Improved Fluorination with Supported Fluoride Reagents

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Potassium and tetrabutylammonium fluorides dispersed on nonsurface-hydroxylated support materials, such as Teflon beads and Nafion cation exchange resin, were found to show enhanced reactivity and/or easy handling for fluorination reactions.

Potassium fluoride is a popular source of fluorine for preparation of organofluorine compounds, due to its stability and cost, thus a variety of methods have been tried to improve its effectiveness for uncleophilic fluorination. Spray dried KF has been shown to have increased reactivity for fluorination of some organic halides compared to ordinary KF and this has been related to the increase in surface area.[1] As an alternative, the surface area of KF may be increased by dispersion on an inorganic support. Alumina supported KF has been shown to have high basicity but poor fluorinating ability, presumably due to its hydroxylated surface. Calcium fluoride, on the other hand, has been reported as a support that allows the fluorinating ability of KF [2] and AgF [3] to be exploited. Finely powdered CaF_2 has a surface area of ca. $10m^2/g$ and KF dispersed over this surface shows good fluorinating ability, consistent with the increased surface area on going from KF($0.1m^2/g$) to spray dried KF($1.3m^2/g$). Inert polystyrene beads have similarly been used to improve the reactivity of KF.[4]

Tetrabutylammonium fluoride(TBAF) is another well known and valuable source of fluoride ion, and is soluble in a variety of common organic solvents. Unfortunately, however, its use is sometimes limited by its physical properties. Thus the commercially available trihydrate is exceedingly hygroscopic and notably 'sticky', preventing it from being easily and rapidly handled during weighing procedures. Resort to drybox conditions maybe necessary for quantitative weighing or for maintaining high reactivity. Furthermore, the reagent has limited thermal stability and readily decomposes if reaction or drying conditions exceed 70-80°C. However, careful drying of the trihydrate under vacuum has been shown to give a highly reactive oil, useful for fluoro-denitration reaction.[5]

In this paper we wish to report our investigation on the use of some high-surface-area non-surface-hydroxylated support materials, such as Teflon and perfluorinated cation exchange polymers, to enhance the reactivity and improve handling of KF and TBAF for fluorination reactions.

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EXPERIMENTAL

Chromosorb T and Fluoropak 80 (Teflon polymers) were obtained from Gasukuro Kogyo, Inc., Japan and were dried at 80°C/0.1mmHg before use. Nafion cation-exchange powder and TBAF trihydrate were from Aldrich Chemicals Ltd. Nafion was converted to the potassium form by treatment with KOH-methanol before being dried at 80°C/0.1mm Hg. Activated charcoal (No.2186) was from Merck and was washed with ether several times before being dried at 60°C/20mmHg. Polystyrene beads, XAD2, were from Amberlite, and were dried at 50°C/0.1mmHg before use. Anhydrous methanol was obtained from Nacalai Tesque, Inc., Japan. Potassium fluoride was from Morita Kagaku Kogyo, Co., Ltd., Japan and was used untreated.

KF-supported Reagents

The supported reagents were prepared by adding the dry support (5-10g) to a solution of KF in methanol (20-30ml), keeping the KF/support ratio at 2mmol/g, followed by rotary evaporation and drying at ca. 80°C/0.1mmHg.

Reactions with solvent: Typically, KF-support (2mmolF$^-$) was added to sulfolane (5-10ml) in a round-bottomed flask. Tetradecane (30μL) was added as an internal standard, a reflux condenser fitted, and the mixture magnetically stirred while being heated to the reaction temperature. After temperature had equilibrated benzyl bromide (115μL, 1.0mmol) was added and the mixture was kept efficiently stirred. Samples of reaction solvent were intermittently removed for GLC analysis.

Reactions without solvent: When no solvent was used the reagent (2-3mmolF$^-$) was rapidly added to a glass ampoule containing benzyl bromide (45μL, 0.4mmol). The ampoule was sealed and immersed in an oil bath thermostatted at the required temperature. After the stated time the ampoule was removed, cooled and cleaned before being placed in a screw-capped test tube with 5ml of MeCN containing tetradecane (30 μL). The ampoule was broken by shaking the test tube, the contents thoroughly mixed, and then the solvent was analyzed by GLC.

TBAF-supported Reagents

The reagents were prepared by dissloving TBAF・3H$_2$O (1.0g, 3mmol) in dry methanol (10-15ml) and then adding support (Fluoropak 80 or XAD2 (3.0g)). The mixture was evaporated to dryness on a rotary evaporator with a water bath at ca. 30°C. A further portion of dry methanol was added and the evaporation repeated. After continued drying of the reagent for 30min on the rotary evaporator it was transferred to a drying pistol and further dried at 50°C under vacuum (0.1mmHg) for 24h or 48h. The resulting reagents (TBAF-FP80, TBAF-XAD2) were white, free-flowing granular powders.

