Synthesis and reactions of 3,3-difluoroallylphosphonates and 3,3-difluoroallyltriphenylphosphonium bromide

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Abstract

3,3-Difluoroallyltriphenylphosphonium bromide (**1**) and 3,3-difluoroallylphosphonates, **2**, have been prepared by the reaction of $CH_2=CHCF_2Br$ with phosphites or triphenylphosphine in good yield. Wittig reaction of **1** with aldehydes gave the corresponding dienes ($ArCH=CHCH=CF_2$) **4**; however, Wadsworth–Emmons reaction of **2** with aldehydes failed to produce the dienes.

Introduction

Recently, fluorinated phosphonates have been investigated as analogues of the corresponding biologically active phosphates or phosphonates [1]. For example, Danzin has demonstrated that 9-(5,5-difluoro-5-phosphonopentyl)guanine is 26-times more effective as a purine nucleoside phosphorylase inhibitor than the non-fluorinated analogue [1a]. Additionally, fluorinated phosphonates are useful precursors for introduction of fluorinated groups into organic molecules by the Wadsworth–Emmons reaction [2]. For instance, reaction of the α-fluorobenzylphosphonate carbanion with aldehydes gives olefins of the structure RCH=CFPh [2a]. We report here the preparation of 3,3-difluoroallylphosphonates **2** as part of our continuing development of methodologies for the synthesis of fluorinated phosphonates. Since fluorinated phosphonium salts are well-known precursors for the introduction of fluorinated groups into organic substrates by the Wittig reaction [3], we also prepared 3,3-difluoroallyltriphenylphosphonium bromide (**1**). The Wadsworth–Emmons reaction of **2** and Wittig reaction of **1** with aldehydes have been investigated.

Results and discussion

Seyferth *et al.* [4] have reported the reaction of $CH_2=CHCF_2Li$, generated from $CH_2=CHCF_2Br$ and RLi at low temperature, with carbonyl compounds to give the corresponding homoallylic alcohols $CH_2=CHCF_2CH(OH)R$ (**3**).

$$CH_2=CHCF_2Br \xrightarrow[RCHO]{RLi/-78\ ^\circ C} CH_2=CHCF_2CH(OH)R \quad (3)$$

Recently, we have developed a convenient methodology for the preparation of the homoallylic alcohols **3** by the reaction of $CH_2=CHCF_2Br$ with Zn at room temperature in the presence of carbonyl compounds [5].

$$CH_2=CHCF_2Br \xrightarrow[RCHO]{Zn/THF/RT} \mathbf{3}$$

Nucleophilic attack on $CH_2=CHCF_2Br$ gives the CH_2–Nu product exclusively. For example, treatment of $CH_2=CHCF_2Br$ with $(RO)_2P(O)CF_2Cu$ affords $(RO)_2P(O)CF_2CH_2CH=CF_2$ in 55% yield [6].

$$CH_2=CHCF_2Br \xrightarrow{(EtO)_2P(O)CF_2Cu} (EtO)_2P(O)CF_2CH_2CH=CF_2$$

Phosphines and phosphites were also found to selectively attack $CH_2=CHCF_2Br$ in an S_N2' manner. Thus, reaction of $CH_2=CHCF_2Br$ with triphenylphosphine gave the corresponding phosphonium bromide **1** in 92% yield. Treatment of phosphites with $CH_2=CHCF_2Br$ afforded the corresponding phosphonates **2**. In the case of $(Pr^iO)_3P$, the reaction pro-

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duced 90% of **2b**. When $(EtO)_3P$ was employed, however, the reaction gave a mixture of **2a** and $(EtO)_2P(O)Et$ in a 93:7 ratio. The latter was formed by the reaction of $(EtO)_3P$ and EtBr, which was generated during the preparation of **2a**.

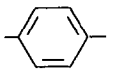
$$CH_2{=}CHCF_2Br \xrightarrow[70\ ^\circ C]{Ph_3P} Ph_3\overset{+}{P}CH_2CH{=}CF_2\ Br^- \quad \textbf{(1)}$$

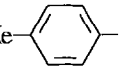
$$CH_2{=}CHCF_2Br \xrightarrow[100\ ^\circ C]{(RO)_3P} (RO)_2P(O)CH_2CH{=}CF_2$$

