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The Preparation of $(EtO)_2P(O)CFHZnBr$ and $(EtO)_2P(O)CFHCu$ and Their Utility in the Preparation of Functionalized α-Fluorophosphonates

Xin Zhang, Weiming Qiu and Donald J. Burton*

Department of Chemistry, The University of Iowa, Iowa City, IA 52242, U.S.A.

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Abstract:

The organometallic reagent, $(EtO)_2P(O)CFHZnBr$, was generated in situ in excellent yields via the reaction of $(EtO)_2P(O)CFHBr$ with zinc metal. Metathesis with Cu(I)Br gave $(EtO)_2P(O)CFHCu$. The reagents exhibit excellent reactivity with substrates, such as allyl halides, alkynyl halides, vinyl halides, aryl halides and acyl or phosphoryl halides, and provide a useful one flask route to functionalized α-fluorophosphonates.

α-Fluorophosphonates have been recognized as mimics for naturally occurring phosphates for many years[1]. Although the α,α-difluorophosphates have been more widely investigated in the last fifteen years, recent experimental and theoretical reports have indicated that the α-fluorophosphonates would be the better mimic for phosphates[2]. The potential of α-fluorophosphonates in the pharmaceutical field has attracted considerable attention for development of useful routes to functionalized α-fluorophosphonates.

Two common methodologies, namely fluorination and the synthon approach, have highlighted recent strategy for the preparation of α-fluorophosphonates. DAST, a common nucleophilic fluorination reagent, has been employed by Hammond in an elegant preparation of α-fluoropropargylphosphonates[3]. The electrophilic fluorination agent, $(PhSO_2)_2NF$, was utilized in the preparation of the fluorinated analog of PMEA, an antiviral agent[4]. Organolithium reagents, such as $(RO)_2P(O)CFHLi$ and $(EtO)_2P(O)CF(SiMe_3)Li$ have been used by Blackburn[5] and Savignac[6] for the introduction of the α-fluorophosphonate moiety. The above approaches utilize expensive, hazardous reagents (often in large excess) or thermally unstable reagents. The development of a stable, reactive, easily prepared reagent, capable of facile functionalization and scale-up, remained a challenge for the synthesis of α-fluorophosphonates and is addressed herein.

We recently reported a new route to α-fluorophosphonates *via* the SET addition of $(EtO)_2P(O)CFHI$ to 1-alkenes, followed by reduction[7]. The $(EtO)_2P(O)CFHI$ precursor was prepared from $(EtO)_2P(O)CFBr_2$ *via* the zinc reagent, $(EtO)_2P(O)CFHZnBr$, as illustrated below:

$$(EtO)_2P(O)CFBr_2 \xrightarrow[THF/RT]{Bu_3P/EtOH} (EtO)_2P(O)CFHBr \quad (80\%) \xrightarrow[2)\ I_2/0°C]{1)\ Zn/THF/RT} (EtO)_2P(O)CFHI \quad (80\%)$$

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$$(EtO)_2P(O)CFHI \xrightarrow[\text{Pd(0) or Cu(0)}]{H_2C=CHR} (EtO)_2P(O)CFHCH_2CHIR \xrightarrow[\text{moist THF}]{Zn/NiCl_2\cdot 6H_2O} (EtO)_2P(O)CFHCH_2CH_2R \quad 63\text{-}80\%$$

The ease of preparation and scale-up of the $(EtO)_2P(O)CFHBr$ precursor prompted us to investigate the utility of $(EtO)_2P(O)CFHZnBr$ as an entry to functionalized α-fluorophosphonates. This reagent is readily prepared on a molar scale in THF in excellent yield with only trace amounts of the reduction by-product, $(EtO)_2P(O)CFH_2$[8]. It can also be prepared in DMF and triglyme at room temperature; in these solvents, the amount of

$$(EtO)_2P(O)CFHBr \xrightarrow[THF/RT]{Zn} \underset{95\%}{(EtO)_2P(O)CFHZnBr} + \underset{<2\%}{(EtO)_2P(O)CFH_2}$$

reduction product slightly increased (up to 10%). The zinc reagent exhibited excellent stability; in THF, >80% of the reagent remained after one week.

$(EtO)_2P(O)CFHZnBr$ reacted readily with electrophiles, such as allyl halides, ethyl chloroformate and diethylchlorophosphate (entries 1-4, Table 1). It was less effective in cross-coupling reactions with vinyl, alkynyl, and aryl halides. Addition of $Pd(PPh_3)_4$ did not improve the cross-coupling reactions.

