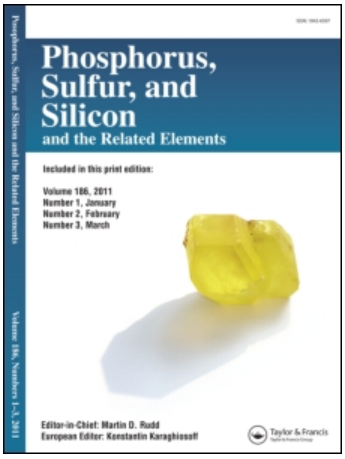

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PREPARATION AND SYNTHETIC APPLICATION OF DIETHYL 2-OXO-1,1-DIFLUOROPHOSPHONATES

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PREPARATION AND SYNTHETIC APPLICATION OF DIETHYL 2-OXO-1,1-DIFLUOROPHOSPHONATES

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Reaction of diethyl(bromodifluoromethyl)phosphonate $(EtO)_2P(O)CF_2Br$ **1** with activated zinc gave [(diethoxyphosphonyl)difluoromethyl]zinc bromide $(EtO)_2P(O)CF_2ZnBr$ **2**, which was acylated with various acylating agents to afford diethyl 2-oxo-1,1-difluorophosphonates $(EtO)_2P(O)CF_2C(O)R$ **4** in good yields. Treatment of phosphonates **4** such as diethyl 2-oxo-1,1-difluoropropylphosphonate $(EtO)_2P(O)CF_2C(O)CH_3$ **4a**, ethyl difluoro(diethoxyphosphonyl)pyruvate $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4e** and N,N-diethyldifluoro(diethoxyphosphonyl)acetamide $(EtO)_2P(O)CF_2C(O)NEt_2$ **4h** with Grignard reagents R'MgX provided 1,1-difluoroolefins $R'(CH_3)C=CF_2$, $R'(CO_2Et)C=CF_2$ and $R'(NEt_2)C=CF_2$, respectively.

Keywords: Difluorophosphonate; zinc agent; acylation; cosolvent; Grignard agents; Wittig-Horner reaction

INTRODUCTION

1,1-Difluoroolefins constitute a class of fluoroorganic molecules with interesting chemical[1] and biological[2] properties. They can readily undergo free radical addition reactions[3] and be reduced to vinyl fluorides.[4] 1,1-Difluoroolefins are also potential mechanism-based enzyme inhibitors[5] and can be used as isosteric replacements for a carbonyl group.[6] The main synthetic methods currently available for the preparation of 1,1-difluoroolefins are based on the reaction of aldehydes with triphenylphosphine and sodium chlorodifluoroacetate in diglyme.[7] Reaction between non-stabilized alkylidenetriphenylphosphoranes and chlorodifluoromethane has been found to be a useful alternative to the Wittig reaction for the synthesis of difluoromethylene olefins.[8] Debromination of bromodifluoro-

methylphosphonium bromides by group IIB metals such as cadmium, zinc or mercury in the presence of aldehydes and fluorinated aldehydes provides difluoromethylene olefins.[9] Reaction of difluoromethyldiphenylphosphine oxide with ketones and aldehydes also gave 1,1-difluoroolefins.[10] The successful preparation of unsymmetrical and symmetrical tetrasubstituted α-fluoro-α,β-esters,[11] α-fluoro-α,β-unsaturated diesters[12,13] and phenyl substituted fluoroolefins[14] via a Wittig-Horner reaction in our group led us to examine the generality of this method for the preparation of 1,1-difluoroolefins. Meanwhile, the reaction of [(diethoxyphosphonyl)difluoromethyl]zinc bromide $(EtO)_2P(O)CF_2ZnBr$ **2**, prepared from diethyl(bromodifluoromethyl)phosphonate $(EtO)_2P(O)CF_2Br$ **1** and activated zinc, with various acylating agents to afford diethyl 2-oxo-1,1-difluorophosphonates $(EtO)_2P(O)CF_2C(O)R$ **4** has been focused in our laboratory.[15,16] Herein, we further describe the preparation of diethyl 2-oxo-1,1-difluorophosphonates and the synthetic application to 1,1-difluoroolefins $R'RC{=}CF_2$ **9** via a Wittig-Horner reaction.