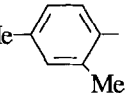
(2a) R = Et
(2b) R = Pr^i

Both **1** and **2** have been investigated as precursors to dienes of the structure $ArCH{=}CHCH{=}CF_2$ (**4**) which have been previously reported in low yield (15–30%) [7, 8]. We found that Wittig reaction of **1** with aromatic aldehydes in DMF or THF at room temperature in the presence of potassium carbonate gave the dienes **4a–d** (ratios of the *Z*- and *E*-isomers were 95:5 to 17:83 as shown in Table 1). The dienes **4a–d** are unstable and were found to decompose in hours or days at room temperature. The reaction carried out in DMF gave higher yields than that in THF. In the presence of potassium carbonate, treatment of **1** with 4-nitrobenzaldehyde in DMF gave the diene **4d** along with 15% (*E*)-4-$NO_2C_6H_4CH{=}CHCH_2CF_2Br$ which was most likely formed by addition of HBr to **4d**. When an aliphatic aldehyde was employed, the reaction did not afford the corresponding diene. Attempted pregeneration of the ylid from **1** failed. Reaction of *in situ* generated ylid from **1** with carbonyl compounds in DMF gave the best results for the preparation of the diene **4** and the results are summarized in Table 1.

$$\mathbf{1} + ArCHO \xrightarrow[RT]{K_2CO_3} ArCH{=}CHCH{=}CF_2 \quad \textbf{(4)}$$

(4a) : Ar = 

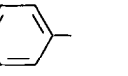
(4b) : Ar = 

(4c) : Ar = 

Yield in THF (%)	Yield in DMF (%)
30	44
—	25
5	20

$$\mathbf{1} + ArCHO \xrightarrow[DMF/RT]{K_2CO_3}$$

$ArCH{=}CHCH{=}CF_2$ (**4d**) 85% + $ArCH{=}CHCH_2CF_2Br$ 15%

Ar = 

In the presence of potassium carbonate, phosphonate **2a** did not react with aldehydes to give the dienes **4** in either THF or DMF. When phosphonate **2a** was treated with BuLi and 4-chlorobenzaldehyde at −78 °C to room temperature, no diene was detected. The anion of the phosphonate **2a** presumably decomposed faster than it is trapped by the aldehyde.

In conclusion, we have demonstrated that the phosphonium salt **1** and phosphonates **2a,b** may be prepared readily by the reaction of $CH_2{=}CHCF_2Br$ with the

TABLE 1. Preparation of $ArCH{=}CHCH{=}CF_2$

Phosphonium bromide or phosphate	Carbonyl compounds	Base	Solvent	Product	
				Yield (%)[a]	*Z/E* Ratio[b]
1	*p*-ClC_6H_4CHO	K_2CO_3	THF	30	**4a**(79:21)
1	*p*-ClC_6H_4CHO	K_2CO_3	DMF	44	**4a**(79:21)
1	*p*-$CH_3C_6H_4CHO$	K_2CO_3	DMF	25	**4b**(83:17)
1	2,4-$Me_2C_6H_3CHO$	K_2CO_3	THF	5	**4c**(95:5)
1	2,4-$Me_2C_6H_3CHO$	K_2CO_3	DMF	20	**4c**(90:10)
1	*p*-$O_2NC_6H_4CHO$	K_2CO_3	DMF	40[c]	**4d**(13:87)
1	$C_7H_{15}CHO$	K_2CO_3	THF	0	
2a	*p*-ClC_6H_4CHO	K_2CO_3	THF	NR[d]	
2a	*p*-ClC_6H_4CHO	K_2CO_3	DMF	NR[d]	
2a	*p*-ClC_6H_4CHO	BuLi	THF	0	

[a]Isolated yield.
[b]Determined by ^1H NMR and ^{19}F NMR spectroscopies.
[c]Contained 15% (*E*)-$NO_2C_6H_4CH{=}CHCH_2CF_2Br$.
[d]NR = no reaction.

corresponding phosphine or phosphites. Wadsworth–Emmons reactions of **2** with aldehydes failed to produce the corresponding diene. However, dienes **4** have been prepared by the Wittig reaction of **1** with aromatic aldehydes at room temperature in the presence of potassium carbonate.

Experimental

All boiling points were determined during distillation and are uncorrected. ^{31}P NMR (36 MHz) spectra were recorded on a JEOL FX 90Q spectrometer; ^{1}H NMR (300 MHz), ^{19}F NMR (282.4 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC 300 spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{1}H NMR and ^{13}C NMR chemical shifts are reported relative to internal TMS. ^{19}F NMR chemical shifts are reported relative to internal $CFCl_3$ and ^{31}P NMR chemical shifts against external H_3PO_4 (85%). ^{13}C NMR and ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. $CDCl_3$ served as the solvent for all NMR spectra. IR spectra were recorded on a Mattson Cygnus 100 FT–IR spectrometer. DMF, THF and K_2CO_3 were obtained from EM SCIENCE. Aldehydes, phosphites and triphenylphosphine were obtained from Aldrich. 3-Bromo-3,3-difluoropropene was obtained from Japan Halon Co. Ltd. All reagents and solvents were used without further purification.

