Fluoride-ion-mediated Hydrolysis of Phosphoric Acid Esters, Amides, and Phosphorous Acid Esters Leading to Phosphorofluoridic, Phosphoramide Fluoridic, and Phosphonic Acid Monoester Salts

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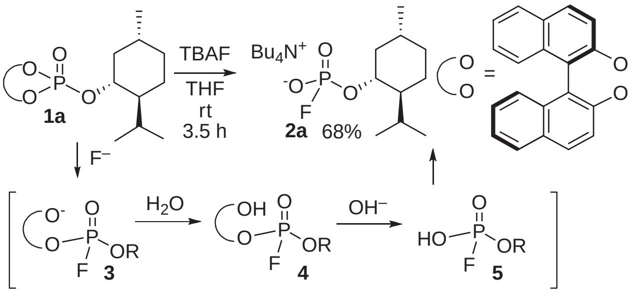
Fluoride-ion-promoted hydrolysis of phosphoric acid esters and amides to give phosphorofluoridic and phosphoramide fluoridic acid monoester salts takes place upon treatment with a THF solution of TBAF, whereas a similar treatment of phosphorous acid esters generates phosphonic acid monoester salts selectively without introduction of fluorine.

The introduction of fluorine into organophosphorus compounds is of great importance because phosphoric acid derivatives bearing P–F bonds display a wide range of biologically interesting properties.[1] The high affinity[2] of fluorine toward phosphorus is the driving force for fluoride-ion-promoted substitution reactions of phosphonic[3] and phosphoric acid derivatives[4] that provide P–F bond containing pentavalent organophosphorus compounds. In addition, oxidative fluorination of dialkyl phosphites is known to give dialkyl fluorophosphates.[5] However, air-sensitive and/or less accessible substrates and reagents are necessary in some cases, and more straightforward methods with readily available starting materials are desired.

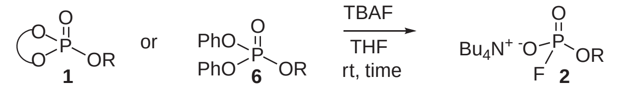
In the course of our current studies with organophosphorus compounds,[6] we observed that site-selective reactions of phosphoroselenoic acid *O*- and *Se*-2-silylethyl esters bearing the binaphthoxy group take place in THF solutions containing tetrabutylammonium fluoride (TBAF).[7] Below, we describe observations made in studies of fluoride-ion-mediated hydrolysis reactions of phosphoric esters, amides, and phosphorous esters occurring in THF solutions of TBAF that lead to the formation of phosphorofluoridate monoester acid and phosphonic acid salts in a highly selective manner.

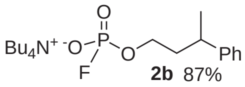
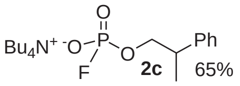
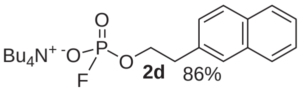
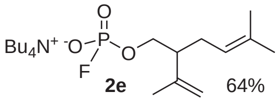
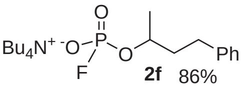
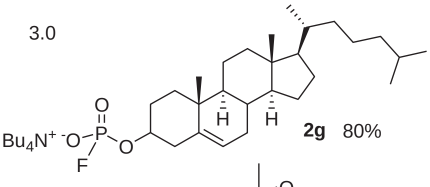
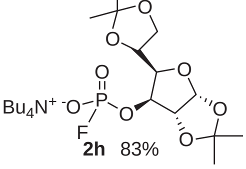
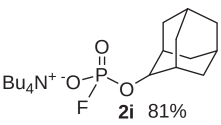
In our initial efforts in this area, the phosphate triester **1a** was treated with a THF solution of TBAF (Scheme 1). The starting ester **1a** was consumed within 4.5 h, and purification of the reaction mixture gave the phosphorofluoridic acid monoester salt **2a** along with 1,1′-bi-2-naphthol. The ^{31}P NMR spectra of **2a** contained a doublet at −5.4 ppm with a characteristic ^{1}J value for coupling between a phosphorus and a fluorine atom. The two ArO–P bonds in **1a** were selectively cleaved, while the alkylO–P bond in the starting material was retained in the product **2a**. The reaction pathway for this process (Scheme 1) likely involves nucleophilic substitution by fluoride at phosphorus to form intermediate **3**, which is protonated by adventitious water in the THF solution of TBAF[8] to give **4** and hydroxide ion.



Scheme 1.