The water contents of the final reagents were measured by the Karl Fischer titration. Duplicate weighed samples were shaken for 30min in screw-capped test tubes with 5.0ml of dry MeCN. The water contents of the solvents were then compared with identical aliquots of MeCN shaken without added reagent. Samples of the TBAF-FP80 reagent dried for 24h at 0.1mmHg

(reagent A) were found to have water contents corresponding to ca. $0.3mol/molF^-$, whereas 48 h drying gave reagent C, with no detectable water. A sample of reagent A was measured for water after storage for several weeks in a screw-capped sample tube (which had been opened several times for removal of reagent), this showed $1.3-1.4molH_2O/molF^-$. A sample of TBAF impregnated on polystyrene (TBAF-XAD2) showed no detectable water after 24h drying at 50°C/ 0.1mmHg.

In a typical reaction TBAF-FP80 (0.63g, $0.5mmolF^-$) was added to 2-chloro-6-nitrobenzonitrile (0.046g, 0.25mmol) dissolved in solvent (5ml) containing tetradecane (30μL) as an internal standard. The mixture, in a screw-capped test tube, was shaken in a water bath at 20°C with a 'Mini-vapor' shaking apparatus. Small samples of the reaction solvent were rapidly withdrawn at intervals for GLC analysis. All reactions were run along side control experiments using commercial TBAF·$3H_2O$.

RESULTS AND DISCUSSION

The activation of KF by dispersion on Teflon polymers (Fluoropak 80 or Chromosorb T), a perfluorinated ion-exchange resin (Nafion-K) or charcoal, was investigated using the fluorination of benzyl bromide (reaction A) as shown in Table 1. When no solvent was employed the pre-supported KF-FP80 reagent was found to be superior to the simple mixture of KF and the support (runs 1 and 2), or the use of other support materials. However, when reactions were run in sulfolane, KF-FP80 showed no activation as compared to the reported 36% yield in 2h using KF alone.[2a] The only reagent which did show increased fluorinating ability was KF-Nafion-K (run 4), which gave 69% yield in 3h. The ionic sites on the surface of this ion-exchange resin may enable KF to be dispersed more evenly than on the non-functionalized polymer surfaces. Also shown in Table 1 are some results for an aryl chloro-fluoro exchange reaction, but the KF-Nafion reagent was less effective than KF-FP80 for this (runs 10 and 11).

Table 1. Fluorination with KF-support reagents

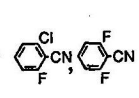| run	reagent[a]	reaction[b]	solvent	T/°C	GLC yield/% (time)[c]
1	KF-FP80	A	none	116	32(3.5h)[d]
2	KF + FP80[e]	A	none	116	—(3.5h)[d]
3	KF-ChT	A	none	116	2(3h)[d]
4	KF-NafionK	A	none	112	8(3h)
5	KF-C	A	none	120	21(3h)
6	KF-FP80	A	sulfolane	120	36(2h)
7	KF-ChT	A	sulfolane	115	16(2h), 61(24h)
8	KF-NafionK	A	sulfolane	108	69(3h), 76(4h)
9	KF-C	A	sulfolane	80	23(16h)
10	KF-NafionK	B	sulfolane	180	8(45m), 13(3h), 19(7h)
11	KF-FP80	B	sulfolane	180	16(45m), 35(3h), 35(7h)[f]
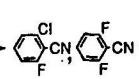
a) KF-FP80 = KF on Fluoropak 80, KF-ChT = KF on Chromosorb T, KF-C = KF on charcoal   b) A = benzyl bromide to benzyl fluoride, B = 2,6-dichlorobenzonitrile to 2-chloro-6-fluorobenzonitrile   c) compare for reaction A, sulfolane, 120 °C; KF (36%, 2 h), KF-CaF_2 (92%, 2h), ref. 2a   d) with up to 25% benzyl ether   e) KF and Fluoropak 80 mixed in quantities as for run 1   f) with 4% 2,6-difluorobenzonitrile.

The efficiency of the KF dispersion was found to be rather variable when using the Teflon polymers and some reagents showed low activity. During preparation it was important to keep the support in the KF solution for as long as possible during rotary evaporation in order to maximize salt dispersion on the support surface. It was noted that although the reagents were well dried before use benzyl ether was formed as a byproduct in yields of up to 25% for reaction A, suggesting that some water was tenaciously held by the reagents. The use of solvent greatly reduced this side reaction. The perfluorinated polymer supports have surface areas of 7-10㎡/g and are thus comparable to CaF_2. Charcoal has a much higher surface area than the other supports but the results suggest that KF is not efficiently dispersed over the surface.