Table 1
Coupling of $(EtO)_2P(O)CFHM$ (M = Zn, Cu)

$$(EtO)_2P(O)CFHM + RX \longrightarrow (EtO)_2P(O)CFHR$$

Entry	M	Solvent(s)	R	X	Yield (%)[a]
1	Zn	THF		Cl	80
2	Zn	THF		Br	80
3	Zn	THF	C(O)OEt	Cl	70
4	Zn	THF	$(EtO)_2P(O)$	Cl	50
5	Cu	THF/DMAC	PhC≡C	Br	74
6	Cu	THF/DMAC	$C_6H_{13}C\equiv C$	Br	71
7	Cu	THF/DMF	(*E*)-PhCH=CH	I	69
8	Cu	THF/DMF	$C_6H_{13}CH=CH$	I	62
9	Cu	THF/DMF	p-$NO_2C_6H_4$	I	63
10	Cu	THF/DMF	C_6H_5	I	34

[a]Isolated yield based on the organohalide

However, mediation of the zinc reagent with Cu(I)Br gave a new reagent, tentatively assigned as the copper reagent, which exhibited excellent cross-coupling reactivity with vinyl, alkynyl, and aryl halides (entries 5-10, Table 1). The "copper reagent" exhibited an ^{19}F NMR

$$(EtO)_2P(O)CFHZnBr + Cu(I)Br \xrightarrow[0° \text{ to } 5°C]{THF/DMF} (EtO)_2P(O)CFHCu$$

signal at -260 ppm (t, J = 56 Hz). Best results were obtained with mixed solvent systems (1:1 vol.) such as THF/DMF or THF/DMAC, presumably to enhance stabilization of the copper reagent by amide solvents. The copper reagent is less stable than the zinc reagent; it completely decomposed in 48 hours at room temperature. However, this stability limitation posed no significant problem in cross-coupling reactions when 1.2-1.5 equivalents of the copper reagent were employed.

In a typical coupling reaction, a 25 mL round bottom flask was charged with 6 mL of dry DMF and (*E*)-1-iodostyrene (0.92g, 4 mmol) and then 6 mL of pre-generated $(EtO)_2P(O)CFHZnBr$ (1.0M, 6 mmol) was slowly added at 0-5°C. Copper (I) bromide (0.87g, 6 mmol) was added to the reaction mixture all at once. The resulting mixture was slowly allowed to warm to room temperature with stirring over 24 hours. The mixture was then diluted with 150 mL of ether. The resulting solid was removed by filtration and the solid was washed with 3 x 25 mL of ether. The combined organic solutions were then washed with water (3 X 40 mL), brine solution (40 mL) and dried over anhydrous $MgSO_4$. After removal of ether, the residue was purified further on a silica gel column using mixture of ethyl acetate and hexanes (1:4) to give 0.75g (68.9%) of (*E*)-PhCH=CHCFHP(O)$(OEt)_2$. HRMS calcd. for $C_{13}H_{18}FO_3P$: 272.0978. Found: 272.0976. ^{19}F NMR ($CDCl_3$): -200.3 (dddd, J = 81.1 Hz, J = 45.8 Hz, J = 15.3 Hz, J = 2.5 Hz) ppm. ^1H NMR ($CDCl_3$): 7.25-7.44 (m, 5H), 6.81 (dtd, J = 16.0 Hz, J = 3.9 Hz, J = 1.0 Hz, 1H), 6.35 (dddd, J = 15.9 Hz, J = 15.3 Hz, J = 7.0 Hz, J = 5.1 Hz, 1H), 5.33 (dddd, J = 45.7 Hz, J = 8.5 Hz, J = 7.0 Hz, J = 1.3 Hz, 1H), 4.16-4.27 (m, 4H), 1.34 (td, J = 7.1 Hz, J = 2.3 Hz, 6H) ppm. ^{13}C NMR($CDCl_3$): 135.2 (m) (overlapping aromatic carbon and vinyl carbon), 128.5, 126.7, 119.7 (dd, J = 25.5 Hz, J = 3.6 Hz), 88.58 (dd, J = 181.2 Hz, J = 172.0 Hz), 63.25 (dd, J = 30.0 Hz, J = 7.3 Hz), 16.27 (m) ppm. ^{31}P NMR ($CDCl_3$): 15.55 (d, J = 81.6 Hz) ppm. GC-MS: 272 (M^+, 4.1), 254 (4.0) 224 (3.8), 196 (10), 178 (2.5), 135 (100), 115 (92.2), 109 (42.8), 81 (26.4). IR (neat, NaCl plate): 3060(s), 3028(s), 2984(s), 2910(s), 1449(s), 1163(s), 799(s). Rf = 0.30 (hexanes : ethyl acetate, 4:1).

In conclusion, $(EtO)_2P(O)CFHZnBr$ and $(EtO)_2P(O)CFHCu$ are readily prepared at room temperature from $(EtO)_2P(O)CFHBr$. The reaction is easily scaled-up and avoids expensive, toxic reagents or thermally unstable intermediates. Functionalization of the zinc and/or copper reagents readily provides a facile regiospecific and stereospecific entry to a variety of functionalized α-fluorophosphonates.

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[8] $(EtO)_2P(O)CFHBr$: ^{19}F NMR, δ - 165 (dd, J = 73 Hz, J = 47 Hz) ppm; $(EtO)_2P(O)CFHZnBr$: ^{19}F NMR, $\delta = -266 \pm 0.5$ ppm (t, J = 52 Hz) in solvents such as THF, THF/DMF, THF/DMAC, DMF and triglyme.