Tetrahedron Letters 50 (2009) 2697–2699

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tetrabutylammonium tetra (*tert*-butyl alcohol) coordinated fluoride-an efficient reagent for the synthesis of fluorine derivatives of phosphorus(V) compounds

Hemendra K. Gupta, Deepak Pardasani, Avik Mazumder, Ajay Kumar Purohit, Devendra K. Dubey *

Vertox Laboratory, Defence Research and Development Establishment, Jhansi Road, Gwalior 474 002, India

A R T I C L E I N F O

Article history:
Received 10 February 2009
Revised 17 March 2009
Accepted 23 March 2009
Available online 26 March 2009

Keywords:
Synthesis
Fluorination
Phosphorus(V) chloride
Phosphorus(V) fluoride
Phosphonofluoridate
Nerve agent
Chemical warfare agent

A B S T R A C T

Direct conversion of phosphorus(V) chlorides to the corresponding phosphorus(V) fluorides was achieved using a solid reagent, tetrabutylammonium tetra (*tert*-butyl alcohol) coordinated fluoride. The phosphorus(V) fluorides were directly synthesized and efficiently isolated in very good yields.

© 2009 Elsevier Ltd. All rights reserved.

Organophosphorus–fluorine compounds (OPFCs) bearing P–F bond have evinced considerable interest among researchers due to their chemical reactivity, which allows them to be used either as mechanistic probes or as potent inhibitors of enzymatic reactions. Organophosphorus insecticides and nerve agents act primarily by inhibiting acetyl cholinesterase enzyme (AChE).[1–5] The biological activity of these compounds is highly structure dependent.[6] Most of them are moisture sensitive and toxic in nature. Therefore, in order to investigate the effective medical and protective counter measures against fluoridates, it is desirable to have an efficient and rapid method for the synthesis of a variety of structurally related P–F compounds.

Several methods have been developed for the synthesis of OPFCs[7–14] from the chloro analogs by halogen metathesis with a fluoride source. However, these methods have several drawbacks viz., variable yields (12–77%), use of expensive and excessive quantity of reagents, applicability to a limited number of substrates, requirement of different and extreme reaction temperatures (−50 °C to 200 °C), and inert atmosphere. The reactions with metal fluorides are heterogeneous in nature. Hence, even with the use of excess quantity of reagents, high temperature and long reaction time are required and the conversion is low. All of these reactions are moisture sensitive and result in the formation of mixture of compounds, posing difficulty in isolation of the pure products. Prompted by these limitations of the aforesaid methods and our interest in exploring new synthetic routes to the synthesis of OPFCs we present herein an efficient protocol for their synthesis.

Reagents containing un-solvated fluoride ion are efficient for the halogen metathesis reactions. The solid reagents and solid-supported reagents have been extensively used in organic synthesis.[15–21] They often react in a fashion similar to their unbound equivalents, but with reduced solvent requirements. Further the solid-supported reagents suffer from low and non-uniform loading of the reactive functionality. Hence, new reagents for these reactions are required which possess the following properties: (i) they should react under homogeneous conditions, in organic medium or under solvent-free conditions (ii) the reaction should be fast with minimal byproducts, and (iii) the reagent should be stable and easy to handle. Recently Kim et al. reported the use of tetrabutylammonium tetra (*tert*-butyl alcohol) coordinated fluoride (TBAF(*tert*-$BuOH)_4$),[22] synthesized from commercially available TBAF hydrate and *tert*-BuOH/hexane for the fluorination of mesylate and various sulfonylated ethers. The salient features of this reagent are that it is a fluoride source, a free flowing solid with low moisture sensitivity and solubility in organic medium. This prompted us to try the reagent for the synthesis of the OPFCs of our interest (Table 1).

This reagent has not been explored for the synthesis of these OPFCs. A model reaction for the synthesis of *N*,*N*-dipropyl-*P*-isopropyl phosphonamidic fluoride was tried using 55.7 mg (0.1 mmol) of

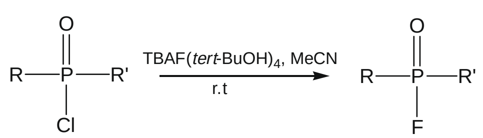
* Corresponding author. Tel.: +91 751 2233488; fax: +91 751 2341148.
E-mail address: dkdubey@rediffmail.com (D.K. Dubey).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.151

