange and subsequent fluorodenitration of 1-chloro-2-nitro-4-(trifluoromethyl)benzene. Traditionally, many commercial organofluorine compounds have been based on fluoroaromatics with the fluorine in an *ortho* or *para* position due to the availability of the precursors from halogen exchange chemistry. Increasing the availability of *meta*-fluoroaromatics would open the door to a wider range of product molecules for pharmaceutical, agrochemical and other applications.

One possible advantageous aspect of fluorodenitration is in the inherently greater leaving group ability of the nitro group as compared to the chloro group which can mean that milder reaction conditions are required. The reduction of reaction temperatures from the high (> 100 °C) values often required with halogen exchange has clear safety advantages and the substitution of high boiling point dipolar aprotic solvents could also reduce concerns over toxicity, side reactions and solvent recovery. The better leaving ability of the nitro group compared to the chloro group can also be exploited in the direct nucleophilic fluorinations of weakly activated substrates. Thus, the halogen exchange route to 4,4′-difluorobenzophenone (the key intermediate in the manufacture of the speciality polymer poly(ether ether ketone), PEEK) starting from the 4,4′-dichloro analogue only occurs under very forcing conditions. However, it has been shown that by starting from the dinitro analogue, good yields of the difluorinated product can be obtained under more moderate conditions (see later).[10]

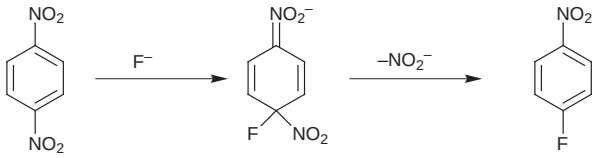
One area where fluorodenitration is of particular use is in radiolabelling. Positron emission tomography, a non-invasive technique which is used in the *in vivo* visualisation of free radicals, requires the use of radiolabelled compounds. Unlike ^{11}C, ^{13}N and ^{15}O, ^{18}F has a sufficiently long half-life to allow the synthesis and administration of such radiolabelled species.[11,12] Fluorodenitration is an attractive means of forming ^{18}F-labelled fluoroaromatics due to both the one-pot and rapid nature of the synthesis. For example, fluorodenitration of 2-nitrobenzonitrile with $Rb^{18}F$ in DMSO gave an 85% yield of the ^{18}F-labelled benzonitrile after only 20 minutes at 150 °C.[12] An added advantage of this methodology is that any other nitro group present to activate the group towards displacement can be easily converted into other functionalities *via* the diazonium salt. A variety of substituted nitroaromatics can be converted to the ^{18}F-labelled compounds, both with electron-donating and electron-withdrawing groups on the ring.

3 Solvents and reagents

Although it is possible to carry out both halogen exchange and fluorodenitration reactions in neat substrate, these reactions require high temperatures and long reaction times. Finger and Kruse were the first to recognise that the use of solvents was advantageous.[5] Reactions were found to occur at lower temperatures than in neat substrate.[5] Another advantage was that the fluorodenitration of 3-nitrophthalic anhydride proceeded safely without thermal runaway when carried out in a solvent.[13] However, the choice of solvent is important. In protic solvents, strong hydrogen bonds are formed between the solvent and the fluoride anion.[14] This results in a reduction in the nucleophilicity of the fluoride and also activates the solvent such that this can then act as a nucleophile, leading to unwanted side-products. However, in dipolar aprotic solvents such as dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF), hydrogen-bonding does not occur to any significant

extent and the nucleophilicity of fluoride is much increased.[14] It is also known that the nucleophilicity and basicity of a fluoride is solvent dependent as well as being sensitive to the level of hydration and the identity of the counter-cation. When not hydrogen-bonding to solvent molecules, fluoride salts are known to be strongly basic, which again can lead to undesired side reactions.

The high polarity of some dipolar aprotic solvents is thought to be a major advantage in carrying out these reactions. Such solvents are thought to stabilise the organic reaction intermediates. Clark and Macquarrie[15] found that for a range of organic substrates the rates of both halogen exchange and fluorodenitration with KF in aprotic solvents were subject to substrate dependent solvent effects. Under otherwise identical experimental conditions, rates were found to follow the order DMSO ≥ DMAc (*N,N*-dimethylacetamide) > sulfolane » acetonitrile. DMSO was found to be the solvent in which the rate of fluorodenitration is greatest despite the low solubility of KF in this solvent. Indeed, there was found to be a poor correlation between the rates of reaction of aromatic compounds in different solvents and the solubility of the fluoride. However, it was found that the order of solvent dependent rate enhancement did correlate with the degree of resonance stabilisation of the intermediate σ-complex. Like other S_NAr reactions,[16] fluorodenitration and halogen exchange are thought to proceed *via* an intermediate in which the α-carbon is sp^3 hybridised. Benzenoid resonance is thus lost in the intermediate,



Scheme 4 Mechanism by which fluorodenitration occurs.