RESULTS AND DISCUSSION

The Michaelis-Arbuzov reaction of triethylphosphite with dibromodifluoromethane in diethyl ether at room temperature gave diethyl(bromodifluoromethyl)phosphonate **1** in good yield (Equation (1)).[17,18] Diethyl(bromodifluoromethyl)phosphonate can serve as a convenient precursor for the one-step preparation of stabilized transition metal complexes.[16,19] Treatment of diethyl(bromodifluoromethyl)phosphonate **1** with acid washed zinc powder at room temperature in monoglyme afforded [(diethoxyphosphonyl)difluoromethyl]zinc bromide $(EtO)_2P(O)CF_2ZnBr$ **2** and small amounts (<5%) of the reduced diethyl (difluoromethyl)phosphonate **3** (Equation (2)). [(Diethoxyphosphonyl)difluoromethyl]zinc bromide **2** was obtained as a colorless, clear solution and could be stored at room temperature for a period of months without significant decomposition. Conversion of [(diethoxyphosphonyl)difluoromethyl]zinc bromide **2** to diethyl (difluoromethyl)phosphonate **3** was also observed and isolated in the progress of hydrolysis of **2** in water.

$$(C_2H_5O)_3P + CF_2Br_2 \xrightarrow{Et_2O,\ RT} (C_2H_5O)_2P(O)CF_2Br \qquad (1)$$

1

$$(EtO)_2P(O)CF_2Br \xrightarrow[RT]{Zn\ (0),\ MG} (EtO)_2P(O)CF_2ZnBr + (EtO)_2P(O)CF_2H \qquad (2)$$

1 2 3

As a result of its thermal stability, **2** is readily reactive toward acylating reagents to yield the corresponding diethyl 2-oxo-1,1-difluorophosphonates $(EtO)_2P(O)CF_2C(O)R$ **4** (Equation (3)).

$$(EtO)_2P(O)CF_2ZnBr + ClC(O)R \xrightarrow[CuBr,\ CH_3CN]{MG\ or\ TG,\ RT} (EtO)_2P(O)CF_2C(O)R \qquad (3)$$

2 4

The results of the preparation of **4** from the reaction of [(diethoxyphosphonyl)difluoromethyl]zinc bromide $(EtO)_2P(O)CF_2ZnBr$ **2** with the corresponding acylating reagents are summarized in Table I.

Addition of freshly distilled acetyl chloride to a MG or TG solution of **2** at room temperature gave 55% and 53% isolated yields of diethyl-2-oxo-1,1-difluoropropylphosphonate **4a**, **4b**, respectively. A similar procedure is applied for the preparation of $(EtO)_2P(O)CF_2C(O)CF_3$ **4c** in 64% ^{19}F NMR yield. The direct synthesis of ethyl difluoro(diethoxyphosphonyl)pyruvate $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4d** from the organozinc reagent **2** and freshly distilled ethyl oxalyl chloride $ClC(O)CO_2Et$ at 0°C was carried out for 48 hours to give 54% isolated yield. However, this situation can be easily ameliorated upon addition of a

TABLE I Preparation of $(EtO)_2P(O)CF_2C(O)R$

$$(EtO)_2P(O)CF_2ZnBr + ClC(O)R \xrightarrow[CuBr,\ CH_3CN]{MG\ or\ TG,\ RT} (EtO)_2P(O)CF_2C(O)R$$

2 4

No.	*R*	*Solvent*	*Cosolvent*	*CuBr (mole %)*	*Time (hours)*	*Isolated yields (%)*
4a	CH_3	MG	—	—	20	55
4b	CH_3	TG	—	—	20	53
4c	CF_3	TG	—	—	20	64[a]
4d	CO_2Et	MG	—	—	48(0°C)	54
4e	CO_2Et	65% MG	35% CH_3CN	1.5	0.5	58
4f	CO_2Et	MG	—	1.5	24	42[a,b]
4g	CO_2Me	65% MG	35% CH_3CN	1.5	0.5	60
4h	NEt_2	65% MG	35% CH_3CN	50	0.5	52
4i	OEt	65% MG	35% CH_3CN	25	0.5	53

[a] ^{19}F NMR yields, $C_6H_5CF_3$ as internal standard. [b] $(EtO)_2P(O)CF{=}CFP(O)(OEt)_2$ and $(EtO)_2P(O)F$ were observed.

catalytic amount (1.5%) of cuprous bromide[20] and 35% acetonitrile as cosolvent to the reaction mixture. The reaction is completed within a half hour to yield $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4e** in 58% isolated yield.

On the other hand, if the reaction is carried out in the presence of 1.5% cuprous bromide without the cosolvent acetonitrile, in addition to the formation of 42% of $(EtO)_2P(O)CF_2C(O)CO_2Et$, a 28% yield of a mixture of isomeric by products (E) and (Z)-(1,2-difluoroethylenediyl)bisphosphonate $(EtO)_2P(O)CF{=}CFP(O)(OEt)_2$ **5** and 30% of the toxic diethyl fluorophosphate $(EtO)_2P(O)F$ **6** are observed in ^{19}F NMR spectrum (Equation (4)). The ^{19}F NMR spectrum of $(EtO)_2P(O)CF{=}CFP(O)(OEt)_2$ **5** was identical to the authentic sample[21] and $(EtO)_2P(O)F$ **6** exhibited a doublet at −82 ppm ($J_{P\text{-}F}$ = 969 Hz, lit.[22] $J_{P\text{-}F}$ = 972 Hz).