Table 1
Fluorination of substrates with different fluoride sources

Entry	R	R′	Fluoride ion source						$^{31}P\{^1H\}$ NMR δ (ppm)	J_{P-F} (Hz)
			TBAF(*tert*-BuOH)$_4$		TBAF·xH_2O		KF			
			Time (min)	Yield[a,b] (%)	Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)		
1	$^iC_3H_7$	NEt_2	5[c]	88	5	78	45	35	44.82	992.14
2	$^iC_3H_7$	NPr_2	5[c]	92	5	74	45	37	44.87	982.25
3	C_3H_7	NPr_2	5[c]	87	5	70	45	42	43.72	972.16
4	C_2H_5	NEt_2	5[c]	88	5	77	45	39	41.79	996.24
5	C_2H_5	NPr_2	5[c]	91	5	71	45	42	41.82	987.17
6	NEt_2	NEt_2	5[c]	92	5	76	45	34	18.30	943.19
7	NPr_2	NPr_2	5[c]	94	5	77	45	45	20.70	946.23
8	CH_3	$O^nC_3H_7$	5[c]	90	5	64	120	70	30.40	1071.50
9	CH_3	$O^iC_3H_7$	5[c]	90	5	65	120	70	28.15	1046.30
10	C_2H_5	OC_2H_5	5[c]	93	5	64	130	67	31.80	1067.50
11	C_3H_7	OC_3H_7	5[c]	87	5	65	130	64	30.67	1069.00
12	$^iC_3H_7$	$O^iC_3H_7$	5[c]	85	5	69	100	68	32.43	1085.70
13	OCH_3	OCH_3	10[d]	91	10	74	180	65	−8.23	975.24
14	OC_2H_5	OC_2H_5	10[d]	87	10	72	210	58	−8.25	970.14
15	$O^iC_3H_7$	$O^iC_3H_7$	10[d]	85	10	69	240	62	−10.2	969.16

The NMR and GC–MS data compared well with authentic samples.
[a] 100% conversion was observed for the reaction with TBAF(*tert*-BuOH)$_4$ by $^{31}P\{^1H\}$ NMR prior to isolation.
[b] The yields depicted for the reactions with the reagent TBAF(*tert*-BuOH)$_4$ represent isolated yields and NMR yields for the TBAF·xH_2O and KF.
[c] These reactions were found to be almost instantaneous with TBAF(*tert*-BuOH)$_4$.
[d] These reactions occurred at 70 °C within 10 min.



Scheme 1. Synthesis of *N,N*-dialkyl-*P*-alkyl phosphonamidic fluorides, *O*-alkyl alkyl phosphonofluoridates and *O,O*′-dialkyl fluorophosphates from their corresponding chloro compounds.

TBAF(*tert*-BuOH)$_4$ and *N,N*-dipropyl-*P*-isopropyl phosphonamidic chloride 11.25 mg (0.05 mmol) at room temperature in MeCN, the reaction was monitored by ^{31}P NMR and GC–MS.[23] (Scheme 1).

Complete conversion of the *N,N*-dipropyl-*P*-isopropyl phosphonamidic chloride to the corresponding fluoride was observed within 5 min. Encouraged by this initial finding, we focused on the reaction with various *N,N*-dialkyl-*P*-alkyl phosphonamidic chlorides, bis(*N,N*-dialkyl)phosphoramidic chlorides, *O*-alkyl alkylphosphonochloridates, and *O,O*′-dialkyl chlorophosphates. The reactions of the *N,N*-dialkyl-*P*-alkyl phosphonamidic chlorides and *O*-alkyl alkylphosphonochloridates with the reagent afforded the corresponding fluorides within 5 min in excellent yields (Table 1, entries 1–12). The chlorophosphates were found to react completely in 10 min at 70 °C (Table 1, entries 13–15). It is noteworthy that the use of TBAF(*tert*-BuOH)$_4$ in slight excess is always advisable to ensure complete conversion. To establish the efficiency of this reagent over commonly used KF and TBAF, comparison for the fluorination of same substrates was also carried out. It was also observed that when these substrates were subjected to fluorine exchange, using TBAF·xH_2O and KF, the yields remain low with both these reagents. Whereas, with KF, the reaction resulted in lower yields (65–75%) even after refluxing the reaction mixture for an extended period of up to 240 min in some cases. This can be attributed to the biphasic nature of the reactants. The reaction with TBAF·xH_2O resulted in lower yields with formation of undesired pyrophosphonamidates and pyrophosphoramidates. The proposed reagent being remarkably less hygroscopic than TBAF·xH_2O, does not lead to the formation of any hydrolytic products. On the other hand TBAF·xH_2O is a deliquescent solid, which leads to lower availability of free fluoride ions and the formation hydrolytic degradation products can be attributed to the moisture present therein.

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. In addition, scale up of the procedure (0.1–10 mmol) did not show any significant change in the isolated yield for the phosphorus(V) fluorides. Despite all the reactants showing complete conversion with the proposed reagent, as observed by $^{31}P\{^1H\}$ NMR spectroscopy, the isolated yield was found to be lower. This can be attributed to the loss of the product during the work-up procedures. Nevertheless the isolated yields obtained from the proposed reagents were higher than those obtained from the other two reagents. The important advantage of this reaction is the completion of reaction within 5 min at room temperature for *N,N*-dialkyl-*P*-alkyl phosphonamidic chlorides and *O*-alkyl alkylphosphonochloridates and 10 min for chlorophosphates at 70 °C.