Scheme 4. Electron-withdrawing groups *ortho* and *para* to the α-carbon therefore stabilise the intermediate resonance forms. The greatest solvent dependencies were found with those substrates with no effective −M groups, whereas those with two −M groups gained very little in going from acetonitrile to the more polar DMSO. This suggests that the stabilisation of the σ-intermediate is of major importance in determining the overall rate of reaction.

From an industrial point of view, the high cost of the solvent makes both use and recovery of major importance to process design. Environmental concerns also make recovery important. As such, there is a growing trend towards the development of low- or no-solvent processes. For example, Chambers and Edwards have recently described the use of perfluorocarbons to "bulk-up" dipolar aprotic solvents and found that it is possible to carry out halogen exchange reactions in 75% perfluoroperhydrophenanthracene, 25% sulfolane using KF and 18-crown-6.[17] The perfluorocarbon could easily be recovered, although the recycled solvent was of reduced efficiency. It is entirely feasible that similar solvent systems may be suitable for fluorodenitration.

4 Fluoride sources

In general, only monovalent fluorides have a sufficiently low lattice energy to be reactive in halogen exchange and fluorodenitration reactions. There are many examples of the use of alkali metal fluorides, although while lithium and sodium fluoride would be preferred on the grounds of cost, they are inactive in these systems. Alkali metal fluorides (apart from lithium) are hygroscopic and must be dried prior to use (as mentioned above, the nucleophilicity of the fluoride is sensitive to the hydration level of the system). The high thermal stability of these salts allows drying by heating under vacuum at 100 °C for several hours.[14] KF is the most often used alkali metal fluoride for these reactions, providing a compromise between reactivity and cost. Alkali metal fluorides are only significantly soluble in some protic solvents (notably water, HF and the lighter carboxylic acids and alcohols). In dipolar aprotics, solubility is low (a value of 0.6×10^{-3} mol dm^{-3} for KF in DMSO has recently been reported[18]). This often necessitates long reaction times and high temperatures which can lead to a multiplicity of products. Many attempts have been made to overcome this low solubility. The use of spray-dried KF has been shown to be advantageous. This is thought to be due to the increase in surface area of the salt which is achieved using this drying method. Smyth *et al.* have also shown that increases in yield can be achieved by slowly recrystallising the fluoride from methanol.[19] Another successful methodology is the use of phase transfer catalysts. Several onium salts have been successfully used, such as tetraphenylphosphonium bromide[8] and tetramethylammonium chloride.[9] Interestingly, Suzuki *et al.*[8] report that tetramethylammonium chloride is poor as a phase transfer catalyst for the fluorodenitration of *meta*-substituted nitroaromatics with KF, with only 12% fluorodenitration occurring in the reaction of 3-nitrobenzonitrile, compared to an 81% yield of this product when tetraphenylphosphonium bromide was used instead. On the other hand, Maggini *et al.*[9] found that tetramethylammonium chloride could successfully be used to achieve high yields of the required fluoroaromatics. Supported phase transfer catalysts have also been used, which have the further advantage of being easily recyclable.[20] One reported method of increasing the solubility of KF is to use a crown ether such as 18-crown-6.[21] It has been shown that this even solubilises KF in non-polar solvents such as benzene. Yoshida *et al.* have successfully used a combination of KF–tetraphenylphosphonium bromide–18-crown-6 to convert chlorobenzaldehydes to the corresponding fluorobenzaldehyde.[22] This is normally very difficult to achieve due to the low level of activation induced by the CHO group. However, harsh reaction conditions are often still necessary to achieve an acceptable rate of reaction.

The solubility of ionic fluorides generally increases with increasing size of the countercation. Quaternary ammonium fluorides have greater solubilities than their alkali metal counterparts in dipolar aprotic solvents, but generally exist in a stable form as hydrated species. Such fluorides have been used for both halogen exchange and fluorodenitration reactions. Tetra-*n*-butylammonium fluoride (TBAF) was found to be capable of fluorodenitrating many substrates under relatively mild conditions. However, hydrolysis by-products were observed in these systems, which were inherently wetter than those based on KF. Similar by-products were observed in the reaction of 3,4-dichloronitrobenzene with TBAF. Unfortunately, complete drying of most quaternary ammonium fluorides has been found to be impossible with the corresponding hydrogen difluoride (bifluoride) and amine being formed from the base-induced decomposition of the salt, Scheme 5. However, it is interesting to note that similar yields of 2-chloro-4-fluorotrifluoromethylsulfone were formed from the corresponding nitroaromatic when either KF with a phase transfer catalyst at 230 °C or TBAF in THF at −78 °C were used.[23]

Scheme 5 Decomposition of TBAF on drying.