Table 1. Fluoride-ion-mediated hydrolysis of phosphoric esters **1** and **6**[a]



Entry	1 or 6	Time/h	Product 2, Yield/%[b]
1	**1b**	4.5	 **2b** 87%
2	**1c**	4.5	 **2c** 65%
3	**6a**	5.0	 **2d** 86%
4	**6b**	4.0	 **2e** 64%
5	**1d**	4.5	 **2f** 86%
6	**6c**	3.0	 **2g** 80%
7	**1e**	2.5	 **2h** 83%
8	**6d**	1.0	 **2i** 81%

[a] Phosphoric esters **1** and **6** were reacted with THF solution of TBAF (1.2–2.0 equiv) at rt. [b] Isolated yields.

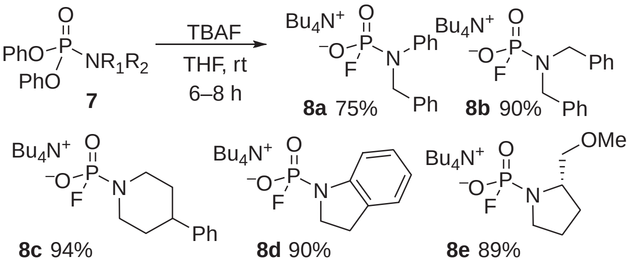
Hydroxide-initiated hydrolysis of **4** then takes place with elimination of 1,1′-bi-naphtholate to give **2a** via **5**.

To demonstrate that this reaction is applicable to the production of less accessible phosphorofluoridic acid monoester salts,[9,10] a variety of phosphoric acid esters containing the binaphthyloxy group (**1** in Table 1) as well as two phenoxy groups (**6** in Table 1) were reacted with TBAF. In each case, reaction proceeds to completion within 5 h, and the tetrabutylammonium salt of the corresponding phosphorofluoridic acid monoester **2** is generated in good yield. The reactions of esters derived from secondary and tertiary alcohols (Entries 5–8) proceed with equal efficiency to provide fluorophosphate monoesters. The presence of alkenyl groups and acetal moieties does not affect the reaction (Entries 4, 6, and 7). Owing to the fact that the salts obtained as products in these processes are soluble in polar solvents, such as acetone, Et_2O, and CH_2Cl_2, and in water, work up of the reaction mixtures involves partitioning between Et_2O and water. The organic layers contain 1,1′-bi-2-naphthol and phenol, and the aqueous layers are then extracted with CH_2Cl_2 to isolate the fluorophosphate salts **2** except for **2g**.

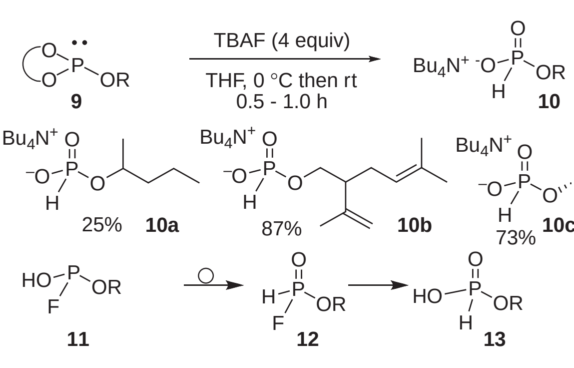
Phosphoramidates **7** also undergo fluoride-promoted hydrolysis when treated with TBAF to produce phosphoramide fluoridic acid monoester salts **8** (Scheme 2). Slightly longer reaction times are required for completion of these reactions. In this process, selective elimination of two phenoxy groups takes place and the N–P bond remains in the products **8**.

In this effort we also explored reactions of phosphorous acid esters **9** with the expectation that selective cleavage of ArO–P bonds would again occur (Scheme 3).

As a matter of fact, reaction of **9** with TBAF, which proceeds to completion in 1 h, efficiently produces phosphonic acid ammonium salts **10** in which two aryloxy moieties of the binaphthyloxy group are eliminated, but a fluorine atom is not introduced. This result stands in striking contrast to the pathway followed in fluoride-induced reactions of phosphate esters **1** and **6**. In this process, substitution reactions at the phosphorus atom of **9** with fluoride and hydroxide proceed sequentially to form intermediate **11** (Scheme 3). Then, **11** undergoes Arbuzov rearrangement to yield the phosphonofluoridic acid monoester **12**, which upon hydrolysis generates **13**, which is deprotonated to give **10**.[11]



Scheme 2.



Scheme 3.

In summary, the results of this investigation demonstrate that fluoride-ion-mediated hydrolyses of phosphoric and phosphorous acid esters and amides are efficient reactions that take place in an highly selectively manner. The findings show that fluoride-promoted hydrolysis of phosphoric acid esters and amides produces phosphorofluoridic and phosphoramide fluoridic acid monoester salts. In contrast, phosphorous acid esters are converted to phosphonic acid monoester salts in reactions with TBAF.[12]

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