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TETRABUTYLAMMONIUM BIFLUORIDE: A VERSATILE AND EFFICIENT FLUORINATING AGENT

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Summary: The use of tetrabutylammonium bifluoride as stable and easily available source of fluoride ion in nucleophilic substitution processes with different substrates is reported.

Our interest in the synthesis of fluorinated analogues of insect sex pheromones[1] has led us to the study of new stable and easily available fluorinating agents. In this line, we report herein the use of tetrabutylammonium bifluoride (TBABF) as a new source of "naked" fluoride ion.

Nucleophilic displacement of halides, tosylates and trifluoromethanesulfonates (triflates) by fluoride ion has been effectively carried out, among other reagents, by KF-18-crown-6 complex,[2] "spray-dried" KF,[3] calcium fluoride-supported alkali metal fluorides[4,5] and tetraalkylammonium fluorides.[6-8] In his paper, Cox and coworkers[7] prepared "anhydrous" TBAF, containing 0.1-0.3 molar equiv. of water, by heating commercially available TBAF.$3H_2O$ at 40-45°C under reduced pressure during several hours. Analysis of the product by ^{19}F NMR revealed the presence of ca. 10% of TBABF, in agreement with previous results reported by Sharma and Fry.[9] In this context, we anticipated that pure, directly prepared, tetrabutylammonium bifluoride could be readily used as a genuine source of nucleophilic fluoride ion. A literature search revealed that a similar reagent, tetraphenylphosphonium bifluoride, had been recently applied to the fluorination of halides, nitroaromatics and as oligomerization reagent.[10,11]

Preparation of tetrabutylammonium bifluoride was accomplished as follows. A 0.7 M solution of ammonium bifluoride was passed through 40 g of Amberlite IRA 410 exchange resin until no further reaction of the column effluent with $AgNO_3$ solution was detected. The resin was washed with distilled water and dried under vacuum. Then, a solution of tetrabutylammonium chloride (1 g) in 20 ml of CH_3CN was passed through the column until no precipitate of the effluent with $AgNO_3$ was observed. After evaporating off the solvent, TBABF was dried at 50°C under 0.1 torr for 24 h. Spectroscopic features of the salt were

consistent with those previously reported.[9,12] TBABF is very soluble in organic polar solvents, such as THF, HMPT, DMSO and CH_3CN, and displays good thermal stability at temperatures below 140°C (only 7.7% of HF and butylamine loss upon heating at 150°C during 10 h).

As shown in the Table, the reaction with different substrates was carried out with an excess of fluorinating agent, generally in a 2:1 to 3:1 ratio, in a 1:1 mixture of THF: HMPT at 95°C under nitrogen.[13] Other solvents, such as CH_3CN, DMSO and toluene, gave inferior results (see entry 9). The progress of the fluorination process was monitored by GLC analysis and the identification of the reaction products was carried out by ^{19}F NMR, mass spectrometry and chromatographic comparison with authentic samples.

As an example of application of the reagent, the preparation of dodecyl fluoride is described. Dodecyl methanesulfonate (100 mg, 0.378 mmole) was added to a solution of TBABF (220 mg, 0.756 mmole) in a 1:1 mixture of anhydrous THF:HMPT (4 ml). The mixture was heated at 95°C (bath temperature) under nitrogen for 6 h. Water was then added and the organic material repeatedly extracted with hexane, washed with brine and dried ($MgSO_4$) to yield 0.064 g (90%) of dodecyl fluoride. ^1H NMR ($CDCl_3$, 80 MHz) δ 4.37 (dt, J = 48 and 6.0 Hz, 2H, $\underline{CH_2}F$), 1.55-1.95 (c, 2H, $\underline{CH_2}CH_2F$), 1.0-1.55 (b, 18H, -$\underline{CH_2}$-), 0.80 (t, J = 6.0 Hz, 3H, $\underline{CH_3}$). ^{19}F NMR ($CDCl_3$, 75.39 MHz) δ -142.02 (tt, $^2J_{H-F}$ = 47.3 Hz, $^3J_{H-F}$ = 23.8 Hz) (relative to CF_3CO_2H) MS m/z (relative intensity) 188 (M^+, 2), 140 (3), 111 (8), 97 (13), 85 (14), 84 (10), 83 (13), 71 (29), 70 (15), 69 (25), 57 (71), 56 (20), 55 (42), 43 (100), 42 (26), 41 (79).