The elimination reactions leading to decomposition of the onium salt require the presence of β-hydrogens in the quaternary ammonium cation, which the simplest tetraalkylammonium fluoride, tetramethylammonium fluoride (TMAF) does not have. TMAF has been found to be thermally stable to

high temperatures. While being commercially available as the tetrahydrate, it is the only tetraalkylammonium fluoride which can be dried to give a completely anhydrous salt.[24] It has been reported that it can be dried successfully by the azeotropic removal of water using cyclohexane or toluene,[25] although recent work has highlighted difficulties with this method.[26] TMAF has been used to fluorodenitrate many nitroaromatics, with the reported yields often being very high.[25] Reaction times are much shorter than those reported with KF, even at the lower temperatures used in these studies. Perhaps most importantly, it has been reported that fluorodenitration with TMAF results in the absence of the hydrolysis by-products in these systems.

Other fluoride sources have been used for nucleophilic fluorination reactions. Tetraphenylphosphonium hydrogendifluoride was found to be capable of successfully fluorodenitrating simple substituted nitroaromatics despite the expected lack of reactivity of the hydrogendifluoride anion with its very strong hydrogen bond.[27] For example, 2-fluoronitrobenzene was formed in 70% yield from 1,2-dinitrobenzene in sulfolane at 100 °C. However, quantitative fluorination with this fluoride source required two equivalents of the hydrogendifluoride. Similar results were obtained when using a tetraalkylammonium hydrogendifluoride for halogen exchange reactions.[28] Polyfluorides were formed, resulting from the scavenging of a molecule of HF from one hydrogendifluoride by another. Tetrabutylammonium hydrogendifluoride and dihydrogentrifluoride have also been used for the fluorination of a range of chloro and nitroaromatics.[29] Interestingly, the reactions were carried out in toluene as solvent, with DMSO, a more traditional solvent, giving both a lower yield of the required product and unspecified by-products.

5 Side reactions

Of course, despite both halogen exchange and fluorodenitration being used specifically to generate fluoroaromatics, each can be considered as a side reaction when the other methodology is desired. Hence, while halogen exchange may be desired, substitution of a nitro group (present in order to activate the chlorine towards displacement) may also occur. There is very little information available as to the relative leaving group abilities of the two groups within the same molecule. Clark *et al.* have examined the reaction of some chloronitroaromatics, of the form **I** and **II**.[23] In all cases, the nitro group was found to be

I **II**

R = CF_3, CN, SO_2CF_3, COOMe

preferentially displaced by both TBAF and KF. A semi-empirical study of the halogen exchange and fluorodenitration of 2,4-dichloronitrobenzene was carried out by Smyth.[30] It was found that, despite experimental evidence that the *ortho*-chlorine is preferentially displaced compared to the *para*-chlorine, the semi-empirical methods indicate that there is no clear preference for displacement by free fluoride ion. It was thus concluded that the favouring of *ortho*-substitution must be due to the nature of the nucleophile. A semi-empirical examination of the reaction with TMAF indicated that *ortho*-halogen exchange is preferred, agreeing with experimental findings. Similarly, for this molecule, halogen exchange is favoured over fluorodenitration. Further information about the relative leaving group ability of chlorine and nitro groups within the same molecule can be gleaned from the reaction of a fluoride with 2-chloro-6-nitrobenzonitrile. The fluorination of this substrate has been examined by many groups, almost all of which have found that denitration is preferred. For example, with both TMAF[26] and tetrabutylphosphonium hydrogendifluoride,[29] fluorodenitration was achieved in high yield, with subsequent rather than competitive dehalogenation occurring. However, with $Rb^{18}F$, a mixture of products was observed with 55% denitration occurring and 17% dehalogenation,[12] which demonstrates that the outcome of these reactions may be difficult to predict, varying with the system used.