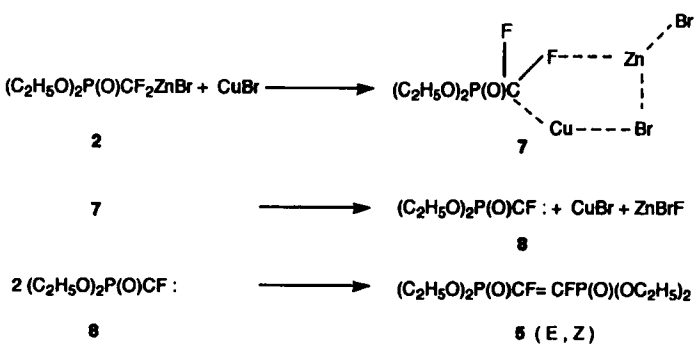
$$(EtO)_2P(O)CF_2ZnBr + ClC(O)CO_2Et \xrightarrow[RT,\ 24\ h]{MG,\ CuBr} (EtO)_2P(O)CF_2C(O)CO_2Et + (EtO)_2P(O)F$$

2 **4f** **6**

$$+\ (EtO)_2P(O)CF{=}CFP(O)(OEt)_2 \qquad (4)$$

5 (E, Z)

The most likely mechanism for the formation of **5** is via the formation of the intermediate [(diethoxyphosphonyl)difluoromethyl]copper complex **7**. Conversion of **7** to **5** could occur via dimerization of fluoro(diethoxyphosphonyl)carbene **8** or its copper carbenoid intermediate (Scheme I). Diethyl fluorophosphate



SCHEME I

$(EtO)_2P(O)F$ **6** was formed from the nucleophilic attack of free fluoride ion on the phosphorus atom of the phosphonate. The cuprous bromide CuBr catalyzed reactions of $(EtO)_2P(O)CF_2ZnBr$ **2** with acyl halides are generally conducted in the presence of acetonitrile as a coordinating cosolvent. Acetonitrile stabilized

the copper complex **7** to prevent the formation of fluoro(diethoxyphosphonyl)-carbene **8** which led to the product of (1,2-difluoroethylenediyl)bisphosphonate $(EtO)_2P(O)CF{=}CFP(O)(OEt)_2$ **5**.

Addition of ethyl oxalyl chloride into a MG solution of [(diethoxyphosphonyl)difluoromethyl]zinc bromide **2**, cuprous bromide and acetonitrile gave ethyl difluoro(diethoxyphosphonyl)pyruvate **4e**. The reaction mixture solution exhibited a doublet at −115 ppm (J = 95 Hz) in the ^{19}F NMR spectrum and a triplet at 4.5 ppm (J = 95 Hz) in the ^{31}P NMR spectrum. The mixture was filtered through a medium fritted glass Büchner funnel under aspirator pressure and the filtrate was poured into water and extracted with CH_2Cl_2. The organic portions were dried over anhydrous $MgSO_4$, decanted, concentrated by rotary evaporation to yield a residue. However, this work-up residue showed a doublet at −120 ppm (J = 95 Hz) in the ^{19}F NMR spectrum and a triplet at 2.2 ppm (J = 95 Hz) in the ^{31}P NMR spectrum. The change of the signals in ^{19}F NMR and ^{31}P NMR spectra indicated that the residue existed of the hydrated form of **4e**. Distillation of the work-up residue through a 10-cm Vigreaux column gave pure **4e** which exhibited a doublet at −115 ppm (J = 95 Hz) in ^{19}F NMR spectrum and a triplet at 4.5 ppm (J = 95 Hz) in ^{31}P NMR spectrum. To confirm the change from the anhydrate form $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4e** to its hydrate form during the work-up procedure, a drop of H_2O was added to a NMR tube in which an isolated $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4e** was contained. The hydrate reaction mixture solution in this NMR tube exhibited the same chemical shifts as the work-up residue in the ^{19}F NMR and ^{31}P NMR spectra. The results indicated that the carbonyl group in $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4e** was easily hydrated in the presence of water. Similarly, in the presence of cuprous bromide and 35% acetonitrile as cosolvent in the reaction mixture, methyl difluoro(diethoxyphosphonyl)pyruvate $(EtO)_2P(O)CF_2C(O)CO_2Me$ **4g**, N,N-diethyl-difluoro(diethoxyphosphonyl)acetamide $(EtO)_2P(O)CF_2C(O)CO_2NEt_2$ **4h** and ethyl(diethoxyphosphonyl)difluoroacetate $(EtO)_2P(O)CF_2C(O)OEt$ **4i** were prepared in 60%, 52% and 53% isolated yields when methyl oxalyl chloride, diethyl carbamoyl chloride and ethyl chloroformate were used as substrates, respectively.

