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FLUORINE IN ENZYME CHEMISTRY: PART 1. SYNTHESIS OF DIFLUOROMETHYLENE-PHOSPHONATE DERIVATIVES AS PHOSPHATE MIMICS

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SUMMARY

Diethyl difluoromethylphosphonylcadmium bromide reacts with allyl and benzyl halides in THF to give the corresponding difluoromethylene-phosphonate derivatives. The reaction with allyl bromide affords a versatile synthetic intermediate which undergoes a variety of synthetic transformations and therefore becomes a key compound in the preparation of elaborated difluoromethylenephosphonates of biological significance.

INTRODUCTION

Fluorine and hydrogen have a unique relationship in organic chemistry [1], which allows the replacement of hydrogen in organic compounds by fluorine, either singly or multiply. This leads to a vast extension of organic chemistry and, most significantly, to a multiplicity of 'unnatural' products. There are many facets to the academic and industrial interest that ensues from replacement [2] of hydrogen by fluorine but not least is the effect in biological processes. This is an area of confirmed [3] importance and in this series we begin the study of synthesis and subsequent enzymic manipulation of various fluorine substituted systems.

Currently [4] there is an intense interest in exploring the potential of difluoromethylenephosphonates as isostereo-electronic

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phosphate mimics in biological systems. Indeed in a preliminary communication [5] we report that a difluoromethylenephosphonate analogue is a substrate for an enzyme on the glycolytic pathway and we believe this modification holds promise for the future in the design of novel enzyme substrates and inhibitors. In spite of recent activity in this area few useful synthetic methods [6,7] exist for the introduction of the difluoromethylenephosphonate moiety into organic nuclei.

RESULTS AND DISCUSSION

We chose to investigate diethyl difluoromethylphosphonylcadmium bromide (1), first described by Burton and co-workers [8], because of the stability problems [9] associated with fluorine containing organolithium compounds. A variety of allyl (2a-2g) and benzyl halides (2h-2j) (see Scheme 1 and Table 1) are converted to the corresponding

$(OEt)_2P(O)CF_2Br \xrightarrow[THF,\ 65^{o}/3\ h]{Cd} (OEt)_2P(O)CF_2CdBr$ (1)

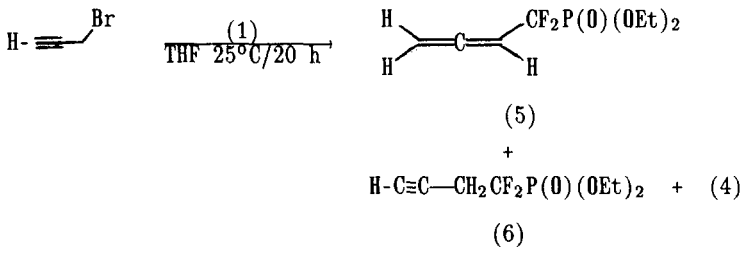
$RR'C{=}CR''CH_2X$ (2a-2g) or $RC_6H_4CH_2X$ (2h-2j) $\xrightarrow{(1)}$ $RR'C{=}CR''CH_2CF_2P(O)(OEt)_2$ (3a-3g) or $RC_6H_4CH_2CF_2P(O)(OEt)_2$ (3h-3j) + $HCF_2P(O)(OEt)_2$ (4)

a, R=R'=R"=H; X=Br
b, R=R'=R"=H; X=I
c, R=R'=CH_3; R"=H; X=Br
d, R=R'=H; R"=CH_3; X=Br
e, R=R'=H; R"=CH_3; X=Cl
f, R=Ph; R'=R"=H; X=Br
g, R=$(CH_3)_2CCH(CH_2)_2$; R'=CH_3; R"=H; X=Br
h, R=H; X=Br
i, R=H; X=I
j, R=p-NO_2; X=Br

SCHEME 1

difluoromethylenephosphonate derivatives (3a-3j) with difluoromethylphosphonate (4) produced as a side product.