Preparation of 3,3-difluoroallyltriphenylphosphonium bromide (1) (nc)

A mixture of triphenylphosphine (15.8 g, 60 mmol) 3-bromo-3,3-difluoropropene (12 g, 60 mmol) and 15 ml benzene was stirred at 70 °C in a sealed tube for 3 h. After removal of the solvent by reduced pressure distillation, the residue was dissolved in methylene chloride. Ether was added to the methylene chloride solution to precipitate the salts. Filtration gave 23.1 g (92%) of **1**, m.p. 223–225 °C. ^{19}F NMR δ: −80.1 (dd, J=27, 17 Hz, 1F); −83.4 (ddd, J=27, 24, 10 Hz, 1F) ppm. ^{31}P NMR δ: 22.5 (dd, J=16, 12 Hz) ppm. ^{1}H NMR δ: 4.51 (dtd, J=24, 8, 4 Hz, CH=); 4.74 (dd, J=13, 8 Hz, CH_2); 7.73–7.92 (m, Ar) ppm. ^{13}C NMR δ: 20.5 (d, J=54 Hz, PCH_2); 68.2 (ddd, J=32, 22, 9 Hz, CH=); 116.9 (d, J=86 Hz); 130.7 (d, J=12 Hz); 133.8 (d, J=10 Hz); 135.5 (s) 157.7 (td, J=293, 13 Hz) ppm.

Preparation of diethyl 3,3-difluoroallylphosphonate (2a) (nc)

A mixture of triethyl phosphite (8.3 g, 50 mmol) and 3-bromo-3,3-difluoropropene (9.0 g, 57 mmol) was stirred at 90–100 °C in a sealed tube for 2.5 h. ^{31}P NMR analysis revealed that the phosphite was completely converted to the phosphonate product. Distillation of the reaction mixture gave 9.5 g (89%) of **2a** which contained 7% $(EtO)_2P(O)Et$ (based on NMR analysis), b.p. 64–68 °C/2 mmHg. ^{19}F NMR δ: −86.4 (dd, J=39, 15 Hz, 1F); −89.6 (ddd, J=42, 24, 12 Hz, 1F) ppm. ^{31}P NMR δ: 25.9 (dd, J=15, 10 Hz) ppm. ^{1}H NMR δ: 1.34 (t, J=7 Hz, CH_3); 2.47 (dd, J=21, 8 Hz, PCH_2); 4.30 (dtdd, J=24, 8, 8, 1 Hz, CH=); 4.13 (m, CH_2O) ppm. ^{13}C NMR δ: 16.4 (d, J=6 Hz); 20.8 (d, J=142 Hz); 62.3 (d, J=7 Hz); 70.1 (t, J=30 Hz); 157.3 (td, J=287, 16 Hz) ppm. FT–IR (cm^{-1}): 2984 (m); 2870 (w); 1752 (s); 1266 (s); 1055 (s); 1031 (s).

Preparation of diisopropyl 3,3-difluoroallylphosphonate (2b) (nc)

A mixture of triisopropyl phosphite (11.5 g, 55 mmol) and 3-bromo-3,3-difluoropropene (10 g, 64 mmol) was stirred at 100–110 °C in a sealed tube overnight. ^{31}P NMR analysis revealed that the phosphite was completely converted to the phosphonate product. Distillation of the reaction mixture gave 12.0 g (90%) of **2b**, b.p. 73–74 °C/2 mmHg. ^{19}F NMR δ: −86.7 (dd, J=42, 15 Hz, 1F); −89.7 (ddd, J=42, 24, 10 Hz) ppm. ^{31}P NMR δ: 23.9 (dd, J=15, 10 Hz) ppm. ^{1}H NMR δ: 1.33 (dd, J=6, 3 Hz, CH_3); 2.42 (ddt, J=21, 8, 2 Hz, CH_2); 4.29 (dtdd, J=24, 8, 6, 2 Hz, CH=); 4.71 (pd, J=6, 2, Hz, CH_2O) ppm. ^{13}C NMR δ: 21.9 (d, J=148 Hz); 24.0 (m); 70.4 (td, J=19, 10 Hz); 70.9 (d, J=7 Hz); 157.2 (td, J=287, 16 Hz) ppm. FT–IR (cm^{-1}): 2981 (m); 2874 (w); 1752 (s); 1254 (s); 1107 (s); 1008 (s); 989 (s).

