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Journal of Fluorine Chemistry 129 (2008) 226–229
JOURNAL OF FLUORINE CHEMISTRY
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Short communication

Dichlorodimethylhydantoin–KF as an efficient reagent for one pot synthesis of dialkylfluorophosphates from dialkylphosphites

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Received 31 October 2007; received in revised form 16 November 2007; accepted 16 November 2007
Available online 24 November 2007

Abstract

Organic–inorganic hybrid reagent dichlorodimethylhydantoin–KF (DCDMH–KF) mixture was explored as an efficient reagent for the direct conversion of dialkylphosphites to their corresponding dialkylfluorophosphates at room temperature and in shorter reaction times through a facile electrophilic–nucleophilic metathesis.

Keywords: Dialkylphosphite; Dialkylfluorophosphate; DCDMH; KF; Dimethylhydantoin

1. Introduction

Organophosphorus–fluorine compounds (OPFCs) bearing P–F bond have evinced considerable interest due to their chemical reactivity that allow them to be used as either mechanistic probes or potent inhibitors of enzymatic reactions. Organophosphorus insecticides and nerve agents act primarily by inhibiting acetylcholinesterase enzyme (AChE) [1–5]. Several methods have been developed for the synthesis of title compounds [6–13], however all these methods have several drawbacks such as involvement of two distinct reaction steps, variable yields (12–77%), use of expensive and excess of the reagent, applicable to limited number of substrates, requiring either low (−50 °C) or high reaction temperature (200 °C), moisture sensitive, inert atmosphere, resulting in the formation of mixture of chloridates and fluoridates, which posses difficulty in isolation of the pure products. Moreover the reactions require dialkylchlorophosphates as starting materials which in turn needs to be prepared either from dialkylphosphites or by applying an additional synthetic step. Prompted by the limitations associated with the synthesis of OPFCs and our interest in exploring the effective medical and protective counter measures against fluoridates, we were keen to develop a rapid and efficient synthetic method for the synthesis of dialkylfluorophosphates.

In recent years the use of organic–inorganic hybrid reagents has received maximum attention and the activity and selectivity of such kind of reagents has increased many folds. In addition, such reagents have good thermal and mechanical strength and are also associated with work-up flexibility of the inorganic matrix too. One such reagent which has come to our notice is, 1,3-dichlorodimethylhydantoin (DCDMH), a low cost, stable, low molecular weight, commercially available, has two active chlorines and used as an excellent reagent for deoximation of ketones, preparation of *gem*-chloronitrosoalkanes, nitrosation of amines and in neutralization of chemical warfare agents [14–16]. To the best of our knowledge, DCDMH–KF (hybrid of organic and inorganic reagent) has not been reported so far as a fluorinating agent in organic synthesis. In continuation of our recent work on the development of new reagents and synthetic procedures for the rapid synthesis of organophosphorus compounds [17,18], herein, we report a rapid, efficient, economic and one pot synthesis of dialkylfluorophosphates directly from dialkylphosphites by making use of DCDMH–KF mixture at room temperature. This method has allowed us to obtain the quantitative yields of the products in reduced reaction times.

2. Results and discussion

In the present study, we envisaged the potential of hybrid reagent of organic and inorganic compound (DCDMH–KF) to react with dialkylphosphites. This is essentially because this

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doi:10.1016/j.jfluchem.2007.11.008

Table 1
Optimisation of solvent for conversion of dialkylphosphites to dialkylfluorophosphates[a]

S. no.	Solvent	Time (min)	Conversion[b] (%)
1	CH_3CN	20	100
2	CH_3CN	15	92
3	C_6H_6	40	52
4	C_6H_6	90	60
5	$PhCH_3$	90	62
6	$HCONMe_2$	40	100[c]
7	Me_2SO	40	95[c]
8	CCl_4	40	48
9	CH_2Cl_2	60	45
10	THF	60	47
11	1,4-Dioxane	60	52
12	Et_2O	60	39
13	CH_3CN (2.5-fold excess)	20	70

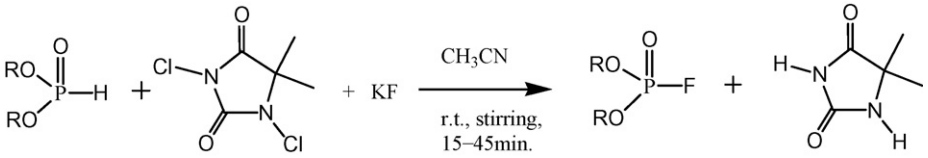
[a] Diisopropylphosphate, DCDMH and KF were used in the mole ratio of 1:1:2.
[b] Conversion is based on ^{31}P NMR and monitored at 162 MHz and GC.
[c] Isolation of pure product was difficult.