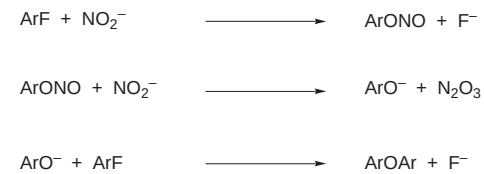
Perhaps the major drawback of both halogen exchange and fluorodenitration is the prevalence of by-products in the reaction mixture. For example, Maggini *et al.*[9] describe the fluorination reactions of 1-chloro-2-nitro-4-(trifluoromethyl)-benzene. The halogen exchange of the chlorine for fluorine is facile and can be achieved in high yield. However, fluorodenitration leads to a complex reaction mixture with other products including 1-hydroxy-2-nitro-4-(trifluoromethyl)benzene, 1-methoxy-2-nitro-4-(trifluoromethyl)benzene and bis[2-nitro-4-(trifluoromethyl)phenyl] ether. Such side-reactions are thought to occur because of the good leaving group ability of fluorine. Fluorine is one of the best leaving groups available for S_NAr reactions.[16] Its high electronegativity can stabilise transient carbanions, allowing relatively facile displacement by nucleophilic attack.

Phenols and ethers are the by-products most often reported and are thought to arise from two routes. Firstly, simple hydrolysis of the product fluoroaromatic leads to by-products, Scheme 6. All the fluoride sources used are known to be

Scheme 6 Formation of phenolic and ether by-products *via* hydrolysis.

hygroscopic and hence complete drying of the reaction systems is extremely difficult. The ability of fluoride to strongly hydrogen-bond to any remaining water results in the formation of phenolic products in the system. The reactivity of the phenols produced is also likely to be greatly enhanced by hydrogen bonding to the fluoride in these systems leading to further side products. The methoxy substituted products observed by Maggini *et al.*[9] in the fluorodenitration of 1-chloro-2-nitro(trifluoromethyl)benzene were attributed to attack by such an activated phenol on the tetramethylammonium chloride phase transfer catalyst used in their systems. They also postulated that the nitroaniline formed in the reaction arose from nucleophilic attack by trimethylamine, formed by phenol attack on the ammonium salt, on the nitrofluorobenzene.

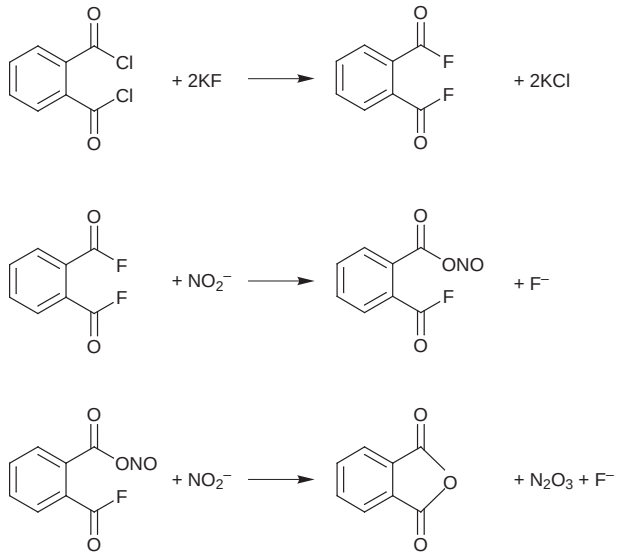
Secondly for fluorodenitration reactions, it has also been suggested that the displaced nitrite ion can become involved in the organic chemistry, acting as a nucleophile, Scheme 7.[8] The



Scheme 7 Formation of phenolic and ether by-products *via* nitrite back attack.

nitrite ion is known to be an ambident nucleophile *i.e.* it has two potential reaction sites. The relative rates of *O*- and *N*-attack on aryl halides have been examined and it has been shown that *O*-

attack occurs preferentially on aryl fluorides in dipolar aprotic solvents, resulting in the formation of nitrite esters. These are thought to have a very short lifetime, decomposing to form phenoxides which can go on to form ethers.[31] As mentioned above, the use of TMAF for fluorodenitration reactions results in the absence of such by-products. This is thought to be due to strong ion-pairing in tetramethylammonium nitrite, stabilising the nitrite anion and so reducing its nucleophilicity.[25] Suzuki *et al.*[8] and Maggini *et al.*[9] both concluded that this re-attack of the displaced nitrite anion was responsible for ether formation in fluorodenitration reactions and independently added phthaloyl dichloride (PDC) to their reaction systems. This led to greatly improved yields of the desired fluoroaromatic. For example, reaction of KF in sulfolane with 3-nitrobenzonitrile in the presence of tetraphenylphosphonium bromide gave 10% of the 3-fluorobenzonitrile with 21% of the bis(3-cyanophenyl) ether. The inclusion of PDC into the reaction mixture increased the yield of the fluoroaromatic to 86%. It was assumed that PDC was acting as an *in situ* trap for the displaced nitrite ion, Scheme 8. Initially, the PDC is converted to phthaloyl difluoride, which