Our principal target (3a) [8] (see later) was obtained in 62% yield after treatment of (1) with allyl bromide (2a). Reactivity follows an order consistent with an SN2 process [10], i.e. for RCH_2Br the reactivity decreases R = CH_2=CH > Ph >> H (no product was obtained even from iodomethane) but we are obviously unable to distinguish an SN2' process in the case of (2a). When the opportunity to determine regiospecificity is introduced (2b-2j) then steric effects may well favour the SN2 process. However reaction with propargyl bromide gave principally allene (5) and a small amount of the alkyne (6) as products suggesting a predominant SN2' process.



(5)

+

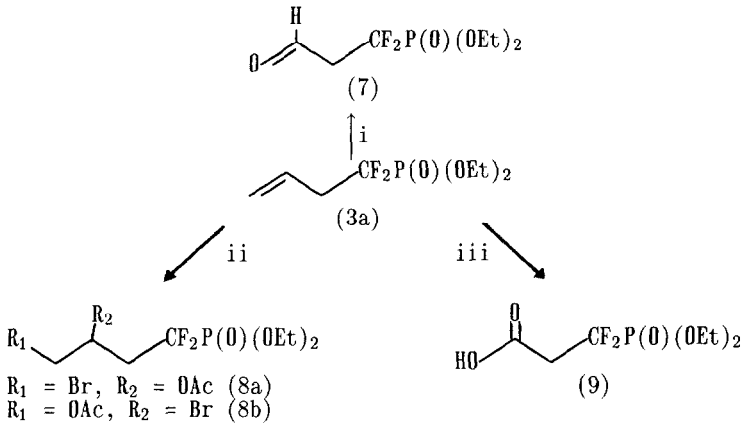
H-C≡C—$CH_2CF_2P(O)(OEt)_2$ + (4)

(6)

A persistent by-product in these reactions is the difluoromethylphosphonate (4). A possible explanation for its occurrence is a concomitant SET process involving the transfer of an electron from the cadmium reagent to the various substrates, followed by generation of the radical, $CF_2P(O)(OEt)_2$ which could abstract hydrogen readily from THF used as solvent.

In most cases the desired difluoromethylenephosphonates (3a-3j) could be separated cleanly from (4) by distillation, however when this proved unsatisfactory they were isolated after decomposition of (4) on treatment of the product mixtures with sodium borohydride in refluxing methanol. It would appear that sodium borohydride slowly decomposes diethyl difluoromethylphosphonate (4) under these conditions giving rise possibly to diethyl phosphite and difluorocarbene in a manner analogous to previous observations [11].

The now facile formation of target molecule (3a) affords an accessible intermediate susceptible to a variety of useful synthetic transformations shown in Scheme II.



i. a, O_3, CH_3OH:CH_2Cl_2 (1:4), -78°C, 6 h; b, DMS -78°C to 20°C.
ii. $Hg(OAc)_2$, Br_2, AcOH, 10°C, 8 h.
iii. $RuCl_3$, KIO_4 (CCl_4:H_3CCN:H_2O; 1:1:2).

SCHEME II

For example, ozonolysis of (3a) provided aldehyde (7) in good yield. Treatment of (3a) with mercuric acetate and bromine effected its smooth conversion to a 50:50 mixture of the isomeric bromoacetates (8a) and (8b). Oxidation of (3a) with ruthenium tetroxide under the biphasic conditions described by Sharpless [12], gave the carboxylic acid (9) in moderate yield. Clearly (3a) is an attractive intermediate for the synthesis of a variety of elaborated difluoromethylphosphonate derivatives on which we are conducting current enzymic investigations.

EXPERIMENTAL

Cadmium powder-100 mesh, 99.5% was obtained from Aldrich Chemicals and vacuum dried prior to use (70°C, 0.01 mmHg). I.r. spectra were recorded on a Perkin Elmer 257 spectrometer. ^{1}H-NMR and ^{13}C -NMR were obtained in $CDCl_3$ at 250 MHz and 62.8 MHz respectively on a Bruker AC-250 instrument. ^{19}F- and ^{31}P-NMR were recorded on the same instrument at 235 MHz and 101.25 MHz respectively. Chemical shifts are quoted relative to

TMS for ^{1}H- and ^{13}C-NMR spectra, relative to fluorotrichloromethane for ^{19}F-NMR and relative to H_3PO_4 for ^{31}P-NMR. All chemicals were of reagent quality and were used without further purification except allyl bromide which was distilled immediately prior to use. Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. Solvents were dried and distilled prior to use.

