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Simple synthesis of some unsaturated 1,1-difluoro-2-hydroxyethylphosphonates

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Abstract

A short synthesis of some 1,1-difluoro-2-hydroxymethylphosphonates in good yields is described. This procedure involves the regioselective 1,2-addition of [(diethoxyphosphoryl)difluoromethyl]lithium toward unsaturated aldehydes and ketones.

Keywords: Difluoromethylenephosphonates; [(Diethoxyphosphoryl)difluoromethyl]lithium; 1,2-Addition

1. Introduction

During the past decades, *gem*-difluoromethylenephosphonates have found widespread use as hydrolytically stable analogues of naturally occurring phosphate esters since they mimic parental phosphates more effectively than their non-fluorinated congeners [1]. It is directly connected with excellent electronic and structural similarity to the phosphate moiety and also resulted from the relative resistance of fluorinated phosphonates to metabolic transformations. Indeed, the importance of α,α-difluoromethylenephosphonates as phosphate analogues and enzyme inhibitors have been already well-established and still remained the current level of interest in biochemical and pharmaceutical studies [2]. Considering these benefits, numerous synthetic methodologies have been so far investigated for introduction difluoromethylenephosphonate function into a variety of organic compounds [3].

Our research attention in this area has focused on the synthesis of some unsaturated 1,1-difluoro-2-hydroxyethylphosphonates *via* condensation of lithiated carbanion with unsaturated aldehydes and ketones also possessing conjugated systems. To the best of our knowledge, only few examples have been described for the preparation of such compounds as precursors in preparation of fluorine-containing analogues of natural unsaturated systems with significant biological importance (*e.g.* fluorinated retinoids or flavonoids) [4]. Moreover, functionalization of unsaturated 1,1-difluoro-2-hydroxymethylenephosphonates would also provide access to difluoromethylene phosphonate derivatives of nucleobases—recently identified as very potent inhibitors of purine nucleoside phosphorylase (PNP inhibitors) [5].

The classical route to diethyl 1,1-difluoro-2-hydroxymethylenephosphonates, originally reported by Obayashi and Kondo, involves the direct addition of [(diethoxyphosphoryl)difluoromethyl]lithium to an appropriate carbonyl compound [6]. In previous studies of Halazy, the above protocol was also successfully applied to a short synthesis of allyl alcohols containing difluoromethylene phosphonate unit [7]. However, the condensation of $LiCF_2P(O)(OEt)_2$ with aldehydes or ketones bearing more than one unsaturated systems, attached directly to a carbonyl group, has not been investigated yet. Therefore, we wish to report a straightforward transformation of diethyl difluoromethylenephosphonate into 1,1-difluoro-2-hydroxyethylphosphonates as a convenient pathway giving difluoromethylene phosphonate derivatives of compounds that form the central core of a variety of important natural products.

2. Results and discussion

The generation of [(diethoxyphosphoryl)difluoromethyl]-lithium can be successfully achieved by treatment of diethyl difluoromethylenephosphonate with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C. Addition of an appropriate carbonyl compound to the solution followed by

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acidic work-up and purification by column chromatography afforded the corresponding hydroxyphosphonates [6,7]. In our methodology, low temperature metallation (Li/H exchange) reaction has been expanded by the use of another potent and hindered base such as *t*-butyllithium. To the best of our knowledge, the proton abstraction from $HCF_2P(O)(OEt)_2$ performed by other bases and reactivity of this lithiated carbanion toward various electrophiles was less studied and only few examples can be found in literature protocols [8]. It should be pointed out, that the production of [(diethoxyphosphoryl)difluoromethyl]lithium requires the use of hindered bases in order to avoid competitive nucleophilic addition of base to diethyl difluoromethylenephosphonate. Furthermore, the conversion of $HCF_2P(O)(OEt)_2$ to $LiCF_2P(O)(OEt)_2$ is best conducted at low temperature due to the thermal instability of the organolithium reagent. At 0 °C it rapidly dissociates to form difluorocarbene and lithio diethyl phosphate, hence all reactions were carried out by us at −90 °C.

The metallation of $HCF_2P(O)(OEt)_2$ with *t*-BuLi followed by trapping with an appropriate aldehyde or ketone gave the corresponding 1,1-difluoro-2-hydroxyethylphosphonates in moderate to good yield as summarized in Table 1.

