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Synthesis and reactivity studies of α,α-difluoromethylphosphinates

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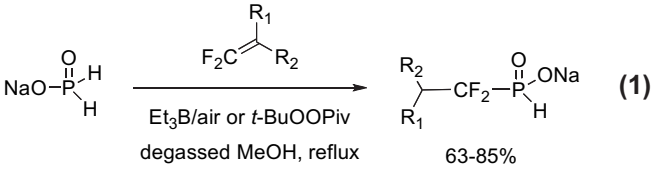
ABSTRACT

The preparation and reactivity of some α,α-difluorophosphinates are investigated. Alkylation of *H*-phosphinates with LiHMDS and $ClCF_2H$ gives the corresponding α,α-difluorophosphinates in good yield. Deprotonation of these reagents with alkyllithium or LDA is then studied. Subtle electronic effects translate into significant differences in the deprotonation/alkylation of the two 'Ciba-Geigy reagents' $(EtO)_2CRP(O)(OEt)H$ (R=H, Me). On the other hand, attempted methylation of difluoromethyl-octyl-phosphinic acid butyl ester resulted in the exclusive alkylation of the octyl chain. Finally, reaction with carbonyl compounds results in the formation of 1,1-difluoro-2-phosphinoyl compounds.

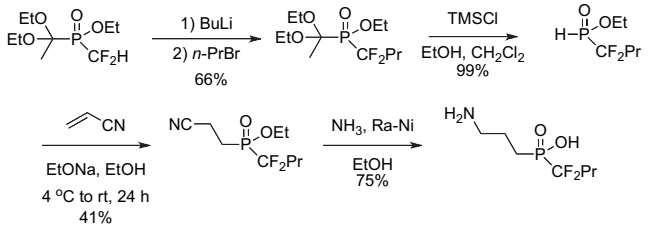
1. Introduction

α-Fluorophosphorus compounds have gained popularity as potential pharmacophores. In the case of phosphonates, the fluorine substituent(s) is known to modulate the pK_a of the phosphonic acid group, sometimes improving the mimicry of a natural phosphate monoester, and the inhibitory potency of the resulting analog.[1] α,α-Difluorophosphinates have been much less studied, and in their case, the effect of fluorine on the pK_a is unimportant since the phosphinic monoacids are always deprotonated at physiological pH. Nonetheless, the CF_2 moiety is a known mimic of an oxygen atom. Using our radical hydrophosphinylation reaction (NaH_2PO_2, Et_3B/air)[2] Piettre and co-workers have pioneered the synthesis of α,α-difluorophosphinates, from 1,1-difluoro-2,2-disubstituted olefins (Eq. 1).[3]



(1)

Fifteen years ago, Hall and co-workers reported the only example we could find of the base-promoted alkylation of a difluoromethylp hosphinate $RP(O)(OEt)CF_2H$, as well as its subsequent elaboration into a GABA analog (Scheme 1).[4] Two GABA analogs $H_2NCH_2CH(X)CH_2P(O)(OH)CF_2H$ (X=H, OH) were also studied, but these were less potent agonists in a $GABA_B$ binding assay than the corresponding non-fluorinated methyl phosphinate by a factor of ~3–5.[4] Phosphonate $H_2N(CH_2)_3P(O)(OH)_2$ behaves instead as an antagonist.[4] The deprotection of the acetal followed by functionalization was also reported in this work (Scheme 1). A few years ago, we reported a general alkylation of *H*-phosphinates, and the preparation of a few α,α-difluoromethylphosphinates.[5] Herein, we report a study of the alkylation of these and other precursors, which expands upon the Hall precedent.[4]



Scheme 1. Hall's synthesis and elaboration of an α,α-difluorophosphinate.[4]

2. Results and discussion

2.1. Synthesis of difluoromethylphosphinate $RP(O)(OEt)CF_2H$ precursors

Three precursors **1**–**3** were synthesized previously (Eq. 2).[5] A fourth compound **4** was synthesized similarly from $(EtO)_2CHP(O)$

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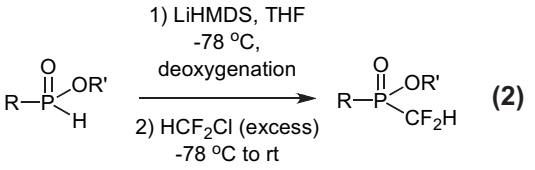
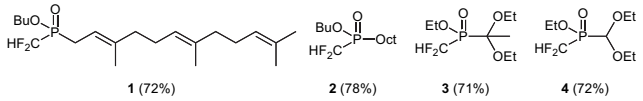
(OEt)H. We have been referring to $(EtO)_2CRP(O)(OEt)H$ (R=H, Me) as the 'Ciba-Geigy reagents', after their development in that company. As will be discussed below, significant differences exist between compounds **3** and **4**.