The high cost of the Nafion resin does not make it appear to be a useful alternative to CaF_2 for activation of KF for fluorination, but the results help confirm that fluorinating ability increases with the effective surface area of the salt.

Table 2 shows that the TBAF-FP80 (reagent A) gave enhanced reaction rate for heterogeneous fluorination in hydrocarbon solvent (xylene) compared to the commercial TBAF·$3H_2O$, although little difference in final conversion was observed (runs 1,2; 9,10; 11,12; 16,17). The more extensively dried TBAF-FP80 (reagent C) showed decreased heterogeneous reactivity (run 3) and the extremely dry TBAF-XAD2 was also less effective (run 4), suggesting a trace of water is important for activation of fluoride.[6] During the course of these reactions a dark-colored immiscible phase was formed, presumably due to reaction byproducts, which appeared to limit the final reaction yields to ca. 50% or less. In several cases acetonitrile was added to make the final reaction mixture homogeneous, and then further analysis by GLC showed that rapid reaction resumed. Thus suggesting that although the TBAF was poisoned for heterogeneous reaction it was not totally inactivated.

Table 2. Fluorinations Comparing TBAF-FP80, TBAF-XAD2, and TBAF·$3H_2O$

run	substrate	solvent	rgt[a]	T/°C	products	GLC yield/% (time)
1		xylene	A	20		45,—(5m); 45,—(30m); 50,—(1h)
2		xylene	B	20		5,—(5m); 43,—(30m); 50,—(1h)
3		xylene	C	20		25,—(30m); 40,—(1h); 88,12(1h)[b]
4		xylene	D	20		10,—(30m); 14,—(1h); 43,2(1h)[b]
5		THF	C	20		75,2(30m); 80,2(1h)[c]
6		MeCN	C	20		70,2(5m); 77,3(30m); 78,3(1h)[c]
7		MeCN	B	20		58,5(5m); 56,6(30m)
8		MeCN	D	20		52,3(5m); 52,3(30m)
9	1-$C_8H_{17}I$	xylene	A	50	1-$C_8H_{17}F$	34(5m); 37(30m); 35(1h)[b]
10	1-$C_8H_{17}I$	xylene	B	50	1-$C_8H_{17}F$	22(5m); 36(30m); 35(1h)[b]
11		xylene	A	70		38,12(2h); 28,4(3h); 41,15(5h)[d]
12		xylene	B	70		18,2(3h); 26,4(5h); 39,30(5h)[d]
13		xylene	C	20		12,1(30m); 30,4(3h)[d]
14		MeCN	A	70		28,2(4h); 31,2(7h); 47,7(11h)[e]
15		MeCN	B	70		40,13(4h); 41,14(7h); 10,9(11h)[e]
16		xylene	A	20		17(30m); 25(90m); 57(90m)[d]
17		xylene	B	20		3(30m); 8(90m); 55(90m)[d]

a) A = TBAF-FP80 dried 24 h, B = commercial TBAF·$3H_2O$, C = TBAF-FP80 dried 48 h, D = TBAF-XAD2 dried 24 h   b) with 32% oct-1-ene   c) compare ref. 5, anhydrous TBAF, THF, room temp., 75,25(90 m)   d) after addition of MeCN to make the reaction mixture homogeneous   e) after further reaction with a fresh batch of reagent at 7 h (ca. 0.5 mmol F⁻).

For homogeneous fluorination in THF or MeCN, the TBAF-FP80 reagents were again more effective than TBAF-XAD2 or the commercial trihydrate for fluoro-denitration of 2-chloro-6-nitrobenzonitrile (runs 5-8). The reaction was more selective with the "anhydrous" TBAF-FP80 than with the previously reported "anhydrous" TBAF oil[5] (runs 5,6). The fluorination of 2,6-dichlorobenzonitrile to give 2-chloro-6-fluorobenzonitrile was also achieved with improved selectivity using TBAF-FP80, although at a slower rate (runs 14,15).

Our results indicate that the simple impregnation of $TBAF \cdot 3H_2O$ on to a high-surface-area inert Teflon polymer ($7-10 m^2/g$) enables it to be efficiently dried and handled as a freeflowing powder. The increased surface area of the reagent leads to faster reaction for heterogeneous fluorination, especially when a trace of water remains, but byproduct poisoning of the reagent limits the extent of reaction. We believe that the advantages of improved reaction rate as well as handling and drying make the TBAF-FP80 reagent useful. Furthermore, the Teflon polymer can easily be removed from the reaction for reuse or used in the form of a column.

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