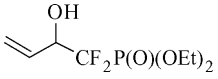
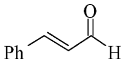
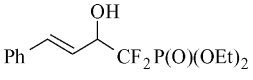
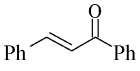
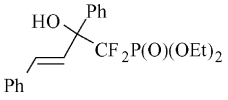
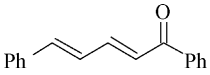
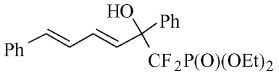
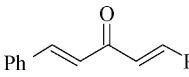
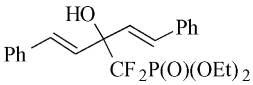
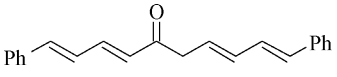
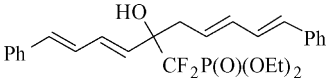
In all cases (entries **1**–**6**), the addition of $LiCF_2P(O)(OEt)_2$ to a carbonyl compound proceeds with complete 1,2-regioselectivity and no 1,4- or 1,6-adducts were identified in the crude reaction mixture using ^{19}F NMR spectral analysis. A possible explanation for this behavior can be poor nucleophilicity of $LiCF_2P(O)(OEt)_2$ caused by the presence of two electronegative fluorine atoms attached directly to a carbanion centre. As a result, the formation of anti-Michael addition products has been only observed.

Generally, unsaturated 1,1-difluoro-2-hydroxyethylphosphonates (entries **1b**, **2b**, **5b** and **6b**) were isolated in excellent yields and all by-products were easily removed during work up. However, the addition of $LiCF_2P(O)(OEt)_2$ to **3a** and **4a** resulted in incomplete conversion to estimated products and only satisfactory yields of **3b** and **4b** were obtained. In these two cases, the steric hindrance of the neighbouring phenyl group could notably reduce the ability of [(diethoxyphosphoryl)difluoromethyl]lithium to act as a nucleophile, giving fluorinated β-hydroxyphosphonates **3b** and **4b** in 31 and 35% yields, respectively.

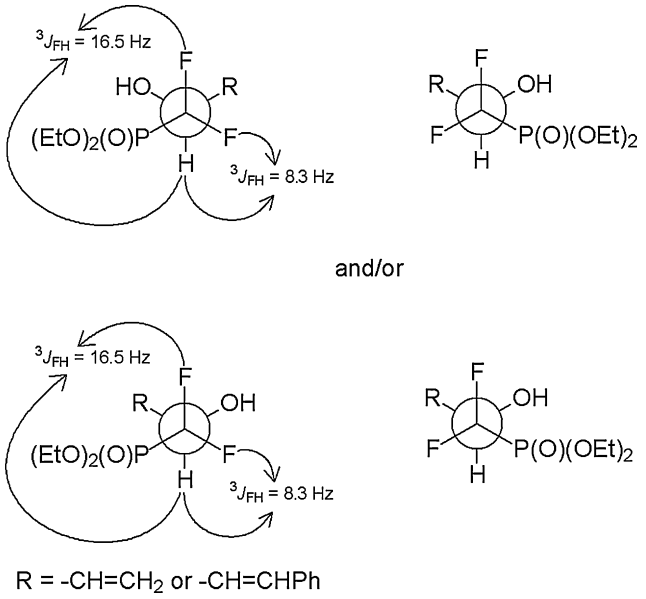
In some cases (**1b**, **2b**), we were able to determine the relative stereochemistry of geminal fluorines from difluoromethylenephosphonate group. The ^{19}F NMR spectra of compounds **5b** and **6b** indicate the magnetic equivalence of two fluorine atoms. Since they appear as doublet with fluorine-phosphorous coupling constant of about 100 Hz, other 1,1-difluoro-2-hydroxyethylphosphonates show much more complicated splitting pattern in ^{19}F NMR spectrum, as the consequence of coexisting couplings of fluorine–fluorine, fluorine–phosphorous and finally fluorine–proton. By reason of the proximity to the stereogenic centre (carbon β), diastereotopic fluorines showed a variation in the degree of chemical shift, giving doublet of doublets (dd) (**3b**, **4b**) and doublet of doublets of doublets (ddd) (**1b**, **2b**) at −116 and −123 ppm, respectively. Furthermore, the vicinal fluorine–hydrogen coupling constant ($^3J_{FH}$) of each fluorine differs (entries **1b** and **2b**), indicating a *syn* and *anti* relationship between relevant fluorines and vicinal proton (Scheme 1). Thus, it follows that four possible conformers could exist (two pairs of enantiomers) and, as a result, a mixture of (*R*) and (*S*) stereoisomers might be obtained (Scheme 1).