The alkylation of *H*-phosphinate esters with lithium hexamethyldisilazide (LiHMDS)[5] and F_2CHCl (R-22) and mild deoxygenation gives good yields of products **1**–**4** (71–78%). As we have reported previously, moderate deoxygenation is necessary to achieve good yields of product (this is because the P(III) anion is easily oxidized).[5,6]

2.2. Functionalization of the difluoromethylphosphinates

Although the $P(O)CF_2H$ group is acidic, electrophilicity of the phosphorus atom is also increased so that P-substitution is an expected competitive pathway. Table 1 shows the outcome of the deprotonation–alkylation process with compound **3** (and methyl iodide as electrophile) as a function of the base employed. *t*-BuLi gives the best results because it is a strong base and less nucleophilic than other butyllithium reagents.

Table 1
Role of the base in the alkylation of **3** with CH_3I

Entry	Base (equiv)	Conditions[a]	Crude NMR yield, ^{31}P and ^{19}F (%)	Isolated yield (%)
1	LDA (1.0)	Deoxygenated	20	—
2	LiHMDS (1.0)	Deoxygenated	0	—
3	*t*-BuLi (1.0)	Deoxygenated	80	—
4a	*t*-BuLi (1.1)	Deoxygenated	100	91
4b		Without deoxygenation	53	—

[a] Unless otherwise noted, all reactions were deoxygenated for 30 min to 1 h prior to adding the base.

The role of electrophile was also investigated (Table 2). Not surprisingly, the less reactive electrophiles gave a lower alkylation yield.

Table 2
Role of the Electrophile in the Alkylation of **3** with *t*-BuLi[a]

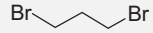
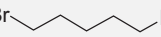
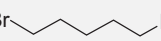
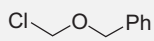
Entry	Electrophile	Crude NMR, ^{31}P and ^{19}F (%)	Isolated yield (%)
1	OctI	100	85
2	OctBr	100	82
4	OctOTs	45	—
3	OctCl	30	—

[a] Conditions: (1) deoxygenation, (2) addition of RX at −78 °C, 30 min after the base, (3) −78 °C to 15 °C, 1.5 h, (4) extractive work-up.

2.3. Scope of the alkylation

Compound **3** was treated with several electrophiles (Table 3). The yields are moderate to good. When 0.5 equiv of a dielectrophile is employed, the disubstituted product is obtained.

Table 3
Reactions of phosphinate **3** with some electrophiles

Entry	Base (1.1 equiv)	Electrophile		Isolated yield (%)
1	*t*-BuLi		0.5 equiv	69[a]
2	*t*-BuLi		0.5 equiv	62[a]
3	*t*-BuLi		1.05 equiv	65
4	*t*-BuLi		1.0 equiv	70
5	*t*-BuLi	Geranyl bromide	1.0 equiv	52

[a] Disubstitution.

Alkylation with a carbohydrate-derived iodide also gave satisfactory results but the product was obtained as the fully hydrolyzed *H*-phosphinic acid (Eq. 3). It is interesting to note that **3** was successful in this reaction, but **4** was not, under otherwise identical conditions. In fact, the reactions of compound **4** are typically very different from that of **3**. Table 4 summarizes the results with methyl iodide and **4** (compare with Table 1). It is expected that the electron-donating methyl substituent in compound **3** will somewhat deactivate the phosphorus atom toward nucleophilic attack. However, the subtle electronic effects translate into significant differences when compared to compound **4**.

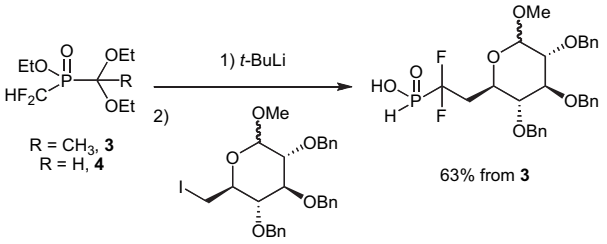


Table 4
Role of the base in the alkylation of **4** with CH_3I

Entry	Base (1.1 equiv)	Conditions[a]	Crude NMR yield, ^{31}P and ^{19}F (%)	Isolated yield (%)
1	LDA	Deoxygenated	100	62
2	BuLi	Deoxygenated	Some addition to P	—
3	*t*-BuLi	Deoxygenated	Addition to P major	—

[a] All reactions were deoxygenated for 30 min to 1 h prior to adding the base.

Compounds $RP(O)(OEt)CF_2R'$ are hydrolyzed very easily during chromatography on silica gel, even in the presence of some base (like Et_3N) in the eluent. This is not surprising due to the increased electrophilicity of the phosphorus atom with the powerful electron-withdrawing CF_2H group. Thus, products are often isolated and/or characterized as the corresponding *H*-phosphinic esters or acids. *H*-Phosphinate esters RP(O)(OEt)H are typically hydrolyzed rather easily, and the difluoro-substituted compounds $RCF_2P(O)(OEt)H$ are even more prone to further hydrolysis to the corresponding *H*-phosphinic acids $RCF_2P(O)(OH)H$.

2.4. Alkylation of 2

Alkylation of compound **2** resulted in an unexpected chain functionalization, as opposed to the difluoromethyl deprotonation/alkylation (Eq. 4).