Synthetic applications of diethyl 2-oxo-1,1-difluorophosphonates $(EtO)_2P(O)CF_2C(O)R$ **4** for the preparation of 1,1-difluoroolefins $R'RC = CF_2$ **9** has also been developed in our laboratory. Treatment of diethyl 2-oxo-1,1-difluoropropylphosphonate $(EtO)_2P(O)CF_2C(O)CH_3$ **4a**, ethyl difluoro(diethoxyphosphonyl)pyruvate $(EtO)_2P(O)CF_2C(O)CO_2Et$ **4e** or N,N-diethyl difluoro(diethoxyphosphonyl)acetamide $(EtO)_2P(O)CF_2C(O)NEt_2$ **4h** with Grignard reagents produces fluorinated olefins, acrylates and enamines (Equation (5)).

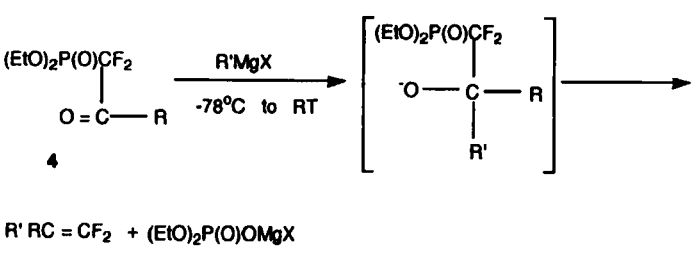
$$(EtO)_2P(O)CF_2C(O)R + R'MgX \xrightarrow[-78^\circ C \text{ to RT}]{THF \text{ or } Et_2O} R'RC=CF_2 \qquad (5)$$

4 9

The mechanism for the formation of difluoroolefins is showed in Scheme II. The initial step in the synthesis of difluoroolefins is the nucleophilic attack of the Grignard reagent R'MgX at the carbonyl carbon of the 2-oxo-1,1-difluorophosphonates to form a betaine type intermediate which is followed by intramolecular elimination of diethylphosphate.[23]

Results for the transformation of 2-oxo-1,1-difluorophosphonates to 1,1-difluoroolefins are given in Table II.

The compounds of the type $R'RC=CF_2$ **9** ($R=CH_3$, CO_2Et or NEt_2) are characterized by the ^{19}F NMR and GC-MS spectra. Table III lists the ^{19}F NMR of the prepared difluoroolefins $R'RC=CF_2$. Difluoroolefin $(C_2H_5)(CH_3)C=CF_2$ **9a** was prepared in 48% ^{19}F NMR yield from the reaction of diethyl 2-oxo-1,1-difluoropropylphosphonate $(EtO)_2P(O)CF_2C(O)CH_3$ **4a** with ethylmagnesium bromide. The ^{19}F NMR spectrum exhibited two doublets at -117.2 ppm (d, J = 41 Hz) and -118.4 ppm (d, J = 41 Hz). In addition, difluoro-α,β-unsaturated esters $R'(CO_2Et)C=CF_2$ or difluoroenamines $R'(NEt_2)C=CF_2$ were prepared via intramolecular Horner-Wadsworth-Emmons reaction. Thus, treatment of ethyl difluoro(diethoxyphosphonyl)pyruvate **4e** or N,N-diethyldifluoro(diethoxyphosphonyl)acetamide **4h** with Grignard reagents (R'MgX) at $-78°C$ gave 40–58% ^{19}F NMR yields of the difluoroolefins. Molecular ions for difluoroenamines **9c**, **9d** and **9e** were observed and the fragmantations pattern were also consistent with the structure formulations.



4 9

SCHEME II

TABLE II Preparation of R'RC = CF_2

$$(EtO)_2P(O)CF_2C(O)R + R'MgX \xrightarrow[-78°C \text{ to RT}]{THF \text{ or } Et_2O} R'RC = CF_2$$

	4			9
No.	*R*	*R'*	*X*	*yields (%)*[a]
9a	CH_3	C_2H_5	Br	48
9b	CO_2Et	n-C_3H_7	Cl	58
9c	NEt_2	C_2H_5	Br	50[b]
9d	NEt_2	n-C_3H_7	Cl	52[b]
9e	NEt_2	i-C_3H_7	Cl	55[b]
9f	NEt_2	CH_2=CH	Cl	40
9g	NEt_2	C_6H_{11}	Cl	42

[a] ^{19}F NMR yields, $C_6H_5CF_3$ as an internal standard. [b]Molecular ions were observed in the GC-MS spectrum.

In conclusion, 2-oxo-1,1-difluorophosphonates $(EtO)_2P(O)CF_2C(O)R$ were prepared in good yields by treatment of [(diethoxyphosphnyl)difluoromethyl]zinc bromide $(EtO)_2P(O)CF_2ZnBr$ with the appropriate acylating reagents. Synthetic application of 2-oxo-1,1-difluorophosphonates to 1,1-difluoroolefins R'RC=CF_2 was achieved from the reaction of phosphonates with Grignard reagents.