In conclusion, we have demonstrated the straightforward procedure to obtain various unsaturated 1,1-difluoro-2-hydroxyethylphosphonates in up to 80% yield by the anti-Michael addition of [(diethoxyphosphoryl)difluoromethyl]lithium to an

Table 1
Preparation of unsaturated 1,1-difluoro-2-hydroxyethylphosphonates

Entry	Carbonyl compound[a] (**a**)	Product (**b**)	Yield % of **b**[b]
1			80
2			76
3			31
4			35
5			77
6			65

[a] All substrates except for **1a** and **2a** were prepared according to the literature procedures [9].
[b] Isolated yields after purification by column chromatography.



Scheme 1. Determination of vicinal fluorine–hydrogen interactions (entries **1b** and **2b**).

appropriate unsaturated carbonyl compound. This bond construction is efficient and could constitute an easy route to difluromethylene phosphonate analogues of some natural products from commercially available substrates.

3. Experimental

3.1. General remarks

All reactions were carried out under argon atmosphere. THF was freshly distilled from sodium benzophenone ketyl. *t*-Butyllithium (1.7 M solution in pentane) was purchased from Aldrich and used without further purification.

^{1}H, ^{13}C, ^{19}F NMR and ^{31}P NMR have been achieved on a Varian Gemini 300 MHz spectrometer in $CDCl_3$ as solvent. TMS was the internal standard in ^{1}H NMR, $CFCl_3$ was used as a reference for ^{19}F NMR and 85% H_3PO_4 in ^{31}P NMR. Chemical shifts for ^{1}H NMR are reported in ppm downfield from TMS and for ^{19}F NMR upfield from $CFCl_3$. ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei unless stated otherwise.

Mass spectra were recorded on a AMD 402 spectrometer, ionisation was achieved through electron impact (EI) with 70 eV.

3.2. Typical procedure for the preparation of 2-hydroxy-1,1-difluoromethylenephosphonate

t-Butyllithium (1.0 ml of 1.7 M solution in pentane, 1.72 mmol) was added dropwise over 15 min to a cold (−90 °C) solution of diethyl difluoromethylenephosphonate (0.32 g, 1.72 mmol) in dry THF (8 ml). The reaction mixture was stirred 10 min at this temperature and then aldehyde or ketone (1.68 mmol) in dry THF (2–4 ml) was added slowly to the yellow solution. After stirring for further 1 h at −90 °C, an aqueous solution of HCl was added and the mixture was allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether (3 × 10 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/ethyl acetate) of the crude product afforded pure 2-hydroxy-1,1-difluoroethylphosphonate.

3.3. Diethyl 1,1-difluoro-2-hydroxybut-3-enylphosphonate (*1b*)

Yield 80% (colorless oil). ^{1}H NMR ($CDCl_3$): δ 6.84 (dd, 1H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, $^{3}J_{H–H(cis)}$ = 1 Hz, $^{2}J_{H–H}$ = 3 Hz, CH=CH), 6.40 (dd, 1H) 6.24 (dd, 1H), 4.67 (m, 1H), 4.25 (m, 4H, –OC*H*$_2$CH$_3$), 3.24 (br. s, 1H, –O*H*), 1.28 (dt, 6H, –OCH$_2$C*H*$_3$). ^{19}F NMR ($CDCl_3$): δ −116.40 (ddd, 1F, $^{2}J_{F–F}$ = 293.9 Hz, $^{2}J_{F–P}$ = 101.7 Hz, $^{3}J_{F–H}$ = 8.3 Hz), −123.63 (ddd, 1F, $^{2}J_{F–F}$ = 305.2 Hz, $^{2}J_{F–P}$ = 103.1 Hz, $^{3}J_{F–H}$ = 16.5 Hz). ^{31}P NMR ($CDCl_3$): δ 6.80 (t, 1P, $^{2}J_{P–F}$ = 102.6 Hz). ^{13}C NMR ($CDCl_3$): δ 137.0, 121.9 (=*C*H), 118.7 (td, $^{1}J_{C–F}$ = 266.1 Hz, $^{1}J_{C–P}$ = 204.5 Hz), 73.0 (m, *C*H–OH), 65.1 (d, –O*C*H$_2$CH$_3$, $^{2}J_{C–P}$ = 7.0 Hz), 16.3 (dd, –OCH$_2$*C*H$_3$, $^{3}J_{C–P}$ = 5.8 Hz). *m*/*z* (EI) 244.3 ($M^{\bullet+}$, 18%), 57.2 (100).

