Communication

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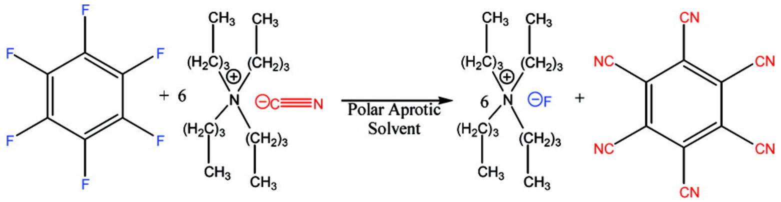
J. Am. Chem. Soc., **2005**, 127 (7), 2050-2051• DOI: 10.1021/ja0440497 • Publication Date (Web): 28 January 2005



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Anhydrous Tetrabutylammonium Fluoride

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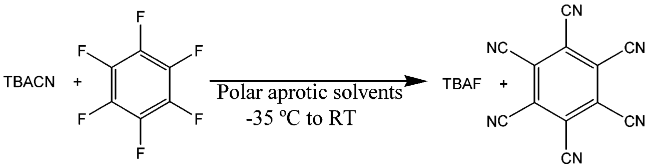
Fluorine substitution is a powerful tool to improve the bioavailability of pharmaceuticals and agrochemicals; thus, an expansive set of nucleophilic and electrophilic reagents has been developed to replace various C−X functional groups with C−F.[1] Simplest among the nucleophilic fluorinating reagents are “anhydrous” or “naked” organic fluoride salts, represented by tetramethylammonium fluoride (TMAF),[2] 1-methylhexamethylenetetramine fluoride (MHAF),[3] and tetramethylphosphonium fluoride (TMPF).[4] These compounds are commonly prepared in a hydrated state and are subsequently dried by heating under dynamic vacuum or by azeotropic distillation. However, the conditions used to dry these salts are often incompatible with a variety of desirable cations. For example, dried tetrabutylammonium fluoride (TBAF)[5] is reported to decompose by Hofmann elimination at room temperature; the salt isolated after dehydration is contaminated with copious amounts of bifluoride ion (HF_2^-) and tributylamine.[6] These considerations have led to the belief that “it is very unlikely that pure, anhydrous tetraalkylammonium fluoride salts have ever, in fact, been produced in the case of ammonium ions susceptible to E2 eliminations.”[6] Here we show that low-temperature nucleophilic aromatic substitution (S_NAr) can be used to generate anhydrous TBAF directly in aprotic solvents, and we discuss the stability and reactivity of “truly” anhydrous TBAF.



The constraints on a fluoride-generating synthesis grounded in S_NAr reactions are quite severe and dictate a careful choice of the nucleophile. Because the enthalpic driving force for fluoride-liberating S_NAr derives almost exclusively from ion-pairing and ΔBDE terms, and because the C_{sp2}−F bond in aromatics is exceptionally strong (126 kcal/mol),[7] only diffusely charged anionic nucleophiles capable of forming strong bonds to carbon should be capable of acting in S_NAr reactions at low temperature in polar aprotic solvents. Cyanide ion, a potent, weakly basic nucleophile that forms strong bonds to sp^2-hybridized carbon (BDE = 133 kcal/mol),[8] is an excellent candidate. Treatment of hexafluorobenzene with tetrabutylammonium cyanide (TBACN) (in 1:1 to 1:6 molar ratios) in the polar aprotic solvents THF, acetonitrile, or DMSO at or below room temperature gave excellent yields of anhydrous TBAF.[9] ^{19}F NMR spectroscopy indicated that the overall yield of TBAF in solution in all cases was >95%. Cyano substitution dramatically increases the fluorinated benzene ring’s susceptibility to further nucleophilic attack, as is evidenced by observation of pentacyanofluorobenzene and hexafluorobenzene as the principal fluorinated aromatic species in the reaction solution, even if 1:1 TBACN/C_6F_6 stoichiometry is employed.

The modest solubility of TBAF in THF at low temperature allows the salt to be precipitated (at −65 °C) and isolated free of aromatic impurities in 70% yield. Freshly isolated TBAF displayed one singlet ^{19}F NMR signal at −86 ppm in THF and four ^1H NMR signals for the TBA cation. The characteristic doublet of HF_2^- at $\delta = -147$ ppm ($J_{H-F} = 120$ Hz) was observed in freshly prepared solution samples and in samples precipitated from THF and redissolved. The concentration of TBA HF_2^- was generally less than 2% that of TBAF. Solid anhydrous TBAF is stable under nitrogen at −35 °C for weeks. TBAF decomposes slowly in THF or in the solid state by E2 elimination if warmed above 0 °C.

