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Acylation of α-Fluorophosphonoacetate Derivatives Using Magnesium Chloride-Triethylamine

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Abstract : Acylation of α-fluorophosphonoacetate derivatives in the presence of magnesium chloride-triethylamine has been described. Acylations of triethyl α-fluorophosphonoacetate **1** and diethyl α-fluorophosphonoacetic acid **7** were proceeded under mild conditions to provide α-fluoro-β-keto esters **3** and α-fluoro-β-keto phosphonates **9**, respectively, in high yields. © 1999 Elsevier Science Ltd. All rights reserved.

Organic fluorine compounds are of importance in organic synthesis because of their use as medicinals, agrochemicals, and in fundamental studies of biochemical and metabolic process.[1] α-Fluoro-β-keto esters have been used as useful intermediates in the preparation of biologically active monofluorinated heterocycles[2] and fluorine-substituted isoprenyl derivatives.[3] Although a number of synthetic methods of α-fluoro-β-keto esters have been developed, they have limitations in terms of the reaction conditions employed and use of toxic and/or hazardous materials. Commonly, α-fluoro-β-keto esters are prepared by the fluorination of β-keto esters with various fluorinating agents such as $FClO_3$,[4] $C_{19}XeF_6$,[5] *N*-fluorobis[(perfluoroalkyl)sulfonyl]imides[6] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).[7] α-Fluoro-β-keto esters are also obtained by Claisen and crossed Claisen condensation of fluoroacetate,[8] reaction of trifluoroethene with acid chlorides under Friedel-Crafts conditions,[9] acylation of (ethoxycarbonyl)fluoro-substituted phosphonium ylide with acid chlorides followed by hydrolysis under basic conditions,[10] and oxidation of fluoroalkyl-substituted carbinols.[11] α-Fluoro-β-keto phosphonates are valuable intermediates for organic synthesis,[12] especially for the preparation of α-fluoro-α,β-unsaturated carbonyl compounds by the Horner-Wadsworth-Emmons condensation.[13] Fluoro olefins[14] are attracting attention in a wide area of biologically active agents like peptide isosteres,[15] enzyme inhibitors,[16] and pheromons.[17] α-Fluoro-β-keto phosphonates are prepared by the acylation of α-fluoro alkylphosphonates[18] and reaction of organometallic reagents with phosphonofluoroacetyl chloride.[12]

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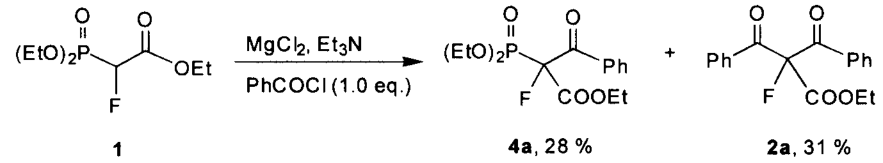
They have limitations in terms of the reaction conditions employed and low yields. In the course of the research on the synthesis and reaction of α-substituted phosphonates, we have reported preparation of α-fluoro carboxylate derivatives from α-fluorophosphonoacetates.[19] This paper describes the acylation of diethyl α-fluoro phosphonoacetate and α-fluorophosphonoacetic acid using magnesium chloride-triethylamine.[20]

Results and Discussion

1. Acylation of triethyl α-fluorophosphonoacetate 1.

Acylation of triethyl α-fluorophosphonoacetate **1** with 1.0 equiv. of benzoyl chloride in the presence of $MgCl_2$-triethylamine afforded mono- (**4a**) and diacylated adduct (**2a**). Formation of diacylated adduct **2a** means that P-C bond cleavage of monoacylated adduct **4a** easily occurs under acylation conditions. Commonly, the P-C bond cleavages of phosphonates are performed by the reduction using metal hydride and acidic or basic hydrolysis.[21]



Triethyl α-fluorophosphonoacetate **1** was treated with $MgCl_2$-triethylamine in dry toluene for 1 h at room temperature and to this suspension was added 2.2 equiv. of aromatic carboxylic acid chloride at 0 °C. Diacylated adduct **2** was formed after stirring for 6 h at room temperature. This adduct **2** was deacylated in the presence of SiO_2 in aqueous ethyl acetate at 40 °C for 1 day affording α-fluoro-β-keto ester **3** in good yield(Table 1).