3.4. Diethyl (3E)-1,1-difluoro-2-hydroxy-4-phenylbut-3-enylphosphonate (*2b*)

Yield 76% (pale-yellow oil). ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 2H, *H*$_{Ar}$), 7.33 (m, 3H, *H*$_{Ar}$), 6.84 (dd, 1H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, $^{4}J_{H–H}$ = 1 Hz, PhC*H*=CH), 6.24 (dd, 1H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, $^{3}J_{H–H}$ = 6 Hz, PhCH=C*H*), 4.65 (m, 1H), 4.25 (m, 4H, –OC*H*$_2$CH$_3$), 3.24 (br. s, 1H, –O*H*), 1.28 (dt, 6H, –OCH$_2$C*H*$_3$). ^{19}F NMR ($CDCl_3$): δ −116.44 (ddd, 1F, $^{2}J_{F–F}$ = 293.9 Hz, $^{2}J_{F–P}$ = 101.7 Hz, $^{3}J_{F–H}$ = 8.3 Hz), −123.63 (ddd, 1F, $^{2}J_{F–F}$ = 305.2 Hz, $^{2}J_{F–P}$ = 103.1 Hz, $^{3}J_{F–H}$ = 16.5 Hz). ^{31}P NMR ($CDCl_3$): δ 6.77 (t, 1P, $^{2}J_{P–F}$ = 102.7 Hz). ^{13}C NMR ($CDCl_3$): δ 135.9, 128.6, 128.3, 126.8 (*C*$_{Ar}$), 135.0, 121.9 (=*C*H), 118.7 (td, $^{1}J_{C–F}$ = 266.1 Hz, $^{1}J_{C–P}$ = 204.5 Hz), 72.9 (m, *C*H–OH), 65.1 (d, –O*C*H$_2$CH$_3$, $^{2}J_{C–P}$ = 7.0 Hz), 16.3 (dd, –OCH$_2$*C*H$_3$, $^{3}J_{C–P}$ = 5.8 Hz). *m*/*z* (EI) 320.4 ($M^{\bullet+}$, 14%), 188.0 (72), 161.0 (72), 133.0 (100), 91.1 (12), 77.1 (16).

3.5. Diethyl (3E)-1,1-difluoro-2-hydroxy-2,4-diphenylbut-3-enylphosphonate (*3b*)

Yield 31% (white solid). ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 10H, *H*$_{Ar}$), 7.00 (d, 1H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, PhC*H*=CH), 6.83 (dd, 2H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, PhCH=C*H*), 4.00 (compl. m, 5H, –O*H*, –OC*H*$_2$CH$_3$), 1.28 (dt, 6H, –OCH$_2$C*H*$_3$). ^{19}F NMR ($CDCl_3$): δ −116.00 (dd, 1F, $^{2}J_{F–F}$ = 293.9 Hz, $^{2}J_{F–P}$ = 101.7 Hz), −118.00 (dd, 1F, $^{2}J_{F–F}$ = 305.2 Hz, $^{2}J_{F–P}$ = 103.1 Hz). ^{31}P NMR ($CDCl_3$): δ 8.83 (dd, 1P, $^{2}J_{P–F}$ = 102.8 Hz). ^{13}C NMR ($CDCl_3$): δ 136.2, 128.6, 128.1, 126.8 (*C*$_{Ar}$), 132.3, 125.1 (CH=CH), 118.5 (td, $^{1}J_{C–F}$ = 272.1 Hz, $^{1}J_{C–P}$ = 204.3 Hz), 65.1 (d, –O*C*H$_2$CH$_3$, $^{2}J_{C–P}$ = 7.0 Hz), 16.2 (d, –OCH$_2$*C*H$_3$, $^{3}J_{C–P}$ = 5.8 Hz). *m*/*z* (EI) 396.4 ($M^{\bullet+}$), 209.3 (100).