In conclusion, we have developed a rapid, efficient and convenient synthesis of a variety of phosphorus(V) fluorides from the corresponding chlorides utilizing a new and efficient source of fluoride ion under mild conditions. Moreover, the procedure offers several advantages including excellent yield, clean reaction, operationally simple and high conversion, which makes it a useful and attractive process for the synthesis of phosphorus(V) fluorides. More importantly, this reaction can be carried out as and when required, yielding pure products. This minimizes the risk of exposure of these potent AChE inhibitors to the personnel.

References and notes

1. (a) Wilson, B. W.; Walkar, C. R. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3194; (b) Bartlett, P. A.; Lamdem, L. A. *Bioorg. Chem.* **1986**, *14*, 356.
2. (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349; (b) Kosolapoff, G. M.. In *Organic Phosphorus Compounds*; Wiley Intertscience: New York, 1950; Vol. 6. pp 319–510.
3. (a) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871; (b) De Frank, J. J. In *Applications of Enzyme Biotechnology*; Kelly, J. W., Baldwin, T. O., Eds.; Plenum: New York, 1991; pp 165–180.
4. (a) Sikder, A. K.; Ghosh, A. K.; Jaiswal, D. K. *J. Pharm. Sci.* **1993**, *82*, 258; (b) Marjit, D. N.; Sharma, U. S. *Indian J. Chem., Sect. A* **1989**, *28*, 958; (c) Sikder, A. K.; Pandey, K. S.; Jaiswal, D. K.; Dube, S. N.; Kumar, D.; Hussain, K.; Bhattacharya, R.; Das Gupta, S. *J. Pharm. Pharmacol.* **1992**, *44*, 1038.
5. (a) Eyer, P. *Toxicol. Rev.* **2003**, *22*, 165; (b) Kim, T. H.; Oh, K. A.; Park, N. J.; Park, N. S.; Kim, Y. J.; Yum, E. K.; Jung, Y. S. *J. Appl. Biomed.* **2006**, 67; (c) Koelle, G. J. *Pharmacol. Exp. Ther.* **1946**, *88*, 232.
6. DeFrank, J. J. In *Applications of Enzyme Biotechnology*; Kelly, J. W., Baldwin, T. O., Eds.; Plenum: New York, 1991; pp 165–180.

7. (a) Gerstenberger, M. R. C.; Haas, A. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 647; (b) Farooq, O. *New J. Chem.* **2000**, *24*, 81; (c) Farooq, O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 839; (d) Saville, B. *J. Chem. Soc.* **1961**, 4624; (e) Wozniak, L. A.; Chworos, A.; Pyzowski, J.; Stec, W. J. *J. Org. Chem.* **1998**, *63*, 8109; (f) Chworos, A.; Wozniak, L. A. *Tetrahedron Lett.* **1999**, *40*, 9337.
8. (a) Schmutzler, R. *Chem. Ber.* **1965**, *98*, 552; (b) Roesky, H. W. *Inorg. Nucl. Chem. Lett.* **1969**, *5*, 891; (c) Heuer, L.; Sell, M.; Schmutzler, R.; Schomberg, D. *Polyhedron* **1987**, *6*, 1295; (d) Heuer, L.; Jones, P. G.; Schmutzler, R. *New J. Chem.* **1990**, *14*, 891.
9. (a) Michalski, J.; Lopusinski, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 294; (b) Dabkowski, W.; Cramer, F.; Michalski, J. *Tetrahedron Lett.* **1987**, *28*, 3561.
10. Konieczko, W. T.; Lopusinski, A.; Michalski, J. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1989**, *42*, 103.
11. Dabkowski, W.; Michalski, J. *J. Chem. Soc., Chem. Commun.* **1987**, 755.
12. Dabkowski, W.; Cramer, F.; Michalski, J. *J. Chem. Soc., Perkin Trans.* **1992**, 1447.
13. Dabkowski, W.; Michalski, J.; Skrzypczynski, Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1986**, *26*, 321.
14. (a) Sierakowski, T.; Kiddle, J. J. *Tetrahedron Lett.* **2005**, *46*, 2215; (b) Bruno, B.; Corriu, R. *Chem. Commun.* **2002**, 795; (c) Norlin, R.; Juhlin, L.; Trogen, L. *Synthesis* **2005**, *11*, 1765–1770.
15. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527.
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.
18. Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Chem. Res.* **1999**, *19*, 97.
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.
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. Kim, D. W.; Jeong, H. J.; Lim, S.; Sohn, M. *Angew Chem., Int. Ed.* **2008**, *47*, 8404–8406.
23. *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 55.7 mg (0.1 mmol) of TBAF(*tert*-BuOH)$_4$ in 5.0 mL of MeCN was added the appropriate phosphorus(V) chloride (0.05 mmol) at room temperature. After the reaction mixture was stirred for the indicated time, the phosphorus(V) fluorides were obtained by vacuum distillation after removing the solvent by distillation.