Diethyl bromodifluoromethylphosphonate

Diethyl bromodifluoromethylphosphonate was prepared by the method of Burton and Flynn [13] from difluorodibromomethane and triethylphosphite in diethyl ether without modification.

Diethyl 1,1-difluorobut-3-enylphosphonate (3a)

A solution of diethyl bromodifluoromethylphosphonate (26.7 g, 0.1 mol) in THF (15 ml) was added to a stirred suspension of cadmium (12 g, 0.10 g-atom) in THF (200 ml) over a 15 minute period at room temperature. The mixture was then heated at 65°C for 3 hours. Sodium iodide (1 g, 6.6 mmol) and allyl bromide (12.1 g, 0.1 mol) were added simultaneously to the mixture and the reaction was stirred for a further 20 hours at 25°C. The resultant solution was filtered and the solvent removed at reduced pressure to afford a clear oil. ^{19}F-NMR analysis revealed a mixture of (3a) and (4) in a ratio of 2.3:1.0. The oil was dissolved in diethyl ether, washed with 10% HCl and the organic phase separated and dried over $MgSO_4$. (3a) Was isolated in 62% yield after purification by distillation (60-62°C, 0.05 mmHg). ^{1}H NMR: 1.4 (6H, t, 7 Hz, $C\underline{H}_3CH_2$), 2.85 (2H, t.t, 19 Hz, CH_2CF_2), 4.3 (4H, p, $CH_3C\underline{H}_2$) 5.1-6.3 (3H, m, CH_2CH; ^{19}F NMR: 112.0 (d.t, 107.5 Hz); ^{31}P NMR: 6.4, (t). (Found C, 42.0; H, 6.5. $C_8H_{15}O_3F_2P$ requires C, 42.1; H, 6.6).

(3b)-(3j) Were prepared from their corresponding allylic and benzylic halides (2b)-(2j) using the above procedure. For specifications see Table 1.

(3b) Spectroscopic data were identical to that of (3a).

(3c) (73°C, 0.02 mmHg); ^{1}H-NMR: 1.46 (6H, t, 6.9 Hz, CH_3CH_2), 1.9 (6H, s, CH_3), 2.7 (2H, t.t, 17 Hz, CH_2CF_2), 4.23 (4H, p, $CH_3C\underline{H}_2$), 4.67-5.36 (2H, m, CH_2=C); ^{19}F-NMR: 111.25 (d.t, 107.8 Hz); ^{31}P-NMR: 6.37(t); (nc) (Found: C, 44.6; H, 7.0. $C_{10}H_{19}O_3F_2P$ requires C, 45.8; H, 7.4).

TABLE 1

Details of $(EtO)_2P(O)CF_2CdBr$ reactions with allyl (2a-2g) and benzyl (2h-2j) halides

Substrate (2)	% Yield[a] of (3)	% Yield[b] of (4)	Solvent	Conditions Temp°C/Time (h)
a	62	27	THF	25/20
b	40 (3a)	42	THF	25/20
c	25	45	THF	25/20
d	27	41	THF	25/20
e	14 (3d)	7	THF	70/4
f	8	3	THF	25/20
g	10	24	THF	25/20
h	17	42	THF/DMSO	60/8
i	21 (3h)	57	THF/DMSO	25/20
j	7	46	THF/DMSO	60/40

[a]Yields based on (3) after distillation.

[b]Determined directly by ^{19}F-NMR before work-up.

(3d) (62°C, 0.02 mmHg); ^{1}H-NMR: 1.12 (6H, t, 7 Hz, $C\underline{H}_3CH_2$), 1.73 (3H, s, CH_3C=), 2.59 (2H, m, 19.5 Hz, CH_2CF_2), 4.25 (4H, p, CH_3CH_2), 4.46-5.01 (2H, m, CH_2=C); ^{19}F-NMR; 111.25 (d.t, 107.8 Hz); ^{31}P-NMR: 5.81(t) (nc) (Found C, 44.6; H, 7.0. $C_9H_{17}O_3F_2P$ requires C, 44.6; H, 7.0).