reagent would generate the corresponding dialkylchlorophosphates *in situ* by the reaction of DCDMH, which has two active chlorine and in turn will get transformed into its dialkylfluorophosphates by the reaction of KF. This was amply demonstrated, when a model reaction of diisopropylphosphite (1.66 g, 10 mmol) with the mixture of DCDMH (0.99 g, 5.0 mmol) and KF (0.64 g, 11 mmol) was examined at room temperature, an exothermic reaction took place which was monitored by ^{31}P NMR and GC. The results of the analysis showed an effective transformation of diisopropylphosphite to diisopropylfluorophosphate via *in situ* generation of diisopropylchlorophosphate in 20 min at room temperature.

Many factors such as change of solvent, mole ratio of the substrate with respect to the reagent, and the structure of the naked fluoride ion, profoundly influence the course of the reaction. For example, polar solvents like DMF, DMSO, and MeCN showed quantitative conversion. Among the polar solvent also, MeCN was found superior to other solvents as fluorination of dialkylphosphite could be carried out cleanly with excellent yields. However, the isolation of pure product was difficult, due to the higher boiling points of DMF or DMSO. It is worthy to note, that excess of solvent gave poor results of conversion. When excess of CH_3CN (entry 13, Table 1) was used in the reaction, we observed poor conversion of dialkylphosphite to dialkylchlorophosphate. Probably it is due to the solubility of one of the by-product, i.e. dimethylhydantoin in CH_3CN. As a result the equilibrium might be shifted in back word direction and reduces the yield of the desired product. Several investigations have also been carried out to understand the influence of mole ratio of the dialkylphosphites with respect to DCDMH and KF. It was established that the mole ratio of 2:1:2.2 were required to obtain maximum yield of the dialkylfluorophosphates. However, the use of little excess of KF than stoichiometric mole ratio gave better results. The results are summarized in Table 1.

Similarly among the activated source of fluorine atom, viz. HF, KF, HgF_2, AgF, NaF and tetrabutylammonium fluoride available commercially or in the literature, KF was found to be the best. No doubt the most basic nucleophilic fluorinating agent is hydrogen fluoride, which is used in large quantity for the industrial production of fluorinated compounds. Hydrogen fluoride, however, is scarcely used in laboratories due to its toxicity and corrosive properties and its low reactivity resulting from high H–F bond energy. Nucleophilic fluorinating agent such as KF is readily available, low cost, easy to handle and

Table 2
Preparation of dialkylfluorophosphates from dialkylphosphites using DCDMH and KF in acetonitrile at room temperature



Entry	R	Time (min) (%)	Yield (mmHg)[a]	b.p. (°C/ppm)	^{31}P NMR (Hz)[b]	J_{P-F}
1	CH_3	15	90	60–62/22	−8.46	975.24
2	C_2H_5	15	89	70–72/17	−8.25	970.14
3	C_3H_7	20	90	78–80/20	−8.41	958.18
4	$^{i}C_3H_7$	20	94	81–83/20	−10.22	968.51
5	$^{n}C_4H_9$	30	91	80–82/10	−9.31	971.30
6	$^{i}C_4H_9$	30	92	92–94/8	−10.24	968.14
7	*sec*-C_4H_9	30	95	95–97/5	−10.66	972.12
8	$CH_2{=}CHCH_2$	35	92	97–98/20	−8.82	968.27
9	C_5H_{11}	35	91	135–137/30	−9.54	962.15
10	$^{i}C_5H_{11}$	30	89	142–143/25	−9.10	967.13
11	$(CH_3)_2CHCH_2CH(CH_3)$	35	87	102–103/2.5	9.62	964.28
12	C_6H_{11}	35	93	118–120/1.0	−9.08	966.69
13	C_6H_5	45	94	115–117/1.0	−20.34	990.01

[a] Isolated yield.
[b] ^{31}P NMR spectra were recorded at 162 MHz in $CDCl_3$. All the products gave satisfactory IR, NMR and GC–MS data and compared with authentic samples.

''naked fluoride anion'' is easily generated because of higher ionic size of the potassium ion. The yields of the dialkylfluorophosphate is also higher when KF was used in comparison to other fluorinating agents.

The reaction of various dialkylphosphites with DCDMH–KF afforded corresponding dialkylfluorophosphates in only 15–45 min with excellent yields (Table 2).

Caution! dialkylfluorophosphates are highly toxic compounds and should be synthesized by trained personals using efficient fume hood. Great caution should be exercised especially while distilling them and residue must be properly decontaminated by using 20% alkali solution.