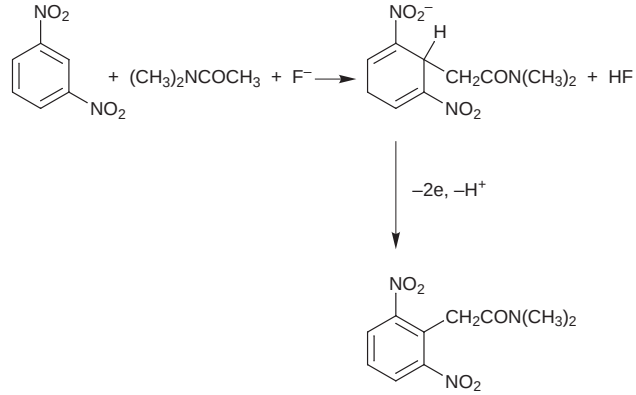
Scheme 8 PDC as a nitrite trap.

then reacts with nitrite to form the nitrite ester. This is thought to react with a further equivalent of nitrite to generate higher nitrogen oxides, phthalic anhydride (PA) and to regenerate fluoride.

There is relatively little evidence for the mechanism of reactions involving PDC described above. Passudetti *et al.*[32] describe how the reaction of KF with 3-nitrophthaloyl dichloride gives an 82% isolated yield of 3-fluorophthalic anhydride, a useful intermediate for the preparation of many compounds. However, as above, the mechanism described for the conversion of the phthaloyl dihalide to the anhydride requires two equivalents of nitrite. Since the only source of nitrite in this system is the 3-nitrophthaloyl dihalide itself, the implication is that the maximum yield of the anhydride obtainable should be 50%. Hence, PDC must be reacting with another source of oxygen in these systems to affect the conversion to the anhydride. Suzuki *et al.*[8] recognised this lack of stoichiometry and suggested a slightly different mechanism whereby FNO was evolved rather than N_2O_3. However, they gave no evidence for the existence of this product in their system.

PDC will react with water to give PA. Dipolar aprotic solvents are notoriously difficult to dry and it is not inconceivable that such a reaction may be occurring in these systems. This would have two effects. Firstly, the number of hydrolysis by-products from the aromatic fluorination would be expected to be decreased, as observed. Secondly, the reaction would form HCl, which might be expected to react with KF to form HF, which would then react with a further KF to form the corresponding bifluoride, KHF_2. This would necessitate the use of excess fluoride, as observed by Suzuki *et al.*[8]

The high basicity of the fluoride in fluorodenitration and halogen exchange reactions can also result in the formation of by-products arising from reaction with the solvents. $-SCH_3$ incorporated products (derived from DMSO) were observed by Finger and Kruse.[5] Recently, it has been reported that solvent-incorporated products occur in the fluorodenitration of 1,3-dinitrobenzene in DMAc.[26] Such addition products are known to occur by attack of a nucleophile on the nitroaromatic, generating an anionic σ-complex, which is then oxidised by further parent nitroaromatic, Scheme 9. However, such a



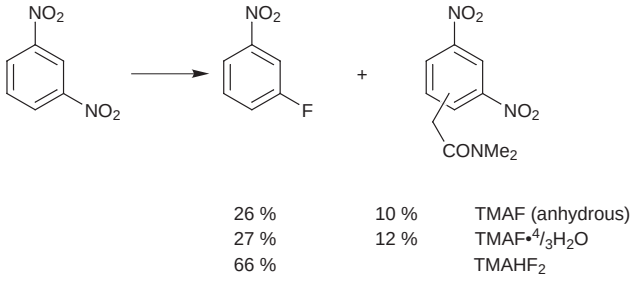
Scheme 9 Attack of a carbon nucleophile on a nitroaromatic.

product requires deprotonation of DMAc, demonstrating the high basicity of the fluoride in these systems. A recent report details the formation of such compounds using acetone and acetonitrile and other carbon-nucleophiles with 1,3-dinitrobenzene. These reactions necessitate the presence of fluoride; remarkably, the conventional strong base potassium *tert*-butoxide was found to be ineffective.[33]

