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Facile Preparation of Tetrabutylphosphonium Fluoride and Its HF Adducts. New Fluoride Anion Sources for Selective Nucleophilic Fluorination

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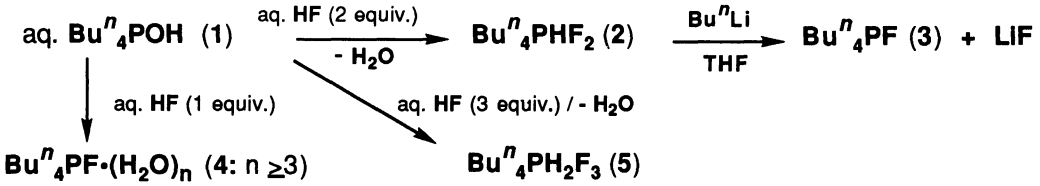
Anhydrous tetrabutylphosphonium hydrogen bifluoride (**2**), dihydrogen trifluoride prepared from aq. tetrabutylphosphonium hydroxide and aq. HF, and tetrabutylphosphonium fluoride prepared from **2** and Bu^{n}Li were shown to be useful fluoride sources for selective nucleophilic fluorination of oxiranes, alkyl halides, alcohols and sulfonates of aliphatic and steroidal species.

New facile fluoride sources are still necessary that are more soluble in non-polar organic media and are more selective in fluorination under mild conditions than the known fluoride sources, i. e., various metal or ammonium fluorides such as KF, KHF_2, CsF, Bu$^n_4$NF, and Bu$^n_4$NF•HF, or amine HF adducts such as pyridine•$(HF)_n$, all of which are hardly soluble in non-polar solvents and often accompany side reactions due to the basicity of fluoride salts or the acidity of excess HF.

As for tetraalkylphosphonium fluorides, Leroy has first conducted fluorination of some substrates with Bu$^n_3$MePF,[1] as prepared from Bu$^n_3$PCH_2 by Schmidbaur's method,[2] and reported moderate yields or selectivities in fluorination. Then Clark has reported of Ph_4PF•HF for preparation of various fluorides in highly polar solvents,[3] and Landini has described general procedures for preparation of (n-alkyl)$_4$PF• $(HF)_n$ (n=1 and 2).[4] However, these methods require multiple steps for preparation of the fluoride salts, which include either elution from ion-exchange column or exhaustive extraction with MeCN for isolation. In fact, none has been reported to date on direct preparation of Bu$^n_4$PF•$(HF)_n$ (n = 0, 1, and 2) (**3**, **2**, and **5** respectively) from facile sources and their application to fluorination in spite of their potentiality as useful fluoride source. We now report new facile methods for preparation of three phosphonium fluorides and some preliminary results revealing their useful features as active fluoride sources.

Our initial attempt to prepare the fluoride (**3**) from the aq. solution prepared from aq. tetrabutylphosphonium hydroxide (**1**) and aq. HF (1 equiv.) failed due to concurrent decomposition of the phosphonium fluoride hydrate (**4**) when dried *in vacuo* even at room temperature, resulting in formation of the bifluoride (**2**), Bu$^n_3$PO, and Bu^{n}H. This differs from the case of hydrated Ph_4PF which decomposes at temperatures over 200 °C.[5] In addition, any hydrate of **3** was not at all extracted with $CHCl_3$, or not separated from aq. solution of **3** unlike the hydrated Ph_4PF.



In contrast, preparation of the anhydrous bifluoride (**2**) was smoothly conducted as follows: To a 40% aq. Bu$^n_4$POH (**1**)[6] (207.4 g; 0.30 mol) containing a few drops of ethanolic phenolphthalein was added 47% aq. HF at 5 - 20 °C until the red color of the solution disappeared (12.8 g of aq. HF consumed).[7] After another 12.8 g of 47% aq. HF was added, the solution was concentrated to dryness *in vacuo* (at 45 °C for 5 h) to leave the crude bifluoride (**2**) (93.3 g; 105%) as a colorless liquid or a crystalline mass (mp 32 °C, triturated in CCl_4). The anhydrous trifluoride (**5**) was similarly prepared as a liquid quantitatively from 1 and aq. HF in a 1 : 3 molar ratio.[7]