Table 1. ^{19}F NMR Data of Anhydrous Fluoride Salts

compd	solvent	chemical shift	ref.
TBAF	THF	−86 ppm	this work
	CD_3CN	−72 ppm	this work
	$(CD_3)_2SO$	−75 ppm	this work
TMAF	$(CD_3)_2SO$	−75 ppm[a]	this work
	CD_3CN	−74 ppm	2
TMPF	CD_3CN	−70 ppm	4

[a] Generated in situ with TMACN.

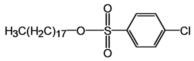
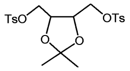
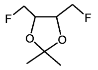
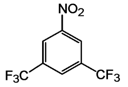
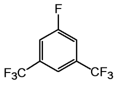
TBAF can be prepared conveniently in situ in polar aprotic solvents at room temperature and used without isolation or purification. Treatment of $(CD_3)_2SO$ or CD_3CN solutions of TBACN with C_6F_6 (at 25 °C) gave highly colored, concentrated (up to 2 M) solutions of TBAF exhibiting the characteristic ^{19}F NMR signals for ion-paired fluoride (Table 1). Small amounts (generally <4%) of HF_2^- are also generated in these solvents. TBAF is stable for hours in CD_3CN and for more than 24 h in DMSO at 25 °C. For sluggish reactions, DMSO is the solvent of choice.

The origins of the unexpected stability of TBAF in THF, CH_3CN, and DMSO lie in the relatively low temperatures used for generation of the salt and in the dehydrating properties of the main reaction byproduct, hexacyanobenzene.[10] Hexacyanobenzene has been shown to add water to form the strong acid pentacyanophenol ($pK_a = -2.9$).[11] Thus, adventitious water is removed from solution during the course of the initial fluoride-generating S_NAr reaction, forming 2 equiv of bifluoride ion per 1 equiv of water and the innocuous byproduct TBA pentacyanophenoxide. Added water (0.08 equiv) is scavenged from TBAF solutions prepared in this manner, as is evidenced by time-dependent changes in the line width and chemical shift of the F^- ^{19}F NMR resonance and by the generation of 0.16 equiv of HF_2^- (see Supporting Information.)

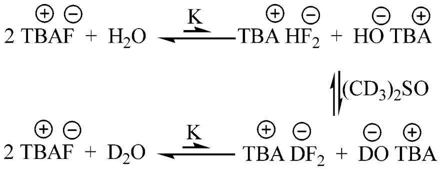
Friedrich has shown that the addition of alkoxide nucleophiles to hexacyanobenzene is rapid under basic conditions and that the resultant pentacyanophenyl alkyl ethers are subject to S_N2 displacement.[12] This pathway is amply demonstrated by the direct fluorination of simple alcohols. For example, if excess TBAF (12 equiv) is generated in situ in $(CD_3)_2SO$ and used directly, benzyl alcohol is converted quantitatively to benzyl fluoride, presumably via the intermediacy of benzyl pentacyanophenyl ether. Thus, generation of TBAF in the presence of hexacyanobenzene can provide DAST-like deoxofluorination of alcohols.