The reagent has been found specially useful for transformation of primary alcohols into the corresponding fluorides through the intermediate tosylates and mesylates (entries 2,3) whereas trifluoroacetates yielded exclusively the starting alcohols (entry 1). This failure is in contrast with the high efficient one-pot transformation of alcohols into the corresponding chlorides, bromides and iodides, via trifluoroacetates, recently reported by us.[14] Reaction with mesylates of secondary alcohols, such as 2-dodecanol, led to a marked decrease in the yield of the expected fluoride due to the formation of a considerable proportion of isomeric alkenes and other side-products (entry 4). As expected, the direct reaction of TBABF with aliphatic alcohols, such as 1-decanol, was unsuccessful, even under drastic conditions (140°C, 24 h in HMPT).

On the other hand, reaction of aliphatic and benzylic halides with TBABF gave comparable or better yields than other methods previously described.[2,3,7,10,11] Complete conversion however, could not be achieved under standard conditions with aliphatic chlorides (entry 5), whereas bromides and iodides needed relatively short reaction times for whole conversion. (entries 6-8). The dehydrohalogenation reaction, almost negligible with chlorides and bromides, amounted up to 24% with iodides. This concomitant basic behavior of the salt has also been reported for "anhydrous" TBAF.[7] Likewise, TBABF is also remarkably useful in the conversion of α-chloro to α-fluoroketones (entry 12), which allows an efficient and straightforward entry to this important class of compounds as enzyme inhibitors.[15,16] The

$$RX + Bu_4N^+ HF_2^- \longrightarrow RF$$

Table. Fluorination reactions with TBABF.

Entry	Substrate	Molar ratio HF_2/Substr.	Solvent	Time(h)	Reaction Products (%)[a] S.m.	RF	Alkene	ROH	Other
1	$C_{10}H_{21}OCOCF_3$	3:1	THF:HMPT	0.5	--	--	--	100	--
2	$C_{12}H_{25}OTs$	2:1	"	14	--	96	--	4	--
3	$C_{12}H_{25}OMs$	2:1	"	6	--	100[b]	--	--	--
4	$CH_3CH(OMs)(CH_2)_9CH_3$	2:1	"	20	6	51	14[c]	--	29[d]
5	$C_{12}H_{25}Cl$	3:1	"	22	12	83	5	--	--
6	$C_{10}H_{21}Br$	2:1	"	3	--	88	--	--	12[d]
7	$C_{18}H_{37}Br$	2:1	"	5	--	79	7	--	14[d]
8	$C_{18}H_{37}I$	3:1	"	2.5	--	76	24	--	--
9	$C_{18}H_{37}I$	3:1	CH_3CN[e]	7	30	60	10	--	--
10	$BrC_{10}H_{20}Br$	4:1	THF:HMPT	3.5	--	76	2	--	22[f]
11	Ph CH_2Br	3:1	"	4	--	100	--	--	--
12	$PhCOCH_2Cl$	2:1	"	4.5	--	100	--	--	--
13	p-NO_2PhCl	3:1	"	57	30	70	--	--	--

[a] By GLC analysis.
[b] A 90% yield on isolated product.
[c] Mixture of 1- and 2-dodecenes.
[d] Unknown.
[e] Run at reflux temperature (80°C).
[f] Assigned as 1-bromo-10-fluorodecane by MS.

reagent is, however, uneffective in promoting aromatic nucleophilic substitution unless the aromatic halides are activated by electron-withdrawing groups, i.e. the nitro group (entry 13).

Further work on new applications of the reagent is in progress.

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