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Single step fluorination of dialkylphosphites: trichloroacetonitrile–KF as an efficient reagent for the synthesis of dialkyl fluorophosphates

A. K. Gupta, J. Acharya, D. Pardasani, D. K. Dubey *

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

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Abstract

The use of trichloroacetonitrile and KF mixture is described as an efficient reagent for the direct conversion of dialkylphosphites to their corresponding dialkyl fluorophosphates via in situ formation of dialkyl chlorophosphates in one-pot.

Keywords: Dialkylphosphites; Dialkyl fluorophosphates; Trichloroacetonitrile; KF

The introduction of a fluorine atom or fluorinated group into organic molecules often changes their physical, chemical and physiological properties, resulting in greater stability and lipophilicity of the molecule.[1] Organophosphorus compounds (OPCs) possessing a P–F bond have received considerable interest due to their chemical reactivity, which allows them to be used as mechanistic probes or potent inhibitors of enzymatic reactions. OP insecticides and nerve agents act primarily by inhibiting acetyl cholinesterase enzymes (AChE).[2–5] Thus the detection of OPCs bearing P–F bonds is an important process. Due to the wide utility of dialkyl fluorophosphates and our interest in the development of rapid detection and protection systems against these chemicals, we decided to reinvestigate their synthesis. A variety of methods have been reported for the synthesis of dialkyl fluorophosphates either from the corresponding dialkyl chlorophosphates or from trialkylphosphites/dialkyl trimethylsilylphosphites using various reagents such as metal fluorides (NaF, KF, AgF), ammonium fluoride, Ag_2PO_3F, sodium tetrafluoroborate, sodiumhexafluorosilicate/hexafluorophosphate, sulfuryl chloride fluoride, thionyl fluoride and the use of phosphoroazolides with benzoyl fluoride.[6–12]

Among these methods, only a few can be carried out conveniently in the laboratory, and most suffer from drawbacks. Some of the drawbacks are the involvement of two distinct reaction steps, and the use of toxic, expensive, unstable, moisture-sensitive and corrosive reagents. Some of the methods require stringent reaction conditions such as sub-zero temperature (−50 °C), long reaction times and hazardous solvents, and give mixtures of products. Moreover, methods using sulfur reagents generate toxic SO_2 as by-product.

Recently, Sierakowski and Kiddle reported the use of the ion-exchange resin Amberlyst A-26 with a fluoride counter ion in THF under an argon atmosphere as a fluorinating reagent to prepare dialkyl fluorophosphates from their corresponding chloridates.[13] However, the resin with fluoride counter ion is expensive and is required in excess to drive the reaction to completion.

Recently, there has been increasing emphasis in finding recyclable low molecular weight environmentally friendly reagents.[14,15] One such reagent is trichloroacetonitrile (TCA), an inexpensive, stable and commercially available chemical which has been used as a source of chlorine in synthetic transformations.[16]

In continuation of our recent efforts on the development of new reagents and synthetic procedures for the rapid synthesis of organophosphorus compounds,[17] we envisaged

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

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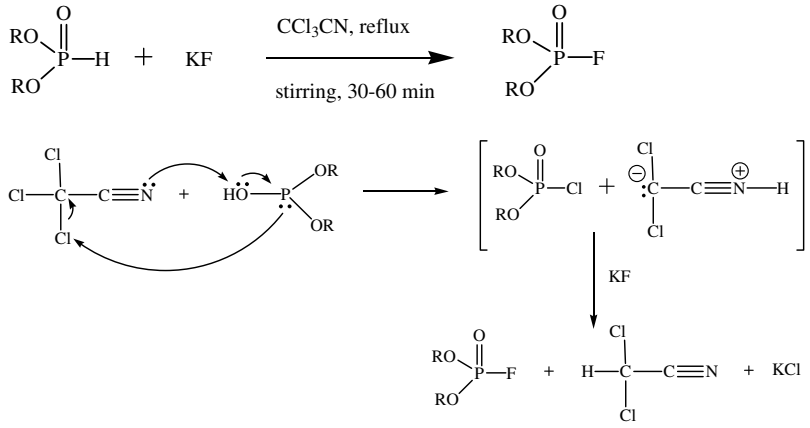
that KF would react with dialkylphosphites in the presence of excess TCA to produce the corresponding dialkyl fluorophosphates via in situ generation of dialkyl chlorophosphates. To the best of our knowledge, a mixture of TCA and KF has not been reported as a fluorinating agent for the direct conversion of dialkylphosphites to dialkyl fluorophosphates. A model reaction of diisopropylphosphite (1.66 g, 10 mmol) with TCA (2.89 g, 20 mmol) and KF (0.64 g, 11 mmol) was performed at reflux temperature and monitored by ^{31}P NMR and GC–MS. The analysis showed the successful formation of diisopropyl fluorophosphate via in situ generation of diisopropyl chlorophosphate (Scheme 1). Encouraged by this initial success, we explored further the generality of the reaction with structurally diverse dialkylphosphites.

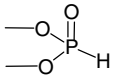
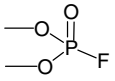
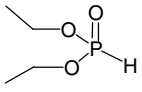
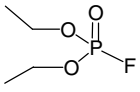
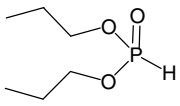
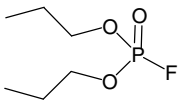
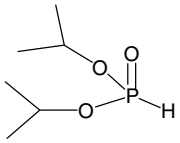
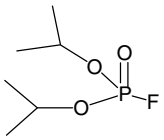
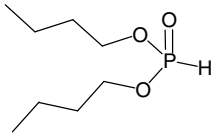
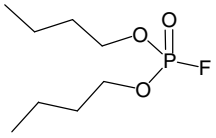
The reaction of various dialkylphosphites with TCA and KF afforded the corresponding dialkyl fluorophosphates within 30–60 min in excellent yields (Table 1). The mechanism depicted in Scheme 1 is based on two observations: first the isolation of dialkyl chlorophosphates, and second the detection of dichloroacetonitrile in the reaction mixture by GC–MS.