TABLE III ^{19}F NMR data of R'RC = CF_2

No.	*Compound*	*Chemical Shift* [a]*(ppm)*	*Coupling Constant (Hz)*	*Solvent*
9a	$(C_2H_5)(CH_3)C=CF_2$	−117.2 (d) −118.4 (d)	$J_{F,F}$ = 41	THF
9b	(n-C_3H_7)(CO_2Et)C=CF_2	−116.2 (d) −116.5 (d)	$J_{F,F}$ = 9.8	THF
9c	$(C_2H_5)(NEt_2)C=CF_2$	−98.0 (d) −104.0 (d)	$J_{F,F}$ = 61	Et_2O
9d	(n-C_3H_7)(NEt_2)C=CF_2	−98.0 (d) −104.0 (d)	$J_{F,F}$ = 63	THF
9e	(i-C_3H_7)(NEt_2)C=CF_2	−95.0 (d) −100.0 (d)	$J_{F,F}$ = 61	THF
9f	(CH_2 = CH)(NEt_2)C=CF_2	−93.0 (d) −97.0 (d)	$J_{F,F}$ = 37	THF
9g	$(C_6H_{11})(NEt_2)C=CF_2$	−94.0 (d) −99.0 (d)	$J_{F,F}$ = 59	THF

[a]Chemical shifts are relative to $CFCl_3$ as external standard.

EXPERIMENTAL

^{31}P NMR spectrum were recorded on a 90-MHz multinuclear spectrometer and are referenced against external 85% H_3PO_4. ^{13}C, ^{1}H and ^{19}F NMR spectra were recorded on a Bruker WM360X spectrometer and are referenced against internal $(CH_3)_4Si$ and $CFCl_3$. FTIR spectra were recorded on a Mattson Cygnus 100 FTIR spectrophotometer. All the mass spectral analyses were performed at 70 eV in the electron-impact mode on a single quadrapole instrument interfaced to a gas chromatograph fitted with a OV-101 column. The Schlenk funnel constructed with a medium pore glass frit was used for the filtration of zinc and air-sensitive materials. Monoglyme (MG), triglyme (TG) and acetonitrile were dried by distillation from CaH_2. Triethyl phosphite were distilled from sodium metal at reduced pressure. Acetyl chloride $CH_3C(O)Cl$, methyl oxalyl chloride $ClC(O)CO_2CH_3$, ethyl oxalyl chloride $ClC(O)CO_2C_2H_5$, diethyl carbamoyl chloride $ClC(O)NEt_2$ and ethyl chloroformate $ClC(O)OC_2H_5$ were distilled prior to use. Normality of Grignard reagents (C_2H_5MgBr, n-C_3H_7MgCl, i-C_3H_7MgCl, $C_6H_{11}MgCl$, and CH_2=CHMgX) were determined by the method of Bergbreiter.[24] Tetrahydrofuran was distilled from sodium benzophenone ketyl at atmospheric pressure prior to use.

Activation of Zn

Zinc metal was activated[20] by treatment of 90 g of zinc powder in 450 mL acetone with conc. HCl (approx. 10 mL) dropwise until the zinc began to settle to the bottom of the beaker. The slurry was then stirred for 10 minutes, 300 mL of water were added and the mixture was stirred for an additional 10 minutes. The zinc was allowed to settle and the supernatant decanted. The zinc metal was filtered through a coarse Schlenk funnel, washed with water (6 × 100 mL) and finally with acetone (4 × 100 mL). The activated zinc was dried at 110°C under full vacuum overnight.

Activation of CuBr

Cuprous bromide was purified[25] by treatment of a mixture of 100 g cuprous bromide and 40 mL of water with 100 mL 48% HBr. After all the cuprous bromide had been dissolved, one liter of water was added to the dark purple solution. The cuprous bromide was precipitated as a light green slurry. The solid was filtered through a Büchner funnel and washed with one liter of water, and if the solid became slightly orange it was washed with 10 mL of 10% aqueous

HBr. The cuprous bromide was then washed with (3 × 100 mL) acetone and (3 × 100 mL) dry ether. The light green-gray powder was transferred to a flask and dried overnight under full vacuum.

Preparation of Diethyl Bromodifluoromethane Phosphonate $(EtO)_2P(O)CF_2Br$ (1)

