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Rapid and efficient solid-supported reagent synthesis of fluorine derivatives of phosphorus(V) compounds

Timothy Sierakowski and James J. Kiddle*

Department of Chemistry, Western Michigan University, 3425 Wood Hall, Kalamazoo, MI 49008, USA

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Abstract—Direct conversion of phosphorus(V) chlorides to the corresponding phosphorus(V) fluorides was achieved utilizing a solid-supported reagent. The phosphorus(V) fluorides were straightforwardly synthesized and efficiently isolated in very good yields.

Fluorine derivatives of phosphorus(V) species (P–F compounds, phosphorofluoridates) represent an important class of organophosphorus compounds. These compounds are recognized as selective phosphorylating agents in synthesis, and efficient inhibitors of several classes of enzyme.[1] The biological activity of these compounds is highly structure dependent.[2] Unfortunately, only two phosphorus(V) P–F compounds are available from commercial sources. Therefore, it would be highly desirable to have an efficient and rapid method for the synthesis of a variety of structurally related P–F compounds from commercially available phosphorus precursors.

Recently, our laboratory required the synthesis of a series of substituted diethyl phosphates for kinetic studies.[3] Diethyl fluorophosphate was necessary as a synthetic intermediate for the construction of another compound, as well as for the study itself. Several approaches were available in the literature falling broadly into two general categories: either halogen metathesis with a metal fluoride, or reaction of an activated fluorine source. Michalski and Łopusiński have achieved fluorination using both sulfuryl chloride fluoride[4] and thionyl fluoride[5] on a limited number of phosphorus species, two and four, respectively. Although the reactions were accomplished primarily using commercially available phosphonic acids, dithioic acids, and a phosphite the major drawback to the practical use of these two methods is that the reagents are both gases. In addition, the products of the reaction of the sulfuryl chloride fluoride method are often contaminated by the corresponding phosphorus(V) chloride. The same research group has also reported the synthesis of phosphorus(V) fluorides from the corresponding phosphoroazolides with benzoyl fluoride.[6,7] Even though the reactions proceed in almost quantitative yield, the starting phosphoroazolides are not commercially available and must be synthesized from the corresponding phosphorus(V) chlorides.[8] In related work, Łopusiński has shown that dialkyl *S*-trifluoromethyl phosphorothioates can be converted to phosphorus(V) fluorides in the presence of nucleophiles via a thiocarbonyl fluoride extrusion reaction.[9,10] Again, the author produced the phosphorus(V) fluorides in very good yields (73–90%), however, again the major drawback to this route is the need to prepare the starting phosphorus compounds, in this case at low temperatures.

A more common method for the synthesis of phosphorus(V) fluorides is halogen metathesis reactions of the corresponding phosphorus(V) chlorides using metal fluorides.[1,11] Recently, Farooq has described a procedure to produce P–F compounds from the corresponding P–Cl compounds by heating a solution of either sodium tetrafluoroborate or hexafluorophosphate in tetraglyme.[12,13] Although all the reactions occurred in a short time (less than 60 min) and used commercially available chloride compounds, the yields of the phosphorus(V) fluorides were highly variable (12–77%). In related work, Chworoś and Woźniak reacted a variety of P=S and P=Se compounds in the presence of aqueous silver fluoride

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Keywords: Synthesis; Phosphorus(V) fluoride; Phosphonofluoridate; Nerve agent; Chemical warfare agent; DFP.

* Corresponding author. Tel.: +1 269 387 5440; fax: +1 269 387 2909; e-mail: james.kiddle@wmich.edu

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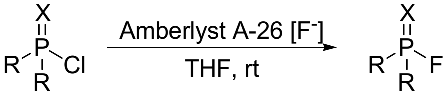
Table 1. Synthesis of phosphorus(V) fluoride compounds using a solid-supported reagent[22]



R	X	Time (h)	Isolated yield[a] (%)	^{31}P NMR δ[b]	^{19}F NMR δ[b]
CH_3O	O	0.5	82	−8.46 ($^1J_{P–F}$ = 973 Hz)	−80.0 ($^1J_{F–P}$ = 984 Hz)
CH_3CH_2O	O	0.5	81	−8.0 ($^1J_{P–F}$ = 990 Hz)	−77.3 ($^1J_{F–P}$ = 982 Hz)
CH_3CH_2O	S	2.0	91	62.9 ($^1J_{P–F}$ = 1082 Hz)	−43.7 ($^1J_{F–P}$ = 1076 Hz)
$(CH_3)_2CHO$	O	0.5	76	−10.2 ($^1J_{P–F}$ = 978 Hz)	−76.8 ($^1J_{F–P}$ = 977 Hz)
PhO	O	1.0	70	−21.0 ($^1J_{P–F}$ = 1002 Hz)	−76.9 ($^1J_{F–P}$ = 997 Hz)
$(CH_3)_2N$	O	2.5	81	18.3 ($^1J_{P–F}$ = 947 Hz)	−82.8 ($^1J_{F–P}$ = 943 Hz)

[a] All reactions showed 100% conversion by ^{31}P NMR prior to isolation.

[b] All compounds demonstrated satisfactory ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR data and were compared with literature values as well as authentic samples.

to furnish the products of both fluorination and oxidations in excellent yields [FP(O)].[14] Unfortunately, the yields reported were calculated from ^{31}P NMR data and may not reflect the isolated yield of the products. Additionally, not all of the starting compounds are commercially available requiring the synthesis of precursors for these transformations.