6 Recent developments

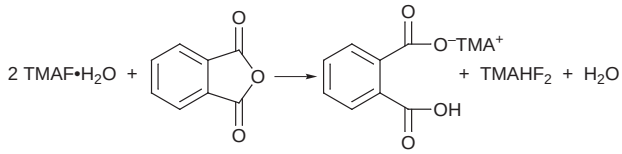
Recent work has concentrated on developing a greater understanding of the chemistry occurring in these systems. The role of water in these systems is now better understood. Sasson *et al.* have shown that there is a critical amount of water necessary for successful halogen exchange.[18] In excess water, no reaction proceeded and ethers and phenols were detected when a hydrated tetraalkylammonium fluoride was used for the attempted fluorination of 3,4-dichloronitrobenzene. However, with KF, the use of 0.2% w/w water in the system was found to be necessary for effective transport of the fluoride from the surface of the solid salt to the organic phase. In this case, no hydrolysis products were observed. Interestingly, although the nature of the fluoride and the inorganic chemistry is often considered, there is little discussion in the literature on the chemistry of nitroaromatics in such reaction mixtures. Nitroaromatics are known to be capable of interacting with basic species in a variety of ways.[34] As well as forming anionic σ-complexes as precursors to nitro displacement, σ-complexes can be formed which do not lead to denitration. In some cases, these are known to be stable and can be isolated from the reaction mixture.[34] It is also known that nitrocompounds can accept electrons, thus forming radical anions. These can go on to form products arising from reduction of the nitro groups. Deprotonation of both the aromatic ring and benzylic hydrogens can also occur. In the light of these possibilities, it is perhaps surprising that the majority of reported side products are attributed to nucleophilic displacement of fluorine.

While the quantity of side products found to occur in the fluorodenitration of 1,3-dinitrobenzene was reported to be unaffected by the addition of water, the use of tetramethylammonium hydrogendifluoride ($TMAHF_2$) instead of $TMAF{\cdot}^4/_3H_2O$ (formed by drying the tetrahydrate under vacuum at 60 °C for 48 hours) resulted in improved yields.[26] As mentioned earlier, both the nucleophilicity and the basicity of fluoride are strongly affected by the level of hydration, the counterion and the reaction medium. The nucleophilicity of $TMAHF_2$ is lower than that of TMAF. Correspondingly the reaction rates for fluorodenitration using $TMAHF_2$ are lower than those using TMAF as the fluoride source. The basicity of the two salts is also different with TMAF leading to a more basic reaction system and, for those nitroaromatics containing relatively acidic hydrogens, yields were found to be greatly increased where the less basic $TMAHF_2$ was used. In line with this hypothesis, anhydrous TMAF (expected to be highly basic) was found to give a somewhat lower product yield than $TMAF{\cdot}^4/_3H_2O$, Scheme 10.[26] Interestingly, the inclusion of



Scheme 10 The fluorodenitration of 1,3-dinitrobenzene using different fluoride sources in *N*,*N*-dimethylacetamide.

PDC was reported to be most beneficial when added to reaction systems involving the fluorodenitration of *meta*-nitroaromatics. Suzuki *et al.*[8] specifically targeted such molecules and the majority of the substrates fluorinated by Maggini *et al.*[9] had a nitro group *meta* to an electron-withdrawing group. Such compounds are expected to have relatively acidic hydrogens, due to the strong electron-withdrawing nature of the nitro group and other such substituents. As postulated earlier, the addition of PDC may simply be acting as a method of removing excess water from the system, but with the added effect of forming hydrogendifluorides *in situ*. Hydrogendifluorides are much less basic than the corresponding fluoride, which may be the reason behind the increased fluoroaromatic product yields observed. It is also interesting to note that 4-nitrophthalic anhydride is known to react with the displaced nitrite from a fluorodenitration reaction[35] but, in the presence of TMAF, PA was found to react to form the tetramethylammonium salt of the acid and tetramethylammonium bifluoride, Scheme 11.[26] The use of this

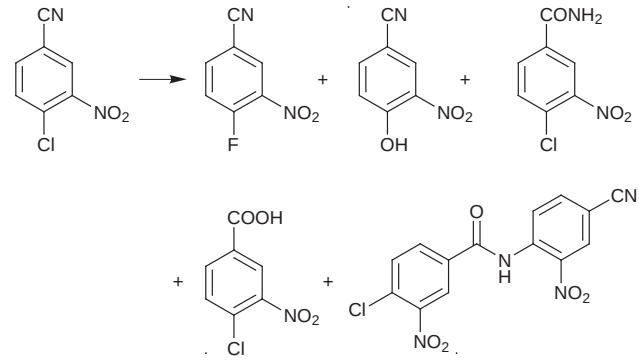


Scheme 11 Reaction of TMAF with phthalic anhydride to give the corresponding bifluoride.

bifluoride formed *in situ* to fluorodenitrate 1,3-dinitrobenzene led to an increased yield compared to that obtained when TMAF was used.