The important advantage of this reaction is the occurrence of the reaction at room temperature and completion of the reaction is indicated by the formation of amorphous precipitation of dimethylhydantoin (DMH) and KCl. The heterogeneous reaction mixture was filtered and filtrate was distilled to get desired products.

In order to study the up-scaling of this method, reaction was carried at 1 mol level of diisopropylphosphite (1.0 mol) with DCDMH (0.5 mol) and KF (1.1 mol) and gave the desired fluorophosphates in 94% yield. It was also observed that when *in situ* generated diisopropylchlorophosphate was isolated and fluorine exchange reaction was performed by the use of KF (1:2) then reaction took longer reaction times (90 min) under reflux conditions and yield is also reduced (74%).

3. Conclusions

In summary, we have described an efficient, convenient, and one pot synthesis of dialkylfluorophosphates from dialkylphosphites at room temperature. Moreover, the procedures offers several advantages including excellent yield, operational simplicity, cleaner reaction with 100% conversion, which makes it a useful and attractive process for the synthesis of dialkylfluorophosphates.

4. Experimental

Chemicals such as PCl_3, alkanols, KF and DCDMH were purchased from E. Merk (India). Diisopropylphosphite and diphenylphosphite were purchased from Aldrich Chemical Company (USA). However, other phosphites used in this study were prepared by the reported procedure [19]. The solvents were dried and redistilled before use. Boiling points are uncorrected. IR spectra were recorded on Bruker FT-IR spectrometer model Tensor 27 on KBr disk. ^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ on Bruker DPX Avance FT NMR at 400 and 162 MHz, respectively, using tetramethylsilane as an internal standard for ^{1}H and 85% H_3PO_4 as an external standard for ^{31}P NMR. A Chemito GC model 1000 instrument was used with flame ionization detector (FID). A capillary column (30 m × 0.25 mm ID, BP5) packed with 5% phenyl and 95% dimethylpolysiloxane (SGE) coated on fused silica was employed. The injection port and detector block were maintained at 280 and 260 °C, respectively, and the column oven was at programmed temperature profile started at 50 °C, ramped up to 280 °C at 25 °C/min. Nitrogen was used as carrier gas (at a flow rate of 30 ml/min). Air for FID was supplied at 300 ml/min and hydrogen at 30 ml/min. In all analysis, 0.2 μl sample were injected and peaks recorded on Iris32 data acquisition station. The GC–MS analyses were performed in EI (70 eV) in full scan mode with an Agilent 6890 GC equipped with a model 5973 mass selective detector (Agilent Technologies, USA). An SGE BPX5 capillary column with 30 m length × 0.32 mm internal diameter × 0.25 μm film thickness was used at temperature program of 80 °C (2 min)–20 °C/min–280 °C (3 min). Helium was used as the carrier gas at a constant flow rate of 1.2 ml/min. The samples were analyzed in splitless mode at injection temperature. The molecular weight of all the synthesized compounds was confirmed by methane chemical ionization (CI) technique in mass spectrometer.

4.1. Preparation of organic–inorganic hybrid (DCDMH–KF) reagent

DCDMH–KF was prepared by combination of DCDMH (1.0 mol, 197.0 g) and KF (2.2 mol, 127.6 g)) in a mortar and pestle by grinding together until a fine, homogenous powder was obtained (25–30 min). It was dried under vacuum at 100 °C for 2 h and stored in a stoppered flask under desiccators. It was used as and when required.

4.2. Typical experimental procedure for fluorination of diisopropylphosphite

Diisopropylphosphite, 16.6 g (0.10 mol) was added to a stirred suspension of DCDMH–KF reagent 16.23 g, (9.85 g, 0.05 mol of DCDMH and 6.38 g, 0.11 mol of KF) in dry acetonitrile (40 ml) at room temperature in one shot. The resulting mixture was stirred at room temperature and an exothermic reaction took place which was monitored by GC and ^{31}P NMR. Reaction mixture was filtered to remove the precipitate by suction. The solid precipitate was washed with 2× 10 mL of DCM. The filtrate and washings were combined. The solvent was removed by distillation and product was obtained by distillation under vacuum. b.p. 81–83/20 mmHg; yield; 17.32 g (94%). Complete workup of the reaction was carried out in efficient fume hood. Fume hood provided the best protection against any exposures to dialkylfluorophosphates in the laboratory and is the preferred ventilation control device. Laboratory coat closed toed shoes, long sleeved clothing was also used while synthesizing and handling the dialkylfluorophosphates. Disposable latex gloves and safety glass were worn as a normal practice during work up of the reaction mixture.

Acknowledgements

We thank Dr. R. Vijayaraghavan, Director, DRDE, Gwalior for his keen interest and encouragement. Authors also thanks Mr Deepak Pardasani for GC–MS and Avik Mazumder for NMR analysis.

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