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Methylhexamethylenetetramine fluoride dihydrate: a new fluorodenitration reagent

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Abstract

Methylhexamethylenetetramine fluoride dihydrate has been prepared by conventional methods. It is moderately soluble in polar aprotic solvents, and shows good thermal stability, enabling it to be dried. The reagent is capable of converting activated nitroaromatics to the corresponding fluoroaromatics, with a high selectivity to monofluorodenitration being observed with some polysubstituted aromatics.

Keywords: Methylhexamethylenetetramine fluoride dihydrate; Fluorodenitration agent; NMR spectroscopy; Mass spectrometry

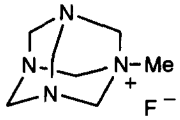
1. Introduction

The versatility of the fluoride ion in organic synthesis (halogen-exchange fluorination, desilylation, various base-catalysed reactions) [1–3] and the limited solubility and poor reactivity of metal fluorides such as potassium fluoride has led to the search for more soluble and more reactive F^- sources. A number of non-metal reagents have been reported including ammonium fluorides (notably $^nBu_4NF$ [4] and Me_4NF [5,6]) and phosphonium fluorides [7], as well as more active forms of metal fluorides such as CsF and supported fluorides [8]. Unfortunately there are significant drawbacks with all known fluoride reagents. The more soluble and reactive reagents such as $^nBu_4NF$ can be thermally unstable and impossible to dry while the essentially heterogeneous reagents suffer from rather poor activity. This means that there is a continuing need for new sources of F^-.

As part of our research in this area we have turned to the inexpensive and stable amine hexamethylenetetramine (which is widely used as a reagent in organic synthesis [9]) as a precursor for conversion to an ammonium fluoride. We now report the preparation and characterisation of a new onium fluoride and its special value in selective fluorodenitration reactions for preparing fluoroaromatics.

2. Results and discussion

Monoquaternisation of hexamethylenetetramine with methyl iodide occurs readily at room temperature in chloroform and the resulting iodide can be recrystallised from acetonitrile/methanol yielding white needles of pure methylhexamethylenetetramine iodide (by NMR and FTIR). Attempts to carry out further quaternisation were largely unsuccessful although dimethylhexamethylenetetramine diiodide was produced in solution (detected by NMR spectroscopy) from the reaction in DMSO. The methylhexamethylenetetramine iodide could be converted into the fluoride MeHMTAF (1) by ion exchange using a fluoride resin although this proved to be tedious and, in practice, rapid exchange with silver(I) fluoride in water was preferred.



(1)

Drying under vacuum at 50 °C afforded a free flowing white powder which was shown by thermogravimetric analysis to contain 2 mol equiv. of water; FTIR, FAB$^+$ MS, ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectral analyses were all consistent with MeHMTAF·$2H_2O$. The observed chemical shift values in the ^{19}F NMR spectrum were solvent-dependent (CD_3OD: $\delta = -150$ ppm; DMSO-d_6: $\delta = -141$ ppm; D_2O: $\delta = -122$ ppm). This suggests that the fluoride does not exist simply as a totally hydrated ion. Combined thermogravimetric–differential scanning calorimetry analysis showed that the fluoride undergoes a phase change at 157 °C which is not accompanied by a weight loss but is not coincident with melting. At 242 °C there is a sharp exotherm and a major