Preparation of 4-chloro-1-(4,4-difluoro-1,3-butadienyl)-benzene (4a) in DMF

A mixture of 1.20 g (2.9 mmol) of **1**, 0.38 g (2.7 mmol) of *p*-ClC_6H_4CHO, 0.45 g (3.3 mmol) of K_2CO_3 and 6 ml DMF was stirred at room temperature for 1 h. The mixture was diluted with 100 ml of ether and washed with NH_4Cl (aq.) and water, dried over Na_2SO_4 and concentrated to give a residue which was further purified by silica gel column chromatography with petroleum ether eluent to afford 0.24 g (44%) of **4a** (*Z*/*E*=79:21). *Z*-Isomer: ^{19}F NMR δ: −83.9 (dd, J=22, 2 Hz); −85.4 (d, J=22 Hz) ppm. ^{1}H NMR δ: 5.38 (ddd, J=23, 11, 1 Hz, C*H*=CF_2); 6.17 (ddt, J=11, 11, 1 Hz, C*H*=CHAr); 6.39 (d, J=11 Hz, C*H*Ar); 7.27–7.32 (m, Ar) ppm. *E*-Isomer: ^{19}F NMR δ: −85.2 (dd, J=22 Hz, J=22 Hz); −86.9 (d, J=24 Hz) ppm. ^{1}H NMR δ: 5.11 (ddd, J=24, 11, 1 Hz, C*H*=CF_2); 6.62 (ddt, J=16, 11, 1 Hz, C*H*=CHAr); 6.40 (d, J=16 Hz, C*H*Ar);

7.27–7.32 (m, Ar) ppm. FT–IR (cm^{-1}): 1714 (s); 1320 (m); 1202 (m).

*Preparation of 4-chloro-1-(4,4-difluoro-1,3-butadienyl)-benzene (**4a**) in THF*

A mixture of 0.50 g (1.2 mmol) of **1**, 0.20 g (1.4 mmol) of p-ClC_6H_4CHO, 0.21 g (1.5 mmol) of K_2CO_3 and 5 ml THF was stirred at room temperature overnight. After work-up, column chromatography (petroleum ether as eluent) gave 0.10 g (30%) of **4a** (Z/E = 79:21).

*Preparation of 4-methyl-1-(4,4-difluoro-1,3-butadienyl)-benzene (**4b**) in DMF*

A mixture of 1.30 g (3.0 mmol) of **1**, 0.34 g (2.8 mmol) of p-$CH_3C_6H_4CHO$, 0.45 g (3.3 mmol) of K_2CO_3 and 3 ml DMF was stirred at room temperature for 4.5 h. After work-up, column chromatography with petroleum ether eluent gave 0.13 g (25%) of **4b** (Z/E = 83:17). Z-Isomer: ^{19}F NMR δ: −85.1 (dd, J = 24, 24 Hz, 1F); −86.6 (d, J = 24 Hz, 1F) ppm. ^1H NMR δ: 5.46 (dddd, J = 22, 12, 2, 1 Hz, C*H*=CF_2); 6.09 (tt, J = 12, 1 Hz, C*H*=CHAr); 6.41 (d, J = 12 Hz, C*H*Ar); 7.15 (m, Ar) ppm. ^{13}C NMR δ: 21.2, 79.5 (dd, J = 27, 16 Hz); 117.9 (m); 128.6, 129.2, 129.9 (dd, J = 11, 4 Hz); 134.1, 137.2, 157.9 (dd, J = 298, 291 Hz) ppm. E-Isomer: ^{19}F NMR δ: −86.4 (dd, J = 28, 26 Hz); −88.2 (d, J = 28 Hz) ppm. ^1H NMR δ: 5.08 (ddd, J = 24, 11, 2 Hz, C*H*=CF_2); 6.59 (ddt, J = 16, 11, 1 Hz, C*H*=CHAr); 6.40 (d, J = 16 Hz, C*H*Ar); 7.27–7.32 (m, Ar) ppm. ^{13}C NMR δ: 21.2, 83.0 (dd, J = 28, 17 Hz); 116.9 (m); 126.2, 129.4, 131.2 (dd, J = 11, 3 Hz); 134.3, 137.6, 156.8 (dd, J = 296, 290 Hz) ppm. FT–IR (cm^{-1}): 2957 (m); 1710 (s); 1318 (s); 1200 (s).

