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Direct, oxidative halogenation of diaryl- or dialkylphosphine oxides with (dihaloiodo)arenes

Jasmin Eljo [a], Graham K. Murphy [a,*]

[a] Department of Chemistry, University of Waterloo, 200 University Ave. W., Waterloo, ON N2L3G1, Canada

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ABSTRACT

The oxidative halogenation of diaryl- or dialkylphosphine oxides with the hypervalent iodine reagents (difluoroiodo)toluene (*p*-TolIF$_2$, **1**) and (dichloroiodo)benzene (PhICl$_2$, **2**) is reported. Phosphoric fluorides could be recovered in 32–75% yield, or they could be trapped with EtOH to give the corresponding phosphinate in typically good yield. Phosphoric chlorides were not readily isolable, and were trapped with alcohol and amine nucleophiles, giving diaryl- or dialkylphos-phinates and phosphinamides in up to 90% yield.

Organophosphorus compounds that possess P(O)–F bonding are a class of biologically-active compound that has received considerable attention over the last century. The biological activity displayed by these synthetic fluorine-containing organophosphorus compounds is highly structure dependent [1]: whereas sarin and soman are highly toxic nerve agents, diisopropyl fluorophosphate (DPF) [2] is a therapeutic agent used in the treatment of chronic glaucoma (Fig. 1). Phosphoric fluorides are selective mechanistic probes, as well as potent cholinesterase enzyme inhibitors, and both the fluorides and chlorides are powerful phosphorylating reagents, serving as precursors to other organophosphorus compounds [3,4].

Oxidative halogenation of P(O)–H compounds is a well-established approach to phosphoric halides. For example, their chlorination has been prepared with chlorine gas [5], with sulfuryl chloride [6] or $CuCl_2$ [7], or with chloramines [8], TCICA [9] or NCS [10]. These chlorination reactions can also be employed in strategies for the synthesis of phosphoric fluorides by simply adding a fluoride source. For example, in reactions with TCICA–KF [11], trichloroacetonitrile–KF [12] or $CuCl_2$–CsF [13], the initially-formed chlorides are intercepted by the fluoride. Electrophilic fluorination of a phosphine oxide is achieved with reagents such as XeF_2 [14], Selectfluor® [15] or DDQ/$CuBr_2$/NaF [16]. Drawbacks of these methods include harsh reaction conditions, the need for excess reagent, or use of reagents that are corrosive, toxic, costly or moisture sensitive, therefore the continued development of synthetic strategies remains important.

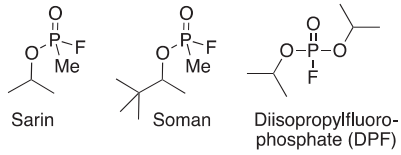

Fig. 1. Examples of biologically active phosphoric fluorides.

Phosphines and phosphine oxides react with hypervalent iodine reagents to undergo oxidative arylation [17], alkynylation [18], vinylation [19] and trifluoromethylation [20] of P–H bonds [21]. Hypervalent iodine reagents commonly effect oxidative halogenation reactions [22], and so they are an attractive strategy for the synthesis of phosphoric halides from secondary phosphine oxides. As part of our ongoing interest in oxidative halogenation reactions of phosphines [23], we were intrigued by the potential for generating phosphoric fluorides and chlorides from secondary phosphine oxides and TolIF$_2$ (**1**) [24] and PhICl$_2$ (**2**) [25], respectively. As oxidants and sources of halide nucleophiles, these reagents offer a facile and eco-friendly approach to the derivatization of organophosphorus compounds [26]. We report here that phosphoric fluorides and chlorides could be rapidly prepared by reacting secondary phosphine oxides with either **1** or **2**, and furthermore that the intermediates could be trapped in situ with nucleophiles to give phosphinate and phosphinamide products.

* Corresponding author.
E-mail address: graham.murphy@uwaterloo.ca (G.K. Murphy).