The use of solid-supported reagents in organic synthesis is a rapidly developing area of growth.[15–21] Solid-supported reagents often perform in a similar fashion to their unbound equivalents, but with reduced solvent requirements. In addition, the increased reagent surface area can improve the reactivity of a particular reagent. Because of the deficiencies in the available methods for the synthesis of phosphorus(V) fluorides, we sought to develop a more efficient method for their syntheses from commercially available phosphorus(V) chlorides using a solid-supported fluoride reagent.

As a first attempt, we examined the equal molar reaction of diethyl chlorophosphate with the ion exchange resin Amberlyst® A-26 with a fluoride counterion in THF at room temperature. The reaction was followed by ^{31}P NMR at 15 min intervals and showed complete conversion of the diethyl chlorophosphate (^{31}P NMR δ = 5.0 ppm) to the corresponding diethyl fluorophosphates (^{31}P NMR δ = −8.0 ppm, d, $J_{P–F}$ = 990 Hz) in 30 min. Filtration of the heterogeneous reaction mixture and concentration of the solvent provided the pure phosphorus(V) fluoride in 81% isolated yield.

With this result in hand, a series of disubstituted phosphorus(V) chlorides were chosen as substrates and reacted under identical conditions to the model system to afford the corresponding phosphorus(V) fluorides in very good isolated yields (Table 1).

As revealed in Table 1, all the phosphorus(V) chlorides reacted smoothly in short reaction times to produce the corresponding phosphorus(V) fluorides in very good yields. The procedure was tolerant of both the ligands on phosphorus and the chalcogen atom bonded to the phosphorus. In addition, scale up of the procedure (2.8–28 mmol) did not show any significant change in the isolated yield for the diethyl fluorophosphate (78%). In general, the reduction in isolated yield for the reactions, despite all showing complete conversion by ^{31}P NMR spectroscopy, is attributed to retention of the product on the resin, and loss of material during the solvent removal.

In conclusion, we have developed an efficient synthesis of a variety of phosphorus(V) fluorides from the corresponding chlorides utilizing a solid-supported source of fluoride ion at room temperature. This methodology represents a simplified procedure over those previously reported avoiding the need to synthesize starting materials to construct the phosphorus(V) fluorides. More importantly, this reaction sequence minimizes exposure to both the starting material and product, which are both potent acetylcholinesterase inhibitors, and offers the rapid isolation of the pure product by filtration.

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References and notes

1. Saunders, B. C. *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine*; Cambridge University Press: Cambridge, 1957.
2. DeFrank, J. J. In *Applications of Enzyme Biotechnology*; Kelly, J. W., Baldwin, T. O., Eds.; Plenum: New York, 1991; pp 165–180.
3. Kiddle, J. J.; Mezyk, S. P. *J. Phys. Chem. A* **2004**, *108*, 9568–9570.
4. Michalski, J.; Łopusiński, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 294.
5. Konieczko, W. T.; Łopusiński, A.; Michalski, J. *Phosphorus, Sulfur, Silicon Rel. Elem.* **1989**, *42*, 103–104.
6. Dabkowski, W.; Cramer, F.; Michalski, J. *Tetrahedron Lett.* **1987**, *28*, 3561–3562.
7. Dabkowski, W.; Cramer, F.; Wasiak, J.; Michalski, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 817–820.
8. Dabkowski, W.; Michalski, J.; Skrzypczynski, Z. *Phosphorus, Sulfur, Silicon Rel. Elem.* **1986**, *26*, 321–326.
9. Łopusiński, A. *Phosphorus, Sulfur, Silicon Rel. Elem.* **1989**, *45*, 137–143.

10. Łopusiński, A. *Phosphorus, Sulfur, Silicon Rel. Elem.* **1990**, *47*, 383–390.
11. Gerstenberger, M. R. C.; Haas, A. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 647–667.
12. Farooq, O. *New J. Chem.* **2000**, *24*, 81–84.
13. Farooq, O. *J. Chem. Soc, Perkin Trans. 1* **1998**, 839–840.
14. Chworoś, A.; Woźniak, L. A. *Tetrahedron Lett.* **1999**, *40*, 9337–9340.
15. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527–4554.
16. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643–5678.
17. Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18–26.
18. Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Chem. Res.* **1999**, *19*, 97–148.
19. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M. S.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195.
20. Clark, J. H.; Rhodes, C. N. *Clean Synthesis Using Porous Inorganic Solid Catalysts and Supported Reagents*; The Royal Society of Chemists: Cambridge, 2000.
21. Ley, S. V.; Baxendale, I. R.; Brusotti, G.; Caldarelli, M.; Massi, A.; Nesi, M. S. *Farmaco* **2002**, *57*, 321–330.
22. General experimental procedure: **Caution!** Phosphorus(V) chlorides and fluorides are potent cholinesterase inhibitors and should be handled using appropriate safety precautions. In a typical experiment, To an argon flushed stirring mixture of 1.0 g (2.8 mmol) of Amberlyst® A-26 [F$^-$] resin in 10 mL of THF was added the appropriate phosphorus(V) chloride (2.8 mmol) at room temperature. After the reaction mixture was stirred for the indicated time the mixture was filtered with suction, and the solvent removed under reduced pressure to furnish the isolated phosphorus(V) fluorides.