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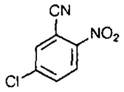
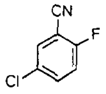
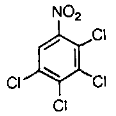
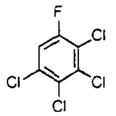
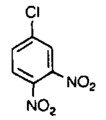
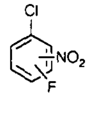
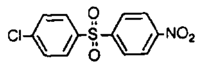
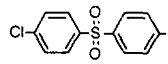
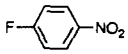
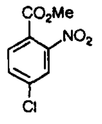
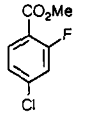
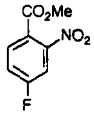
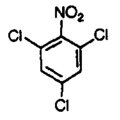
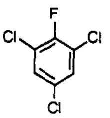
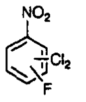
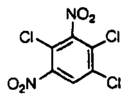
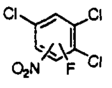
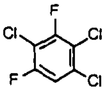
weight loss corresponding to decomposition (FTIR spectroscopy revealed the presence of HF_2^- after long-term heating of the fluoride at only 105 °C in a vacuum oven suggesting that lower temperatures than this should be used for dehydration/activation of the reagent). This can be compared to a decomposition temperature of 235 °C for tetramethylammonium fluoride (TMAF) which like MeHMTAF is not susceptible to Hofmann elimination, the normal decomposition pathway for ammonium fluorides [5]. It is also important to note that MeHMTAF·$2H_2O$ only picks up water at a very slow rate and is significantly less hygroscopic than hydrated TMAF, making it a very easy reagent to handle. For this reason the dihydrate was routinely used in the reactions described below.

A series of chloronitroaromatics were reacted with MeHMTAF·$2H_2O$ to test the activity of the reagent in nucleophilic aromatic fluorinations, and to study its relative activity in fluorodenitration versus fluorodechlorination (halex) – TMAF is known to be a particularly effective fluorodenitration reagent partly because it forms a stable nitrite which is less likely to back-attack the fluoro product leading to a loss in yield and the formation of phenolic and ether side-products [5]. Reactions were routinely run in DMSO at 100 °C using 2 mol of MeHMTAF·$2H_2O$ per mol of substrate and were monitored by GC–MS. The results from these initial screening experiments are summarised in Table 1.

Reactions with the activated substrates were generally rapid and mostly selective towards fluorodenitration. The selectivity, both in terms of monofluorodenitration versus halex or difluorination and fluorination versus phenolic/ether or other non-fluorinated side-products, is particularly impressive with the more reactive substrates and compares favourably to TMAF. Thus in the reaction of 3,4-dinitrochlorobenzene, while MeHMTAF gave 75% conversion to the monofluorodenitration products only (after 1 min), TMAF gave a mixture of fluorodenitration and phenolic products (31% and 33% conversion, respectively, after 5 min). Reaction of MeHMTAF with 2,3,4,5-tetrachloronitrobenzene gave 84% conversion to 2,3,4,5-tetrachlorofluorobenzene only (after 5 min), whereas with TMAF after the same period, there was only partial selectivity to the monofluorodenitration product with 48% conversion to 2,3,4,5-tetrachlorofluorobenzene and 32% conversion to difluorotrichlorobenzenes.

Table 1
Reactions of MeHMTAF·$2H_2O$ with chloronitrobenzenes [a]

Substrate	Reaction time (min)	Product(s)	GC yield (%)
	5		91
	5		84
	1		75[b]
	30		75
			4
	120		50[c]
			6
	30		7
			20
	30		78
			7

[a] Reactions were carried out in DMSO at 100 °C using 2 mol equiv. of MeHMTAF·$2H_2O$ unless stated otherwise.
[b] 95% after 6 min at 65 °C.
[c] 89% after 17 h using 3 mol equiv. of the fluoride.

The reactivity of MeHMTAF is lower than TMAF and this is readily illustrated by the attempted reaction of the poorly activated 1,3-dinitrobenzene (an important target for fluorodenitration because of the difficulty of *meta*-fluorination) which reacted at a reasonable rate with TMAF (70% after 4 h [5]) but reacted slowly with MeHMTAF (6% after 6 h), although removal of the two water molecules from MeHMTAF (by vacuum drying at 100 °C) did result in a small improvement (15% fluorination in 2 h with little increase thereafter – it should be noted that the anhydrous fluoride was poorly soluble even in DMSO at 100 °C whereas the dihydrate was freely soluble). Attempts to use in situ azeotropic drying of MeHMTAF in DMSO were generally unsuccessful because of F^--catalysed decomposition of the DMSO. This occurred more readily than with TMAF suggesting that MeHMTAF may be more basic than TMAF, and this is further indicated by the more rapid colouration of nitromethane with MeHMTAF. More detailed studies on the use of MeHMTAF as a base as well as on other aspects of the chemistry of the compound are under way and will be reported in a subsequent article.