(3e) Spectroscopic data were identical to that of (3d)

(3f) (140-145°C, 0.01 mmHg); ^{1}H-NMR: 1.32 (6H, t, 7.2 Hz, $C\underline{H}_3CH_2$), 2.89 (2H, t.t, 18 Hz, CH_2CF_2), 4.34 (4H, p, CH_3CH_2), 6.18 (1H, d.t, 15.8 Hz, $CH_2C\underline{H}$), 6.55 (1H, d, 15.8 Hz, $C\underline{H}$-C_6H_5), 7.28 (5H, s, C_6H_5); ^{19}F-NMR: 110.41 (d.t, 104.4 Hz, 18 Hz); ^{31}P NMR: 6.67(t); (nc) (Found C, 54.7; H, 6.1. $C_{14}H_{19}O_3F_2P$ requires C, 55.3; H, 6.3).

(3g) ^{1}H NMR: 1.35 (6H, t, 7 Hz, $C\underline{H}_3CH_2$), 1.62 (3H, s, CH_3), 1.77 (3H, s, CH_3), 2.02-2.35 (4H, m, CH_2CH_2), 2.65-2.75 (2H, t.t, 17 Hz,

CH_2CF_2), 4.2 (4H, p, CH_3CH_2), 4.9-5.6 (2H, m, CH=); ^{19}F-NMR; 110.45 (d.t, 107.5 Hz); ^{31}P-NMR: 6.82(t).

(3h) (99-102°C, 0.01 mmHg); ^{1}H-NMR: 1.20 (6H, t, 7 Hz, $C\underline{H}_3CH_2$), 3.34 (2H, d.t, 17 Hz, CH_2CF_2), 4.12 (4H, p, $CH_3C\underline{H}_2$), 7.11-7.32 (5H, m, C_6H_5); ^{19}F-NMR: 113.23 (d.t, 107.33 Hz); ^{31}P NMR: 5.63(t). (nc) (Found C, 51.4; H, 6.1. $C_{12}H_{17}O_3F_2P$ requires C, 51.8; H, 6.1).

(3i) Spectroscopic data were identical to that of (3h).

(3j) ^{1}H-NMR: 1.25 (6H, t, 7.1 Hz, CH_3CH_2), 3.25 (2H, d.t, 18.2 Hz, CH_2CF_2), 4.12 (4H, p, $CH_3C\underline{H}_2$), 7.1-7.32 (4H, m, C_6H_6); ^{19}F NMR: 112.45 (d.t, 106.43 Hz); ^{31}P-NMR: 6.12(t).

Diethyl 1,1-difluoro-2,3-butandienephosphonate (5) and Diethyl 1,1-difluoro-3-propynphosphonate (6)

Propargyl bromide (11.9 g, 0.1 mol) was added to a mixture of cadmium and diethyl bromodifluoromethylphosphonate under the conditions described above to afford a mixture of (5), (6) and (4) in the ratio 2.8:1:10.8. After distillation (60°C, 0.03 mmHg) (5) and (6) could be isolated as a mixture in 27% yield. IR (neat) for (5); 1935, 1950 cm^{-1}; ^{13}C-NMR for (5): 73.21 (H_2C=), 200.7 (t, =C=), 86.64 (d.t, $C\underline{H}CF_2$, 27.41 Hz), 115.46 (d.t, CF_2, 258.5 Hz, 185.1 Hz), 64.5 (OCH_2), 16.4 (CH_3); ^{19}F-NMR for (5): 107.16 (d.d, 113.19 Hz, 10.5 Hz); ^{31}P-NMR for (5): 5.07(t); ^{13}C NMR for (6): 117.11 (t, CF_2, 219.9 Hz), 80.69 (C≡C), 64.60 ($H\underline{C}$≡C), 64.42 (OCH_2), 16.04 (CH_3); ^{19}F-NMR for (6): 111.67 (d.t, 112.25 Hz, 17.88 Hz); ^{31}P for (6): 5.0 (t); (nc) (Found: C, 42.2; H, 5.6; F, 16.4. $C_8H_{13}O_3F_2P$ requires C, 42.5; H, 5.2; F, 16.8).