3.6. Diethyl (3E,5E)-1,1-difluoro-2-hydroxy-2,6-diphenylhexa-3,5-dienylphosphonate (**4b**)

Yield 35% (yellow solid). ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 10H, H_{Ar}), 6.96 (m, 3H), 6.14 (d, 1H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, PhCH=C*H*), 4.00 (compl. m, 5H, –O*H*, –O$CH_2$$CH_3$), 1.28 (dt, 6H, –OCH$_2CH_3$). ^{19}F NMR ($CDCl_3$): δ −116.00 (dd, 1F, $^{2}J_{F–F}$ = 293.9 Hz, $^{2}J_{F–P}$ = 101.7 Hz), −118.24 (dd, 1F, $^{2}J_{F–F}$ = 305.2 Hz, $^{2}J_{F–P}$ = 103.1 Hz). ^{31}P NMR ($CDCl_3$): δ 8.79 (dd, 1P, $^{2}J_{P–F}$ = 102.8 Hz). ^{13}C NMR ($CDCl_3$): δ 136.2, 128.6, 128.1, 126.8 (C_{Ar}), 134.4, 132.3, 125.1 (CH=CH), 118.5 (td, $^{1}J_{C–F}$ = 272.1 Hz, $^{1}J_{C–P}$ = 204.3 Hz), 65.1 (d, –O*C*H$_2$CH$_3$, $^{2}J_{C–P}$ = 7.0 Hz), 16.2 (d, –OCH$_2$*C*H$_3$, $^{3}J_{C–P}$ = 5.8 Hz). *m/z* (EI) 424.4 ($M^{\bullet+}$, 2%), 237.2 (100).

3.7. Diethyl (3E)-1,1-difluoro-2-hydroxy-4-phenyl-2-[(E)-2-phenylvinyl]but-3-enylphosphonate (**5b**)

Yield 77% (white crystals). mp 92–94 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 4H, H_{Ar}), 7.25 (m, 6H, H_{Ar}), 6.94 (d, 2H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, PhC*H*=CH), 6.44 (d, 2H, $^{3}J_{H–H(trans)}$ = 15.9 Hz, PhCH=C*H*), 4.59 (br. s, 1H, –O*H*), 4.20 (m, 4H, –O$CH_2$$CH_3$), 1.28 (td, 6H, –OCH$_2CH_3$). ^{19}F NMR ($CDCl_3$): δ −119.04 (d, 2F, $^{2}J_{F–P}$ = 103.1 Hz). ^{31}P NMR ($CDCl_3$): δ 7.41 (t, 1P, $^{2}J_{P–F}$ = 102.8 Hz). ^{13}C NMR ($CDCl_3$): δ 136.2, 128.6, 128.1, 126.8 (C_{Ar}), 132.3, 125.1 (CH=CH), 118.5 (td, $^{1}J_{C–F}$ = 272.1 Hz, $^{1}J_{C–P}$ = 204.3 Hz), 65.1 (d, –O*C*H$_2$CH$_3$, $^{2}J_{C–P}$ = 7.0 Hz), 16.2 (d, –OCH$_2$*C*H$_3$, $^{3}J_{C–P}$ = 5.8 Hz). *m/z* (EI) 422.4 ($M^{\bullet+}$, 5%), 235.3 (100), 117.2 (36), 91.1 (32), 77.1 (18).

3.8. Diethyl (3E,5E)-1,1-difluoro-2-hydroxy-6-phenyl-2-[(1E,3E)-4-phenylbuta-1,3-dienyl] hexa-3,5-dienylphosphonate (**6b**)

Yield 65% (yellow solid). mp 99–104 °C. ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 10H, H_{Ar}), 6.74 (m, 6H, CH=CH), 6.00 (d, 2H, $^{3}J_{H–H(trans)}$ = 15.0 Hz, CH=CH), 4.43 (br. s, 1H, –O*H*), 4.20 (m, 4H, –O$CH_2$$CH_3$), 1.28 (td, 6H, –OCH$_2CH_3$). ^{19}F NMR ($CDCl_3$): δ −119.04 (d, 2F, $^{2}J_{F–P}$ = 103.1 Hz). ^{31}P NMR ($CDCl_3$): δ 7.41 (t, 1P, $^{2}J_{P–F}$ = 102.8 Hz). ^{13}C NMR ($CDCl_3$): δ 136.9, 128.6, 127.6, 126.5 (C_{Ar}), 134.4, 132.7, 127.8 (CH=CH), 118.5 (td, $^{1}J_{C–F}$ = 272.1 Hz, $^{1}J_{C–P}$ = 204.3 Hz), 65.1 (d, –O*C*H$_2$CH$_3$, $^{2}J_{C–P}$ = 7.0 Hz), 16.3 (d, –OCH$_2$*C*H$_3$, $^{3}J_{C–P}$ = 5.8 Hz). *m/z* (EI) 474.4 ($M^{\bullet+}$, 4%), 287.2 (28), 157.2 (34), 143.2 (97), 91.1 (100), 83.0 (65).

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