A 100 mL three-necked flask equipped with a septum port, a Teflon-coated magnetic stirring bar, and a reflux water condenser topped with a nitrogen tee tube leading to a source of nitrogen and mineral oil bubbler was charged sequentially with 300 mL of dry diethyl ether and 0.6 mol (99.0 g) of triethyl phosphite. The contents of the flask were cooled to 0°C via an ice bath. To the cooled solution, 0.64 mol (134 g) of dibromodifluoromethane (CF_2Br_2) was added dropwise via a syringe. The contents of the flask were refluxed for 24 hours, followed by removal of the ether, excess dibromodifluoromethane and ethyl bromide via rotary evaporation at reduced pressure. The resultant clear liquid was then distilled under vacuum through a 6'' vigreaux column at 67–69°C and 2.4 mmHg to yield 156 g (96%) of the titled compound. GLPC purity: 98%; ^{19}F NMR: − 62.0 (d, J_{FCP} = 90.3); ^{31}P NMR: − 0.78 (t, J_{PCF} = 90.3); ^{1}H NMR: 4.42 (q, 4H, J = 7.1), 1.42 (t, 6H, J = 7.1); GC-MS m/z (relative intensity): 268(M^+ + 1, 0.02), 267(M^+, 0.53), 187(M^+-Br, 7.51), 137(M^+-CF_2Br, 90.99), 81(100.00); FTIR spectrum (CCl_4 solution, cm^{-1}): 2996 (m), 2985 (m), 2360 (m), 1652 (m), 1539 (m), 1456 (m), 1287 (m).

Preparation of [(Diethoxyphosphonyl)difluoromethyl] Zinc Bromide $(EtO)_2P(O)CF_2ZnBr$ (2)

A solution of 500 mL dry monoglyme and 1.0 mol (65.4 g) of acid washed zinc powder was placed in a 2L three-necked flask under N_2, then 1.0 mol (267.0 g) of diethyl(bromodifluoromethyl)phosphonate was added dropwise via an addition funnel in order to avoid a vigorous exothermic reaction. After stirring for 2 days at room temperature, the solution was filtered through a Schlenk funnel to remove any excess of zinc powder, leaving $(EtO)_2P(O)CF_2ZnBr$. ^{19}F NMR (MG): − 126.1 (broad d, J_{FCP} = 93); ^{31}P NMR (MG): 13.3 (t, J_{PCF} = 93).

Diethyl (difluoromethyl)phosphonate $(EtO)_2P(O)CF_2H$ (3)

bp 72–74°C/4.2 mmHg; ^{19}F NMR: −135.8 (d,d, J_{FCP} = 90, J_{FCH} = 49); ^{31}P NMR: 5.77 (t, J_{PCF} = 90); ^{1}H NMR: 6.01 (t,d, 1H, J_{HCF} = 49, J_{HCP} = 27),

4.25 (d,q, 4H, J_{HCOP} = 8.3, J = 7.1), 1.38 (t, 6H, J = 7.1). ^{13}C NMR: 117.0 (t,d, J_{CF} = 256, J_{CP} = 213), 64.8 (s), 64.7 (s), 16.5 (s), 16.4 (s); GC-MS m/z (relative intensity): 173(M^+-CH_3, 0.04), 159(M^+-C_2H_5, 0.23), 137(M^+-CF_2H, 3.52), 109(M^+-CF_2H-CH_2=CH_2, 20.6), 81(M^+-CF_2H-2CH_2=CH_2, 43.4), 51(M^+-$(EtO)_2P(O)$, 10.16); FTIR spectrum (CCl_4 solution, cm^{-1}): 2985(m), 2960(m), 2944(m, C-H), 1376(m), 1371(m, C-F), 1220(m, P=O), 1070(m), 1064(m, P-O-C).

General Procedure for Preparation of $(EtO)_2P(O)CF_2C(O)R$ 4 as Described for the Preparation of Ethyl Difluoro(diethoxyphosphonyl)-pyruvate $(EtO)_2P(O)CF_2C(O)CO_2Et$ (4e)

A 250 mL three-necked flask equipped with a septum port, a glass stopper, a Teflon-coated magnetic stirbar, and a reflux water condenser topped with a nitrogen tee tube leading to a source of nitrogen and mineral oil bubbler was charged sequentially with 25.0 mL of a 2.0 M monoglyme (MG) solution of $(EtO)_2P(O)CF_2ZnBr$. To this solution was added 12.5 mL of dry CH_3CN and CuBr (0.75 mmols, 0.11 g). Ethyl oxalyl chloride (70.0 mmols, 6.8 mL) was then added dropwise and the mixture stirred at room temperature for 0.5 hour. The mixture was then filtered through a medium fritted glass Büchner funnel under aspirator pressure, the filtrate was poured into 100 mL of water and extracted twice with 50 mL of CH_2Cl_2. The organic portions were dried over anhydrous $MgSO_4$, filtered, concentrated by rotary evaporation, and vacuum distilled through a 10-cm vigreaux column at 94–95°C and 0.15 mmHg to give 8.4 g (58%) of the titled compound. GLPC purity: 99%; ^1H NMR: 4.30 (q, 6H, J = 7.1), 1.40 (t, 9H, J = 7.1); ^{13}C NMR: 181.8 (t, d, J_{CCF} = 24, J_{CCP} = 16), 158.5 (s), 115.5 (t, d, J_{CF} = 275, J_{CP} = 199), 65.8 (s), 65.7 (s), 63.5 (s), 16.3 (s), 16.2 (s), 13.9 (s); ^{19}F NMR: −115 (d, J_{FCP} = 95). ^{31}P NMR: 4.5 (t, J_{PCF} = 95); GC-MS m/z (relative intensity): 291(M^+ + 3, 0.02), 290(M^+ + 2, 0.08), 289(M^+ + 1, 1.25), 132(100.00); FTIR spectrum (CCl_4 solution, cm^{-1}): 2986(m), 2933(m, C-H), 1759(s), 1745(s, C=O), 1281(m), 1277(w), 1251(w, P=O), 1164(s), 1097(s, C-F), 1088(m, C-O-C).