The bifluoride (**2**) was readily dehydrofluorinated with Bu^{n}Li to generate the fluoride (**3**) as follows: To crude 2 (647 mg; 2.17 mmol) dissolved in THF (4 ml) was added a 1.67 mol dm^{-3} hexane solution of Bu^{n}Li (1.3 ml; 2.11 mmol) at 20 °C under N_2. Removal of the solvents *in vacuo* left a mixture of **3** and LiF as a colorless oil.[7]

All the anhydrous phosphonium salts, **2**, **3**, and **5**, are freely soluble in water and in most of non-polar solvents such as benzene and xylene but insoluble in hexane. Since the phosphonium hydrogen fluorides, **2** and **5**, are thermally stable up to 180 °C, well fluid at room temperature, and miscible with most of organic substrates, the reactions can be conducted without solvent. All the phosphonium salts being highly hygroscopic, the crude products were forwarded to subsequent reactions.

Table 1. Fluorination of *p*-methylbenzyl bromide

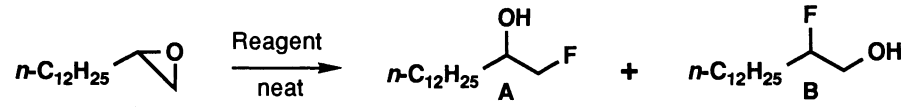
Entry	Reagent [a]	Temp / °C	Time / h	Yield / % [b]
1	**3**	20	< 0.25	92
2	**2**	20	4	99
3	**5**	60	28	93

a) The bromide (1 mmol) was treated with each reagent (3 mmol) in THF (1 ml).
b) Yield of *p*-methylbenzyl fluoride after isolation.

Table 1 compiles the data for nucleophilic fluorination of *p*-methylbenzyl bromide with the phosphonium salts whose nucleophilic activities seem to become more moderate by increasing number of HF bound with Bu$^n_4$PF (**3**) that is most active among the fluoride anion sources.[8]

Treatment of dodecyloxirane with **2**, **3**, and **5** without any solvent gave two fluorohydrins **A** and **B** in high yields (see Table 2), in which **3** was the most active and selective for production of **A**, suggesting an S_N2 attack of fluoride anion at the less hindered position of the oxirane. This is contrary to the cases with pyridine•(HF)$_n$ and SiF_4 which fluorinate selectively the more branched carbon of oxiranes.[9] The S_N2 attack has been also suggested to the reactions with KHF_2,[10] and Pr$^i_2$NH•(HF)$_3$,[11] where steric effect is dominant over electronic effect.

Table 2. Fluorination of dodecyloxirane



Entry	Reagent	Temp / °C	Time / h	Total yield / % [a]	Ratio (**A** : **B**) [b]
1	**3**	20	20	82	97 : 3
2	**2**	100	4	94	93 : 7
3	**5**	100	10	92	78 : 22

a) Yields of a mixture of **A** and **B** after isolation. b) Ratios estimated on ^{19}F NMR analysis.

Fluorination of tetradecyl chloride, bromide, mesylate or tosylate (entry 1 in Table 3) with the bifluoride (**2**) generally gave tetradecyl fluoride in more than 80% selectivities which are comparable to those by the conversion with Bu^n_4NF. Fluorinations with the trifluoride (**5**) required more forcing conditions and the conversion with the fluoride (**3**) mainly yielded a mixture of 1- and 2-tetradecenes by elimination. In contrast, treating 2-tetradecyl sulfonates with **2** gave obviously better results, in which the selectivity for fluorination was superior to the conversion with Bu^n_4NF (see entry 3). Generally two moles of **2** were necessary to complete the fluorination.