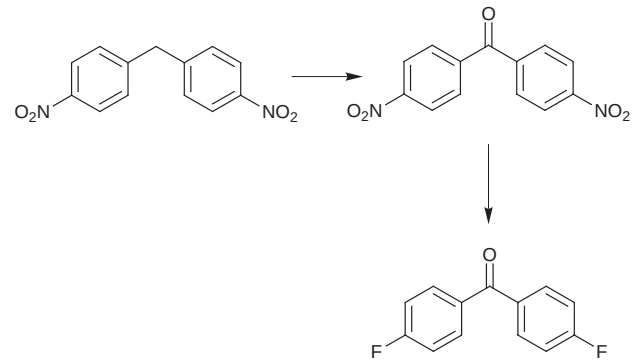
The fluorodenitration of nitroaromatics with TMAF and $TMAHF_2$ has been examined in more detail in an attempt to identify the side products occurring. With substrates giving high yields when fluorodenitrated, ethers were detected. For the more demanding substrate 1,3-dinitrobenzene, solvent addition products were observed.[26]

The high basicity of typical fluorodenitration reaction systems has also been found to have other effects. Azeotropic drying of the TMAF–DMSO system was shown to lead to base-catalysed solvent decomposition, giving the methylsulfinyl anion.[36] It was found that the attempted halogen exchange of 4,4′-dichlorobenzophenone with TMAF in DMSO leads to the formation of 1,1-di(4-chlorophenyl)ethene. Although no other products directly attributable to the methylsulfinyl anion were detected in fluorodenitration reactions, it is expected that such reactions occur given the known high reactivity of this species. Azeotropic drying of the TMAF–DMSO system was also found to lead to unexpected hydrolysis by-products when used in the attempted fluorodenitration of 4-chloro-3-nitrobenzonitrile. These included the benzamide, the acid and a second amide, Scheme 12, all presumed to arise from base-catalysed hydrolysis reactions. Detection of these products indicates that this method of drying the system is perhaps not as effective as suggested in the earlier reports. This work also thus shows another possible, previously unreported route to side-products, again indicating the complexity of the systems is greater than has been generally assumed.



Scheme 12 The reaction of 4-chloro-3-nitrobenzonitrile with azeotropically-dried TMAF in DMSO.

While the high basicity of the fluoride is thought to lead to by-products in fluorodenitration reactions, it is possible to exploit this in a number of ways. Fluoride catalysed H–D exchange was also found to be possible between d_6-DMSO with 4,4′-dinitrodiphenylmethane.[10] In an oxygenated system, the base-catalysed oxidation of this substrate and other nitroaromatics was found to be possible. Interestingly, the carbonyl group thus formed produced sufficient activation for fluorodenitration to subsequently occur, providing a new one-pot synthesis of the industrially important monomer, 4,4′-difluorobenzophenone, Scheme 13.[10] However, it was found that



Scheme 13 Formation of 4,4′-difluorobenzophenone by oxidation followed by fluorodenitration.

a similar attempted base-catalysed oxidation followed by fluorodenitration of 4-nitroethylbenzene led to low yields of the corresponding fluoroacetophenone, with indications that aldol condensations were occurring.

7 Conclusions and future trends

Halogen exchange is well developed and widely used as an industrial method for the formation of fluoroaromatics. Recent improvements have centred around the development of new reagents to overcome the poor solubility of the commonly used alkali metal fluorides in the solvents used. Economic and cost concerns have driven work investigating the use of alternatives for the dipolar aprotic solvents, which can degrade in the presence of the strongly basic fluoride and are difficult to recover. However, in recent years, fluorodenitration has been shown to be a valid preparative route to a wide range of fluorinated aromatic compounds. It is possible to fluorinate nitroaromatics carrying a variety of functional groups including cyano, nitro, trifluoromethyl, chloro and trifluoromethylsulfone. Unlike with halogen exchange reactions, it is possible to fluorodenitrate *meta*-substituted nitroaromatics successfully, even those containing only a single activating group. Recent results have highlighted that the chemistry occurring in fluorodenitration systems involving fluorides, activated nitroaromatics and dipolar aprotic solvents is not as straightforward as has often been assumed. Side reactions do occur, but are not simply as a result of nucleophilic displacement of the fluorine or the nitro groups. The recognition that the success of reactions can be compromised if the fluorinating reagent is too basic is unsurprising when one considers the known interactions of nitroaromatics with bases. However, the results do show that the reaction conditions can be tuned to suit the particular substrate, with improved results being obtained for the more demanding *meta*-substituted substrates such as 1,3-dinitrobenzene by using $TMAHF_2$ rather than TMAF. Clearly, it is essential to be aware of all of the side reactions that can occur with any particular nitroaromatic substrate. While the use of onium fluorides such as TMAF has enabled the methodology to be extended to a potentially wide range of substrates, it must be appreciated that its greater nucleophilicity will also generally be accompanied by a higher system basicity. In many cases, it will be sensible to tolerate a reduction in the overall activity through the avoidance of over drying or the use of the hydrogen difluoride salt, so as to reduce the formation of unwanted by-products. Thus, by tuning the activity of the system through mild KF-based reactions to those employing TMAF to suit the particular substrate and desired product combination, it should prove possible to usefully exploit fluorodenitration in an increasing range of applications.

