Fluorodenitrations using Tetramethylammonium Fluoride

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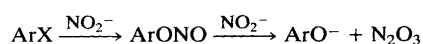[b] Department of Chemistry, University of York, Heslington, York, UK YO1 5DD

Tetramethylammonium fluoride activated by azeotropic drying *in situ* is an efficient reagent for the fluorodenitration of nitroaromatics.

The availability and low cost of nitroaromatics make fluorodenitration an attractive alternative to halogen exchange for the synthesis of selectively fluorinated aromatic molecules *via* nucleophilic fluorination.[1] Unfortunately aromatic fluorodenitrations are often accompanied by side reactions leading to the formation of significant amounts of phenolic and diaryl ether by-products. This is believed to be due to reactions of the displaced nitrite ion—either by direct attack by NO_2^- on the fluoroaromatic ($ArF + NO_2^- \rightarrow ArONO \rightarrow ArO^-$), or by initial decomposition of the nitrite to an oxide followed by attack by the oxide on the ring (*e.g.* $KNO_2 \rightarrow K_2O$; $ArF + K_2O \rightarrow ArO^-$).[2] These side reactions have largely restricted successful fluorodenitrations to just a few highly active substrates[3] although the use of a nitrite trap such as phthaloyl dichloride can enhance reaction efficiency.[2,4] We now report a convenient, facile and efficient method for aromatic fluorodenitration based on the use of tetramethylammonium fluoride.

Tetramethylammonium fluoride (TMAF) is commercially available as a tetrahydrate but it can be easily and inexpensively prepared from the reaction of the chloride (TMAC) in aqueous methanol.[5] Using a 1.8 mol dm^{-3} solution of TMAC in aqueous methanol (4% water by weight) containing 1.25 mol equiv. KF, we obtained after filtration and concentration of the filtrate on a rotary evaporator, a white solid (93% of theoretical yield assuming complete conversion to TMAF) containing 82% TMAF (by F$^-$ analysis) and 15% H_2O. The reactivity of ionic fluorides can generally be improved by drying[6] and this has the additional advantage of preventing product hydrolysis ($ArF \rightarrow ArOH$). TMAF may

be the only quaternary ammonium fluoride which can be prepared in a truly anhydrous form although the procedure is tedious.[7] After drying either commercial TMAF or synthesised TMAF (<0.1 mmHg, 130 °C, 7 days) we obtained a hygroscopic white solid which gave 100% conversion (1.2 mol equiv. F$^-$) of 2-nitrobenzonitrile to 2-fluorobenzonitrile after 1 h at 80 °C in dimethyl sulfoxide (DMSO). Remarkably, by employing the much simpler procedure of distilling off a benzene or cyclohexane–H_2O azeotrope from a solution of undried TMAF in DMSO, followed by addition of the 2-nitrobenzonitrile substrate and stirring at 80 °C, complete fluorodenitration was again achieved within 1 h (>90% 2-fluorobenzonitrile isolated). No phenols or ethers were detected in either reaction and, unlike most methods of fluorodenitration no brown fumes were observed.† This may indicate that tetramethylammonium nitrite (which can be isolated from the reaction mixture) is effectively stable in this system with the cation inhibiting NO_2^- attack on the ring (perhaps through tight $Me_4N^+\cdots ONO^-$ ion pairing) or decomposition to the oxide (which the large cation is unlikely

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† It is interesting to suggest that brown fumes may be an indication of side product formation in nucleophilic denitrations:

$$ArX \xrightarrow{NO_2^-} ArONO \xrightarrow{NO_2^-} ArO^- + N_2O_3$$

or

$$2KNO_2 \rightarrow K_2O \ (+ArX \rightarrow ArO^-K^+) + N_2O_3$$

Table 1 Fluorodenitrations of aromatic substrates using TMAF[a]

Starting material	Reaction time/h	Major product	Yield[b] (%)
2-Nitrobenzonitrile	1	2-Fluorobenzonitrile	100
1,3-Dinitrobenzene	4[c]	3-Fluoronitrobenzene	70[d]
Methyl 4-chloro-2-nitrobenzoate	1.5	Methyl 4-chloro-2-fluorobenzoate	76[e]
Methyl 2,4-dinitro-benzoate	1[f]	Methyl 4-fluoro-2-nitrobenzoate	66[g]
2,4-Dinitrobenzo-nitrile	0.2[h]	2,4-Difluorobenzo-nitrile	100
2-Nitrobenzaldehyde	1	2-Fluorobenzaldehyde	60[i]

[a] Reactions were carried out using 1.2 mol equiv. TMAF in DMSO at 80 °C (unless stated otherwise). The TMAF was dried *in situ* before adding the substrate by azeotropically removing the water with benzene or cyclohexane for 2–12 h. Products were confirmed by mass and ^{19}F NMR spectral data. [b] Determined by GC; isolated product yields were generally *ca.* 10% less than the GC yield. [c] Reaction carried out at 100 °C with 2 mol equiv. TMAF to increase yield. [d] Along with 29% starting material. [e] Along with several minor products resulting from difluorination, halogen exchange and decarboxylation and 16% starting material. [f] Reaction carried out at 60 °C with 2 mol equiv. TMAF. [g] Along with 20% methyl 2-fluoro-4-nitrobenzoate and 12% starting material. [h] Reaction carried out using 3 mol equiv. TMAF. The 2-fluoro-4-nitrobenzonitrile is the major product using smaller quantities of TMAF. [i] Along with 40% starting material.

to favour). We have previously reported the formation of Ph$_4$P$^+$···ONO$^-$ in fluorodenitrations using KF/Ph$_4$PBr.[8]

We have found azeotropically dried TMAF to be effective in the fluorodenitration of a range of aromatic substrates (Table 1). In the case of the more reactive substrates, it gives at least comparable yields to those from reactions employing more conventional conditions but in much shorter reaction times (*e.g.*, methyl 4-chloro-2-nitrobenzoate gives 70% of the fluorodenitration product after 6 h at 80 °C using TMAF, or 27 h at 130 °C using KF/Ph$_4$PBr). Substrates that do not react under such conventional conditions such as 1,3-dinitroben-zene may react with TMAF (Table 1).

Our procedure employs a relatively simple and inexpensive route to a form of TMAF which enables fluorodenitrations to occur without phenol or ether by-product formation. *In-situ* drying gets around the problem of handling a hygroscopic solid while maintaining the advantages of a soluble and highly reactive fluoride agent.

References

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