It is noteworthy that the use of TCA in excess is always advisable as it acts as a chlorinating agent as well as solvent. It was also observed that when isolated diisopropyl chlorophosphate was subjected to fluorine exchange, the



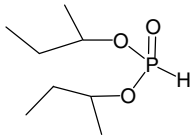
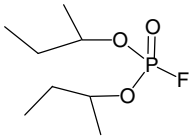
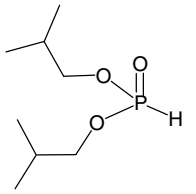
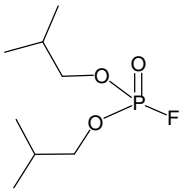
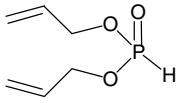
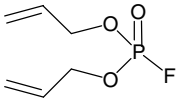
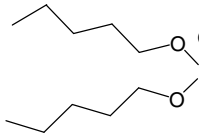
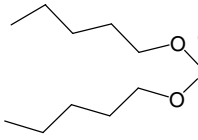
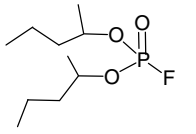
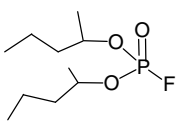
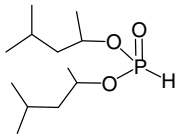
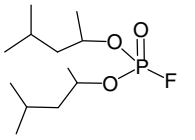
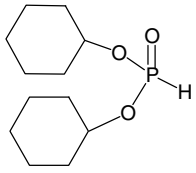
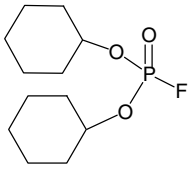
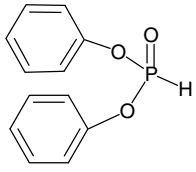
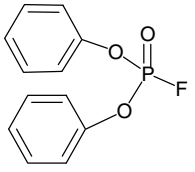
Scheme 1. Formation of dialkyl fluorophosphates from dialkylphosphites using CCl_3CN and KF.

Table 1
Preparation of dialkyl fluorophosphates from dialkyl phosphites and KF in TCA under reflux conditions[18]

Entry	Dialkylphosphite	Product	Time (min)	Yield[a] (%)	Bp (°C/(mm/Hg))	^{31}P NMR[b] (ppm)	J_{PF} (Hz)
1			15	90	60–62/22	−8.46	975.24
2			15	89	70–72/17	−8.25	970.14
3			20	90	78–80/20	−8.41	958.18
4			20	92	81–83/20	−10.22	968.51
5			30	91	81–83/20	−9.31	971.30

(*continued on next page*)

Table 1 (*continued*)

Entry	Dialkylphosphite	Product	Time (min)	Yield[a] (%)	Bp (°C/(mm/Hg))	^{31}P NMR[b] (ppm)	J_{PF} (Hz)
6			30	92	92–94/8	−10.24	968.14
7			30	95	95–97/5	−10.66	972.12
8			35	92	97–98/20	−8.80	966.92
9			35	91	135–137/30	−9.54	962.15
10			30	89	142–143/25	−9.10	967.13
11			30	88	102–103/2.5	9.62	964.28
12			35	93	118–120/1.0	−9.08	966.69
13			45	94	115–117/1.0	−20.34	990.01

All the products gave satisfactory IR, NMR and GC–MS data and compared well with authentic samples.
Caution! Dialkyl fluorophosphates are highly toxic compounds and should be synthesized by trained personnel in a fume hood. Great caution should be exercised especially while distilling them and any residue must be properly decontaminated using 20% alkali solution.

[a] Isolated yield. The ^{31}P NMR analysis of the reaction mixtures showed no traces of dialkylphosphites.

[b] ^{31}P NMR spectra were recorded at 162 MHz in $CDCl_3$.

reaction resulted in lower yields (65–75%) even after an extended time of 120 min. It indicated that TCA and KF work better when simultaneously present in the reaction mixture.

The important advantage of this reaction is the occurrence of the reaction in one pot and its completion within 1 h. Completion of the reaction was indicated by the conversion of crystalline KF into amorphous KCl. The

heterogeneous reaction mixture was filtered and the filtrate was distilled to give the desired products.

We also carried out the reaction on large scale; diisopropylphosphite (166 g, 1.0 mol), TCA (289 g, 2.0 mol) and KF (64 g, 1.1 mol) gave the product diisopropyl fluorophosphate in 92% yield.

In summary, we have described an efficient, convenient and one-pot synthesis of dialkyl fluorophosphates from dialkylphosphites at room temperature. Moreover, the procedure offers several advantages including excellent yield, operational simplicity, cleaner reaction and 100% conversion.

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18. *Typical experimental procedure:* Diisopropylphosphite (16.6 g, 0.10 mol) was slowly added to a stirred suspension of TCA (28.9 g, 0.05 mol) and KF (6.38, 0.11 mol) at room temperature. The resulting mixture was stirred and refluxed for the time mentioned in Table 1, with monitoring by GC and ^{31}P NMR. After the completion of the reaction, the reaction mixture was cooled to room temperature and filtered to remove the KCl. The solid precipitate was washed with 2×10 mL of ether. The filtrate and washings were combined. The solvent was removed by distillation and the product was obtained by distillation under vacuum. Bp 83–84/20 mmHg; Yield; 16.95 g (92%).