3. Experimental details

3.1. Apparatus

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using a JEOL EX 270 spectrometer at 270.05, 67.90 and 254.05 MHz, respectively. Analysis by GC–MS used a Finnigan Mat Magnum system fitted with a capillary column (50 m) and ion trap system. Combined thermogravimetric–differential scanning calorimetry was obtained using a PL Thermal Sciences STA 625 instrument and FT-IR spectra were recorded on a Perkin-Elmer 1720 FT-IR instrument.

3.2. Synthesis of methylhexamethylenetetramine iodide (MeHMTAI)

Hexamethylenetetramine (5.0g, 36 mmol) was placed in a round-bottomed flask and dissolved in 70 cm^3 of chloroform. The flask was fitted with a reflux condenser and cooled in an ice bath after which 3 mol equiv. of methyl iodide (6.7 cm^3, 107 mmol) was slowly added to the stirred solution over 5 min. Methylhexamethylenetetramine iodide quickly formed as a white precipitate. After stirring overnight the solution was filtered and the solid washed with chloroform and ether. The resulting white powder was then recrystallised from MeCN/MeOH to yield white needles of pure methylhexamethylenetetramine iodide.

^{1}H NMR (DMSO-d_6) δ: 2.5 (s, $1 \times N^+–CH_3$); 4.5 (d.d., $3 \times N–CH_2N$); 5.1 (s, $3 \times N^+–CH_2–N$) ppm. ^{13}C NMR (DMSO-d_6) δ: 43.5 ($N^+–CH_3$); 70.4 ($N–CH_2–N$); 80.4 ($N^+–CH_2–N$) ppm.

3.3. Conversion of methylhexamethylenetetramine iodide (MeHMTAI) to methylhexamethylenetetramine fluoride dihydrate (MeHMTAF·2H_2O)

MeHMTAI (6.1 g, 21.6 mmol) was dissolved in 10 cm^3 of distilled water. AgF (2.74 g, 21.6 mmol) was dissolved in 20 cm^3 of distilled water and pipetted into the MeHMTAI solution. The resulting yellow AgI precipitate was filtered off and the filtrate placed on a rotary evaporator to remove the water. Any brown solids formed during water removal as a result of dissolved silver salts were filtered off. Rotary evaporation was continued until a thick oil was produced, which on cooling formed a white solid. Drying overnight in a vacuum oven at 50 °C yielded MeHMTAF·2H_2O as a white free flowing powder.

^{1}H NMR (CD_3OD) δ: 2.5 (s, $1 \times N^+–CH_3$); 4.6 (d.d, $3 \times N–CH_2–N$); 5.1 (s, $3 \times N^+–CH_2–N$) ppm. ^{13}C NMR (D_2O) δ: 43.5 ($N^+–CH_3$); 70.4 ($N–CH_2–N$); 80.4 ($N^+–CH_2–N$) ppm. ^{19}F NMR (CD_3OD, $CFCl_3$ as internal reference) δ: −150 ppm (solvent-dependent). FAB$^+$ MS *m/z*: 155 (MeHMTA$^+$); 112; 85. Analysis: $C_7H_{19}N_4O_2F$ requires: C, 39.99; H, 9.11; N, 26.65; F, 9.04%. Found: C, 39.88; H, 8.92; N, 25.91; F, 9.36%.

3.4. General procedure for fluorodenitration reactions

In a round-bottomed flask, 0.4 mmol of aromatic substrate was dissolved in 10 cm^3 of dried DMSO and stirred. The flask was fitted with a reflux condenser, thermometer, argon inlet and bubbler, and heated to 100 °C using an oil bath, after which 2 mol of MeHMTAF·2H_2O per mol of substrate was added. Samples were removed periodically, diluted with ether, washed with water and analysed by GC–MS.

Acknowledgements

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