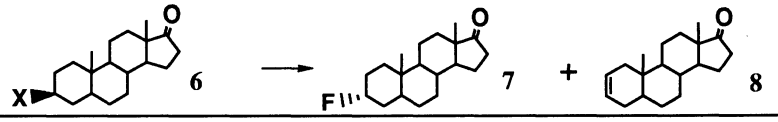
Table 3. Fluorination of alkyl tosylates [a]

Entry	Substrate	Reagent	Reaction time / h	Product & yield / % Fluoride	Tetradecenes
1	*n*-$C_{14}H_{29}OTs$	**2**	15	*n*-$C_{14}H_{29}F$ / 95	0
2	*n*-$C_{12}H_{25}CH(OTs)Me$	**2**	10	*n*-$C_{12}H_{25}CHFMe$ / 86	5
3	*n*-$C_{12}H_{25}CH(OTs)Me$	Bu^n_4NF	5	*n*-$C_{12}H_{25}CHFMe$ / 56	26

a) Reactions were conducted with 3 mol equiv. of each reagent in THF at 20 °C.

It has been known to be more difficult to fluorinate steroidal secondary alcohols with high selectivity since geometry of leaving groups are suited for elimination rather than fluorination. However, the results of fluorination of 3β-sulfonyloxy-androstan-17-one (see Table 4) indicated that **2** was more selective for the fluorination of the 3α fluoride (**7**) than Bu^n_4NF.

Table 4. Fluorination of 3 β–oxy derivatives (**6**) of androstan-17-one



Entry	Reagent	**X** of **6**	3α Fluoride (**7**)	2,3-Ene (**8**)	Yield / %
1	**2** [a]	i: **OTs**	77	15	
		ii: **OMs**	80	16	
2	Bu^n_4NF [b]	**OTs**	67	30	
3	**2** + **MsF** [c]	**OH**	82	12	
4	**DAST** [d]	**OH**	47	44	

a) Three mol equiv. in THF at 60 °C for 10 h. b) In N-methylpyrrolidine at 80 °C.[12]
c) Three mol equiv. of **2** and 2 mol equiv. of **MsF** at 80 °C for 5 h (without solvent).
d) In CH_2Cl_2 at 20 °C.[12]

A more distinct feature of **2** was demonstrated when the 3β-hydroxyandrostanone is fluorinated (Entry 3), in which a combination of **2** with MsF was more selective in fluorination than DAST (Entry 4).[12] In this connection, we note that Bu^n_4NF does not fluorinate aliphatic secondary OH groups when employed in combination with MsF or TsF.[13] Finally, 1-bromoadamantane was converted to 1-fluoroadamantane in 91% yield on treatment with 3 equiv. of **3** at 150 °C for 5 h without solvent.

As thus described, the phosphonium fluorides, **2** and **3**, and probably **5**, will serve as a new set of the most lipophilic and useful reagents, whose natures as nucleophile, base or acid appear to be in a convenient range and optionally applicable to selective fluorination of a wide variety of organic substrates.

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6) The aq. phosphonium hydroxide was provided by Hokko Chemical Ind. and available in large quantity. See Japan Kokai Pat. 62-212397 (1987) for reference.
7) A pH value of the mixture at this point was 8.1 and those of hydrated **2** and **5** (1.0 mmol of each in 40 ml of H_2O) were about 4.0. Satisfactory elemental analysis data were obtained for **2** and **5**. NMR spectroscopic data for **2**: ^1H NMR ($CDCl_3$) δ 0.97 (m, 12 H), 1.50 (m, 16 H), 2.30 (m,, 8 H), 16.0 (br, 1 H); ^{19}F NMR ($CDCl_3/CFCl_3$) δ -156.1. NMR data for **5**: ^1H NMR ($CDCl_3$) δ 0.97 (m, 12 H), 1.52 (m, 16 H), 2.23 (m, 8 H), 11.3 (br, 2 H); ^{19}F NMR ($CDCl_3/CFCl_3$) δ -167.4. NMR data for **3** (taken as dissolved with LiF): ^1H NMR ($CDCl_3$) δ 0.97(m), 1.50 (m), 2.40 (m); ^{19}F NMR (THF/$CFCl_3$) δ -145.5.
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