Diethyl-2-oxo-1,1-difluoropropyl Phosphonate $(EtO)_2P(O)CF_2C(O)Me$ (4a)

Yield: 55%; GLPC purity: 99%; bp 92–94°C/4.4 mmHg; ^1H NMR: 4.32 (q, 4H, J = 7.1), 2.44 (s, 3H), 1.39 (t, 6H, J = 7.1); ^{13}C NMR: 196.4 (t,d, J_{CCF} = 24, J_{CCP} = 15), 113.3 (t,d, J_{CF} = 272, J_{CP} = 197), 65.4 (s), 65.3 (s), 25.3 (s), 16.3 (s), 16.2 (s); ^{19}F NMR: −119 (d, J_{FCP} = 97); ^{31}P NMR: 3.8 (t, J_{PCF} = 97);

GC-MS m/z (relative intensity): 203(M^+-CH_2=CH_2 + H, 0.05), 188(M^+-CO_2Me + H, 12.66), 160(188-CH_2=CH_2, 9.78), 132(188-2CH_2=CH_2, 100), 137(M^+-CF_2COMe, 2.44), 93(M^+-$(EtO)_2P(O)$, 14.02); FTIR spectrum (CCl_4 solution, cm^{-1}): 2985(m), 2915(m, C-H), 2870(m), 1746(s, C=O), 1443(m), 1278(m, P=O), 1240(m), 1100(s, C-F), 1051(m, C-O-C).

Diethyl-2-oxo-1,1-difluoro-3,3,3-trifluoro propylphosphonate $(EtO)_2P(O)CF_2C(O)CF_3$ (4c)

^{19}F NMR yield: 64%; ^{19}F NMR (THF): −116.9 (d, q, J_{FCP} = 93, J_{FCCCF} = 7.3), −75.3 (t,d, J_{FCCCF} = 7.3, J_{FCCCP} = 4.7); ^{31}P NMR (THF): 0.53 (t, J_{PCF} = 93).

Methyl difluoro(diethoxyphosphonyl)pyruvate $(EtO)_2P(O)CF_2C(O)CO_2Me$ (4g)

Yield: 60%; GLPC purity: 98%; bp 94–96°C/0.25 mmHg; ^1H NMR: 4.35 (q, 4H, J = 7.1), 3.95 (s, 3H), 1.40 (t, 6H, J = 7.1); ^{13}C NMR: 181.5 (t, d, J_{CCF} = 24, J_{CCP} = 15), 158.2 (s), 115.6 (t, d, J_{CF} = 275, J_{CP} = 199), 65.5 (s), 65.4 (s), 53.6 (s), 16.3 (s), 16.2 (s); ^{19}F NMR: −115.1 (d, J_{FCP} = 95); ^{31}P NMR: 2.1 (t, J_{PCF} = 95); GC-MS m/e (relative intensity): 275(M^+ + 1, 0.94), 274(M^+, 1.00), 246(M^+-CH_2=CH_2, 16.67), 229(M^+-OEt, 21.63), 215(M^+-CO_2Me, 0.82), 198(43.25), 175(43.45), 147(45.83), 146(100.00), 109(63.49), 96(53.17), 81(62.70); FTIR spectrum (CCl_4 solution, cm^{-1}): 2985(m), 2933(m), 2915(m, C-H), 1742(s, C=O), 1444(m), 1370(m), 1251(m, P=O), 1151(s), 1096(s, C-F), 1082(m, C-O-C).

N,N-diethyldifluoro(diethoxyphosphonyl)acetamide $(EtO)_2P(O)CF_2C(O)NEt_2$ (4h)

Yield: 52%; GLPC purity: 99%; bp 98–101°C/0.20 mmHg; ^1H NMR: 4.32–4.28 (m, 4H), 3.48–3.45 (m, 4H), 1.36–1.32 (m, 12H); ^{13}C NMR: 160.8(t, d, J_{CCF} = 17, J_{CCP} = 15), 114.5 (t, d, J_{CF} = 211, J_{CP} = 130), 65.3 (s), 65.2 (s), 41.8 (s), 16.3 (s), 16.2 (s), 14.3 (s); ^{19}F NMR: −109 (d, J_{FCP} = 95); ^{31}P NMR: 4.1 (t, J_{PCF} = 95); GC-MS m/z (relative intensity): 289(M^+ + 2, 0.19), 288(M^+ + 1, 1.72), 287(M^+, 3.75), 150(M^+-$(EtO)_2P(O)$, 2.72), 137(M^+-$CF_2CO_2NEt_2$, 0.06), 100($CONEt_2$, 81.18), 72(NEt_2, 100). FTIR spectrum (CCl_4 solution, cm^{-1}): 2983(m), 2935(m), 1456(m), 1441(m), 1280(m, P=O), 1031(m, C-O-C).