Diethyl 1,1-difluoro-3-oxopropylphosphonate (7)

Ozone was bubbled through a solution of (3a) (9.0 g, 0.04 mmol) in a solvent mixture of dichloromethane (160 ml) and methanol (35 ml) at -78°C until the solution turned blue (approx. 4 hours). Nitrogen was then bubbled through the reaction to remove excess ozone. Once the blue colour had disappeared dimethyl sulphide (6 g, 0.096 mol) was added at -78°C and the solution left to come to room temperature. The solvent was removed at reduced pressure and distillation (80-83°C, 0.06 mmHg) of the residual oil afforded aldehyde (7) in 75% yield. IR (neat): 1700 cm^{-1}; ^{1}H -NMR: 1.16 (6H, t, 7 Hz, $C\underline{H}_3CH_2$), 2.68 (2H, d.t, 20 Hz,

CH_2), 4.0 (4H, p, $CH_3\underline{CH_2}$), 9.37 (1H, s, CHO); ^{13}C-NMR; 15.75, 46.89, 64.63, 116.29, 193.5; ^{19}F-NMR: 110.97 (d.t, 106 Hz, 20 Hz); ^{31}P-NMR: 4.62(t); (nc) (Found: C, 36.5; H, 5.6. $C_7H_{13}O_4F_2P$ required C, 36.5; H, 5.6)

Diethyl 1,1-difluoro-3-bromo-4-acetoxyphosphonate (8a) and diethyl-1,1-difluoro-3-acetoxy-4-bromophosphonate (8b)

A solution of bromine (11.42 g, 71.4 mmol) in glacial acetic acid (15 ml) was added over a period of 3 hours to a solution of (3a) (16.28 g, 71.4 mmol) and mercuric acetate (13.62 g, 42.8 mmol) in glacial acetic acid (30 ml) at +10°C. The reaction was stirred for a further 8 hours at 20°C and then filtered. The mercuric salts were washed with cold diethyl ether and then the combined filtrate and washings poured into ice cold water. The organic layer was separated and washed sequentially with saturated potassium carbonate solution, brine and water. The organic extract was dried over $MgSO_4$ and the solvent removed at reduced pressure. The crude mixture was purified by distillation (120-125°C, 0.01 mmHg) to afford a 50:50 mixture of (8a) and (8b) in 80% yield. ^{1}H-NMR: 1.37 (6H, t, 7 Hz, $C\underline{H_3}CH_2$), 2.06 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.31-2.75 (m, CH_2CF_2), 4.27 (p, $CH_3\underline{CH_2}$), 4.18-4.5 (m, CH_2CH), 3.78-4.10 (m, CH_2-CH); ^{19}F-NMR: 111.56 (d.t, 105.43 Hz, 21.5 Hz); ^{31}P-NMR: 105.43(t); (nc) (Found Br, 21.3; F, 10.2. $C_{10}H_{18}BrF_2O_5P$ requires Br, 21.0, F, 10.4).

Diethyl 3,3-difluoro-3-phosphonopropionic acid (9)

Potassium periodate (17.48 g, 76 mmol) and ruthenium(III) chloride trihydrate (61 mg, 0.23 mmol) were added to a biphasic solution of (3a) (4.37 g, 19.4 mmol) in carbon tetrachloride (27 ml) acetonitrile (27 ml) and water (57 ml) and the solution stirred vigorously for 30 hours at room temperature. Dichloromethane was added and the solution filtered through Hyflo. The organic layer was separated and the aqueous layer washed (3 x 20 ml) with dichloromethane. The combined washings and filtrate were dried over $MgSO_4$ and the solvent removed at reduced pressure to afford a clear oil. Purification by silica gel chromatography (CH_2Cl_2:EtOAc; 1:4) gave (9) in 41% yield. IR (neat): 3350, 1245, 1275 cm^{-1}; ^{1}H-NMR: 1.3 (6H, t, $C\underline{H_3}CH_2$), 3.04 (2H, d.t,

18.82 Hz, CH_2CF_2), 4.19 (4H, q, CH_2O), 7.37 (1H, s, OH); ^{19}F-NMR: 111.16 (d.t, 105.19 Hz); ^{31}P-NMR: 4.99(t); (nc) (Found C, 34.3, H, 5.4. $C_7H_{13}O_3F_2P$ requires C, 34.1; H, 5.3).

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