8 References

1 M. R. S. Gerstenberger and A. Haas, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 647.
2 J. H. Clark, D. Wails and T. W. Bastock, *Aromatic Fluorine Chemistry*, CRC, New York, 1997.
3 H. B. Gottlieb, *J. Am. Chem. Soc.*, 1936, **58**, 532.
4 J. R. Beck, *Tetrahedron*, 1978, **34**, 2057.
5 G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, 1956, **78**, 6034.
6 H. Suzuki and Y. Kimura, *J. Fluorine Chem.*, 1991, **52**, 341.
7 J. H. Clark and D. K. Smith, *J. Fluorine Chem.*, 1985, **26**, 2233.
8 H. Suzuki, N. Yazawa, O. Furusawa and Y. Kimura, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2010.
9 M. Maggini, M. Passudetti, G. Gonzales-Trueba, M. Prato, U. Quintily and G. Scorrano, *J. Org. Chem.*, 1991, **56**, 6406.
10 D. J. Adams, J. H. Clark and H. McFarland, *J. Fluorine Chem.*, 1998, **92**, 127.
11 G. Bormans and M. R. Kilbourn, *J. Labelled Compd. Radiopharm.*, 1995, **36**, 103.
12 M. Attina, F. Cacace and A. P. Wolf, *J. Chem. Soc., Chem. Commun.*, 1983, 108.
13 D. J. Milner, *Synth. Commun.*, 1985, **15**, 485.
14 J. H. Clark, *Chem. Rev.*, 1980, **80**, 429.
15 J. H. Clark and D. J. Macquarrie, *J. Fluorine Chem.*, 1987, 591.
16 J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.
17 R. D. Chambers and A. R. Edwards, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3623.
18 Y. Sasson, S. Neguissie, M. Royz and N. Mushkin, *Chem. Commun.*, 1996, 297.
19 T. P. Smyth, A. Carey and B. K. Hodnett, *Tetrahedron*, 1995, **51**, 6363.
20 Y. Yoshida, Y. Kimura and M. Tomoi, *Chem. Lett.*, 1990, 769.
21 C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, 1974, **96**, 2250.
22 Y. Yoshida and Y. Kimura, *Chem. Lett.*, 1988, 1355.
23 A. J. Beaumont, J. H. Clark and N. A. Boechat, *J. Fluorine Chem.*, 1993, **63**, 25.
24 K. O. Christe, W. W. Wilson, R. O. Wilson, R. Bau and J. Feng, *J. Am. Chem. Soc.*, 1990, **112**, 7619.
25 N. Boechat and J. H. Clark, *J. Chem. Soc., Chem. Commun.*, 1993, 921.
26 D. J. Adams, J. H. Clark and D. J. Nightingale, *Tetrahedron*, in the press.
27 S. J. Brown and J. H. Clark, *J. Fluorine Chem.*, 1985, **30**, 251.
28 C. Rieux, B. Langlois and R. Gallo, *C. R. Seances Acad. Sci.*, 1990, **310**, 25.
29 Y. Uchibori, M. Umeno, H. Seto, Z. Qian and H. Yoshioka, *Synlett*, 1992, 345.
30 T. Smyth and A. Carey, *Tetrahedron*, 1995, **51**, 8901.
31 D. H. Rosenblatt, W. H. Dennis Jnr and R. D. Goodwin, *J. Am. Chem. Soc.*, 1973, **95**, 2133.
32 M. Passudetti, M. Prato, U. Quintily and G. Scorrano, *J. Fluorine Chem.*, 1990, **50**, 251.
33 M. Cervera and J. Marquet, *Tetrahedron Lett.*, 1996, **37**, 7591.
34 E. Buncel, in *The Chemistry of the amino, nitroso and nitro compounds and their derivatives*, S. Patai Ed., J. Wiley and Sons, New York, 1982.
35 R. L. Markezich, O. S. Zamek, P. E. Donahue and F. J. Williams, *J. Org. Chem.*, 1977, **42**, 3435.
36 D. J. Adams, J. H. Clark, H. McFarland and D. J. Nightingale, *J. Fluorine Chem.*, 1999, **94**, 51.

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