Ethyl difluoro(diethoxyphosphonyl)acetate $(EtO)_2P(O)CF_2C(O)OEt$ (4i)

Yield: 53%; GLPC purity: 99%; bp 67–69°C/0.10 mmHg; ^1H NMR: 4.41 (q, 2H, J = 7.1), 4.33 (q, 4H, J = 7.1), 1.40 (t, 3H, J = 7.1), 1.38 (t, 6H, J = 7.1); ^{13}C NMR: 181.0 (m), 109.8 (t, d, J_{CF} = 275, J_{CP} = 202), 65.6 (s), 65.5 (s), 63.7 (s), 16.3 (s), 16.2 (s), 13.9 (s); ^{19}F NMR: −116 (d, J_{FCP} = 98); ^{31}P NMR: 2.8 (t, J_{PCF} = 98); GC-MS m/e (relative intensity): 259(M^+-1, 0.05), 231(M^+-Et, 2.86), 215(M^+-OEt, 7.50), 187(M^+-CO_2Et, 11.07), 148(52.50), 137(M^+-CF_2CO_2Et, 57.14), 132(98.57), 109(100.00), 93(47.86), 81(95.71), 65(85.57); FTIR spectrum (CCl_4 solution, cm^{-1}): 2985(m), 2940(m), 2933(m, C-H), 1765(s, C=O), 1444(m), 1303(m), 1286(m, P=O), 1283(s), 1151(s), 1033(s, C-F), 1029(s), 1027(m, C-O-C).

General Procedure for Preparation of $R'RC=CF_2$ 9 as Described for the Preparation of 1,1-difluoro-2-diethylamino-1-buten $(C_2H_5)(NEt_2)C=CF_2$ (9c)

A solution of 9.0 mmol (2.58 g) of $(EtO)_2P(O)CF_2C(O)NEt_2$ and 24 mL of dry diethyl ether were cooled to −78°C via a dry ice/i-PrOH slush bath under N_2. To the cooled solution, 9.0 mmol (3.0 mL) of a 3.0M diethyl ether solution of ethylmagnesium bromide was added dropwise via syringe. The resultant mixture was allowed to warm to room temperature over 4 hours and stirred at that temperature overnight. ^{19}F NMR analysis of the reaction mixture indicated the complete consumption of the $(EtO)_2P(O)CF_2C(O)CO_2Et$ to give 50% ^{19}F NMR yield of the titled compound at −98.0 ppm (d, J_{FCF} = 61 Hz) and −104.0 ppm (d, J_{FCF} = 61 Hz). The reaction mixture was poured into n-pentane (90 mL), filtered and concentrated by atmospheric distillation to give a yellow residue. Distillation of the residue at 90–98°C and 150 mmHg gave the titled compound. GC-MS m/z (relative intensity): 163(M^+, 3.53), 148(M^+-CH_3, 5.54), 134(M^+-Et, 2.71), 91(M^+-NEt_2, 2.05), 74(16.25), 73(10.40), 59(24.64), 45(36.96), 44(38.39), 43(23.39), 40(100.00).

1,1-difluoro-2-diethylamino-1-pentene $(n\text{-}C_3H_7)(NEt_2)C=CF_2$ (9d)

^{19}F NMR yield: 52%; ^{19}F NMR: − 104 (d, J_{FCF} = 63), − 98 (d, J_{FCF} = 63); GC-MS m/e (relative intensity): 177(M^+, 6.34), 162(M^+-CH_3, 15.19), 148(M^+-Et, 5.53), 134(M^+-C_3H_7, 2.58), 130(31.94), 86(M^+-NEt_2-F, 14.41), 72(26.74), 58(97.22), 56(18.40), 44(47.22), 43(18.40), 42(21.79) 41(14.24), 40(100.00)

1,1-difluoro-2-diethylamino-3-methyl-1-butene (i-C_3H_7)(NEt_2)C=CF_2 (9e)

^{19}F NMR yield: 55%; bp 68–70°C/75 mmHg; ^{19}F NMR: − 100 (d, J_{FCF} = 61), − 95 (d, J_{FCF} = 61); GC-MS m/z (relative intensity): 178(M^+ + 1, 2.39), 177(M^+, 27.92), 162(M^+-Me, 100), 148(M^+-Et, 11.77), 134(M^+-C_3H_7, 5.60), 106(M^+-NEt_2 + H, 4.99), 94(22.73), 68(15.67), 44(14.12), 42(18.91), 41(22.73), 40(36.36).

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