10.1021/ja0440497 CCC: $30.25

Table 2. Fluorination of Various Substrates Using Anhydrous TBAF

Run	Substrate	Reagent	Solvent	Conditions	Product	Yield[a] (%)	Comments	Ref.
1	$PhCH_2Br$	1.3~1.5 eq. TBAF	CD_3CN	-35 ºC, <5 min	$PhCH_2F$	100		This work
2	$PhCH_2Br$	2 eq. TBAF "anhydrous"	THF	RT, 8 h	$PhCH_2F$	>90	$PhCH_2OH$ (5%)	5
3	CH_3I	1.5 eq.TBAF	CD_3CN	-40 ºC, <5 min	CH_3F	100		This work
4	CH_3I	$CoCp_2F$	THF	RT, 6 h	CH_3F	100		13
5	$CH_3(CH_2)_7Br$	TBAF	THF	RT, <5 min	$CH_3(CH_2)_7F$	40~50	(remainder alkene)	This work
6	$CH_3(CH_2)_7Br$	6 eq. TBAT	CH_3CN	Reflux, 24 h	$CH_3(CH_2)_7F$	85		14
7	$CH_3(CH_2)_7Br$	2 eq. TBAF "anhydrous"	THF	RT, 1 h	$CH_3(CH_2)_7F$	48	40% octanol	5
8		TBAF	THF	RT, <5 min	$CH_3(CH_2)_{17}F$	100		This work
9		4 eq. TBAF	THF, or CD_3CN	RT, <5 min		>90		This work
10		1.3 eq TBAF	CD_3CN	RT, <2 min		>95		This work
11	PhCOCl	1 eq. TBAF	THF	RT, <2 min	PhCOF	100		This work
12	Tosyl-Cl	1 eq. TBAF	THF	RT, <2 min	Tosyl-F	100		This work

[a] Yields were calculated by integration of starting material and product signals in the ^1H and/or ^{19}F NMR spectra.



$$\begin{array}{c} 2\,\overset{\oplus\,\ominus}{\text{TBAF}} + H_2O \overset{K}{\rightleftharpoons} \overset{\oplus\;\ominus}{\text{TBA HF}_2} + \overset{\ominus\;\oplus}{\text{HO TBA}} \\ \Big\Updownarrow (CD_3)_2SO \\ 2\,\overset{\oplus\,\ominus}{\text{TBAF}} + D_2O \overset{K}{\rightleftharpoons} \overset{\oplus\;\ominus}{\text{TBA DF}_2} + \overset{\ominus\;\oplus}{\text{DO TBA}} \end{array}$$

Figure 1. Simplified scheme for hydroxide-catalyzed deuterium exchange.

Given that fluoride, the smallest anion (ionic radius = 1.33 Å),[7] forms extremely strong bonds to protons (H−F BDE = 136 kcal/mol, HF_2^- BDE = 46 kcal/mol) F^- is expected to be an aggressive Brønsted base. Christe et al. have shown that TMAF deprotonates CD_3CN over the course of several hours, consuming F^- to form DF_2^-.[2] A similar process is observed with TBAF in CD_3CN; nevertheless, no decomposition of the TBA cation is observed over 24 h. In contrast, no H−D exchange is observed in solutions of TBAF in $(CD_3)_2SO$ over the same time period. These results do not allow a reliable estimate of the ion-pair basicity of F^- in polar aprotic solvents, since slow rates of proton transfer may preclude generation of a true equilibrium mixture. An additional complication is that any proton transfer to fluoride ion is followed by a rapid conversion of HF to HF_2^- (Figure 1). While $(CD_3)_2SO$ does not undergo proton exchange with residual HF_2^- in anhydrous TBAF solutions, if a $(CD_3)_2SO$ solution of purified TBAF (precipitated from THF) is spiked with water (0.08 equiv) a slow (2 h) conversion of HF_2^- to DF_2^- is observed. Deuterium exchange occurs without a detectable increase in the bifluoride ion concentration, suggesting that deprotonation of water by TBAF is thermodynamically disfavored under these conditions (see Figure 1 and Supporting Information). Upon standing, hydrated DMSO solutions of purified TBAF evolve butene and tributylamine by E2 elimination, implicating hydroxylic impurities as likely actors in TBAF decomposition.

Reactions employing TBAF generated in situ are summarized in Table 2. For nucleophilic fluorination, anhydrous TBAF is comparable to, or exceeds, the reactivity of other nucleophilic fluorinating agents. In head-to-head comparisons, TBAF exhibits dramatically enhanced rates of fluorination compared to dynamic vacuum-dried "anhydrous" TBAF,[5] $CoCp_2F$,[13] or TBAT.[14] Neither heating nor a gross excess of TBAF is generally required to effect substitution (Table 2).

Taken together, the results presented here show that exceptionally nucleophilic, highly soluble fluoride ion sources featuring an ammonium cation can be prepared readily even if the cation is thought susceptible to E2 elimination. The self-dehydrating nature of the S_NAr method makes it an exceptionally forgiving synthetic route to TBAF and related anhydrous fluoride salts.

Acknowledgment. We thank the National Science Foundation and the Nebraska Research Initiative for support of this research.

Supporting Information Available: Experimental details for fluoride ion generation and reactions of TBAF. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0440497