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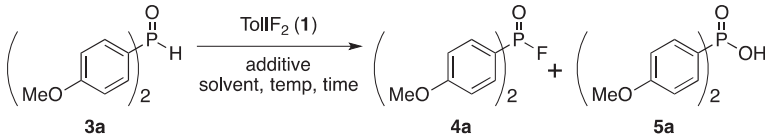
Table 1
Optimization of the phosphoric fluoride synthesis.[a]

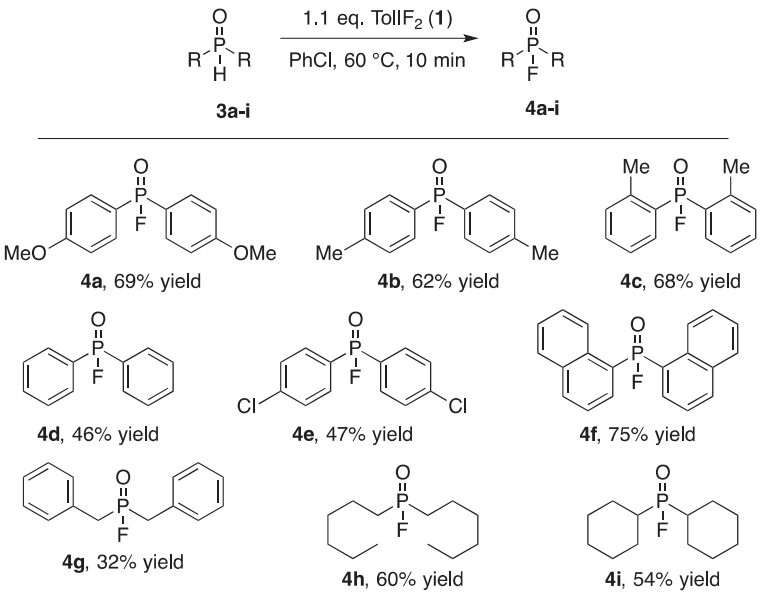


Entry	Solvent	Temp (°C)	TolIF$_2$ (equiv)	Additive (mol%)	Time	**4a%** yield
1	CH_2Cl_2	rt	1.1	–	1 h	50
2	$CHCl_3$	rt	1.1	–	1 h	46
3	DCE	rt	1.1	–	1 h	53
4	PhCl	rt	1.1	–	1 h	58
5	THF	rt	1.1	–	1 h	51
6	CH_3CN	rt	1.1	–	1 h	38
7	PhCl	40	1.1	–	10 min	64
8	PhCl	60	1.1	–	10 min	69
9	PhCl	110	1.1	–	10 min	60
10	PhCl	60	1.4	–	10 min	67
11	PhCl	60	1.02	–	10 min	55
12	PhCl	60	1.1	$BF_3{\cdot}OEt_2$ (10)	10 min	67
13	PhCl	60	1.1	TiF_3 (10)	10 min	57
14	PhCl	60	1.1	TiF_4 (10)	10 min	52
15	PhCl	60	1.1	FeF_3 (10)	10 min	57

[a] Reaction conditions: To **1** in solvent (0.25 mL) at temp (°C) was added **3a** and stirred. Isolated yields.

Our investigation into the synthesis of phosphoric fluorides began by reacting bis(4-methoxyphenyl)phosphine oxide (**3a**), prepared via Grignard addition into diethyl phosphite, and TolIF$_2$ (**1**) in CH_2Cl_2 at room temperature. After 1 h, ^{31}P NMR indicated the consumption of **3a**, and phosphoric fluoride **4a** was recovered in 50% yield (Table 1, entry 1). Various other solvents were screened, and while the reaction proceeded in chlorinated, ethereal and even highly polar solvents, we found chlorobenzene to give **4a** in 58% yield (entries 2–6; see Supporting information for complete optimization table). The reaction temperature was then gradually increased from room temperature to 110 °C, and we found 60 °C to be optimal, giving **4a** in 69% yield (entries 7–9). Increasing the loading of TolIF$_2$ (**1**) failed to increase the yield of **4a** (entry 10), whereas lowering it to nearly equimolar caused a significant decrease in yield (entry 11). The addition of Lewis acidic activating agents [23b,27] failed to improve the reaction (entries 12–15), presumably because the phosphine oxides are sufficiently nucleophilic to engage the iodane without prior activation. Throughout these trials, we consistently observed diaryl phosphinic acid **5a**, and ^{31}P NMR analysis of the reaction mixture showed this to be present prior to reaction workup. Using recrystallized reagents and conducting the reaction in a glovebox or with activated molecular sieves failed to prevent its formation. Nonetheless, the desired oxidative fluorination proved to be a viable strategy for phosphoric fluoride synthesis from secondary phosphine oxide precursors.

With the optimized conditions in hand, we tested a variety of substituted diarylphosphine oxides (**3b–i**) in the fluorination reaction (Scheme 1). Substrates possessing strongly (**3a**, *p*-OMe) or moderately electron-donating (**3b**, *p*-Me and **3c**, *o*-Me)



Scheme 1. Oxidative fluorination of diaryl- and dialkylphosphine oxides.