*Preparation of 2,4-dimethyl-1-(4,4-difluoro-1,3-butadienyl)benzene (**4c**) in THF*

A mixture of 4.2 g (10 mmol) of **1**, 1.70 g (13 mmol) of 2,4-$(CH_3)_2C_6H_3CHO$, 1.7 g (12 mmol) of K_2CO_3 and 40 ml THF was stirred at room temperature overnight, then stirred at 55 °C overnight. After work-up, column chromatography with petroleum ether as eluent gave 100 mg (5%) of **4c** (Z/E = 95:5).

*Preparation of 2,4-dimethyl-1-(4,4-difluoro-1,3-butadienyl)benzene (**4c**) in DMF*

A mixture of 1.30 g (3.0 mmol) of **1** 0.27 g (2.3 mmol) of 2,4-$(CH_3)_2C_6H_3CHO$, 0.45 g (3.3 mmol) of K_2CO_3 and 3 ml DMF was stirred at room temperature overnight. After work-up, column chromatography with petroleum ether as eluent gave 80 mg (20%) of **4c** (Z/E = 90:10). Z-Isomer: ^{19}F NMR δ: −85.5 (dd, J = 25, 25 Hz); −86.8 (d, J = 25 Hz) ppm. ^1H NMR δ: 2.22 (s, 3H); 2.31 (s, 3H); 5.24 (ddd, J = 25, 11, 1 Hz, CH=CF_2); 6.18 (dd, J = 11, 11 Hz, C*H*=CHAr); 6.46 (d, J = 11 Hz, C*H*Ar); 6.97–7.10 (m, Ar) ppm. ^{13}C NMR δ: 19.8, 21.2, 89.4 (dd, J = 28, 16 Hz); 118.5 (m); 126.3, 128.9, 129.0 (m); 131.0, 132.9, 136.3, 137.3, 157.6 (dd, J = 297, 291 Hz) ppm. FT–IR (cm^{-1}): 2956 (m); 1714 (s); 1316 (s); 1197 (s). E-Isomer: ^{19}F NMR δ: −86.4 (dd, J = 27, 25 Hz); −88.3 (d, J = 26 Hz) ppm. ^1H NMR δ: 2.22 (s, 3H); 2.31 (s, 3H); 5.08 (ddd, J = 24, 11, 2 Hz, C*H*=CF_2); 6.59 (dd, J = 16, 11 Hz, C*H*=CHAr); 6.40 (d, J = 16 Hz, C*H*Ar); 6.97–7.10 (m, Ar) ppm.

*Preparation of 4-nitro-1-(4,4-difluoro-1,3-butadienyl)-benzene (**4d**) in DMF*

A mixture of 1.30 g (3.0 mmol) of **1**, 0.40 g (2.6 mmol) of p-$O_2NC_6H_4CHO$, 0.46 g (3.3 mmol) of K_2CO_3 and 5 ml DMF was stirred at room temperature for 1 h. After work-up, column chromatography with hexane/methylene chloride (5:1) as eluent gave 0.22 g (40%) of products, which contained 74% (E)-**4d**, 11% (Z)-(**4d**) and 15% (E)-$O_2NC_6H_4CH$=$CHCH_2CF_2Br$. Z-Isomer: ^{19}F NMR δ: −81.8 (dd, J = 22, 16 Hz); −86.6 (d, J = 15 Hz) ppm. ^1H NMR δ: 5.42 (ddd, J = 23, 12, 1 Hz, CH=CF_2); 6.34 (t, J = 12 Hz, C*H*=CHAr); 6.48 (d, J = 11 Hz, C*H*Ar); 7.49 and 8.16 (m, Ar) ppm. E-Isomer: ^{19}F NMR δ: −82.8 (dd, J = 22, 19 Hz); −84.0 (d, J = 18 Hz) ppm. ^1H NMR δ: 5.21 (ddd, J = 23, 12, 1 Hz, C*H*=CF_2); 6.84 (dd, J = 16, 11 Hz, C*H*=CHAr); 6.53 (d, J = 16 Hz, C*H*Ar); 7.49–8.16 (m, Ar) ppm. (E)-$O_2NC_6H_4CH$=$CHCH_2CF_2Br$: ^{19}F NMR δ: −66.3 (t, J = 10 Hz) ppm. ^1H NMR δ: 3.07 (m, CH_2); 6.31 (dt, J = 16, 7 Hz); 6.70 (d, J = 16 Hz); 7.49 and 8.16 (m, Ar).

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