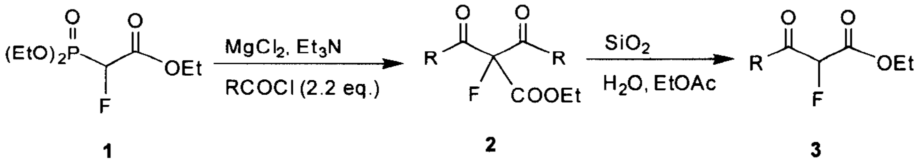
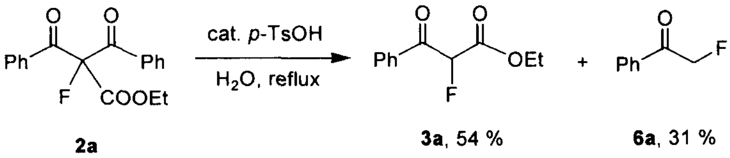


Table 1. Preparation of α-fluoro-β-keto esters 3.

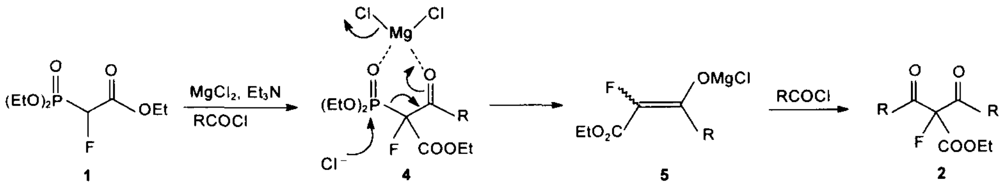
Comp. 3	R	Yield[a](%)	Comp. 3	R	Yield[a](%)
a	C_6H_5	78	**d**	*m*-Br, C_6H_4	83
b	*p*-CH_3, C_6H_4	88	**e**	2,4-Cl_2, C_6H_3	94
c	*p*-Cl, C_6H_4	82	**f**	2,4-Cl_2, 5-F, C_6H_2	81

[a] Isolated yields are based on triethyl α-fluorophosphonoacetate **1**.

Acylation of **1** with aliphatic carboxylic acid chlorides, such as propionyl chloride and pivaloyl chloride did not proceed cleanly and gave complex mixtures. Hydrolysis of **2a** under conventional conditions in the presence of catalytic *p*-TsOH in refluxing water for 4 h afforded a mixture of **3a** and α-fluoroacetophenone **6a**.[24]



A possible explanation of reaction pathway (**1** to **2**) involves acylation, cleavage of P-C bond, formation of magnesium enolate **5**, and second acylation. Evidence in support of such mechanism is provided by the isolation of **3** from the reaction of **4** with NH_4Cl in the presence of $MgCl_2$-triethylamine.



We have found that the acylation of triethyl α-fluorophosphonoacetate **1** in the presence of $MgCl_2$-triethylamine provides a convenient route to α-fluoro-β-keto ester **3**. The advantages of this synthetic route are high yields of products and the mild reaction conditions.

2. Acylation of diethyl α-fluorophosphonoacetic acid 7.

Diethyl α-fluorophosphonoacetic acid **7** was treated with triethylamine and trimethylsilyl chloride in dry toluene for 1 h at room temperature and to the resulting trimethylsilyl diethyl α-fluorophosphonoacetate **8** was added magnesium chloride and carboxylic acid chloride. The reaction mixture was stirred for 6h at room temperature, and hydrolyzed with aqueous NH_4Cl solution affording α-fluoro-β-keto phosphonate **9** in good yield. As shown in Table 2, a number of aromatic and aliphatic carboxylic acid chlorides participated nicely in the reaction. In general, the aromatic carboxylic acid chlorides gave higher yields than the aliphatic carboxylic acid chlorides. The aromatic carboxylic acid chlorides containing electron-rich and electron-deficient substituents reacted with equal efficiency(**9a**-**9f**). In the aliphatic carboxylic acid chlorides, primary and secondary acid chlorides gave good yields(**9g** and **9h**). Replacing magnesium chloride with magnesium bromide gave slightly lower yields. A possible explanation of reaction pathway involves formation of trimethylsilyl diethyl α-fluorophosphonoacetate **8**, acylation of **8** with carboxylic acid chlorides in the presense of magnesium chloride as chelating agent, and decarboxylation. Compared with general synthetic route for the preparation of α-fluoro-β-keto phosphonates by the acylation of α-fluoro alkylphosphonate,[7] which requires a strong base such as *n*-BuLi, the present procedure is safe and convenient. Also, the present procedure provides good yields under mild reaction conditions. The present synthetic route is recommended as a practical preparation of α-fluoro-β-keto phosphonates **9**.

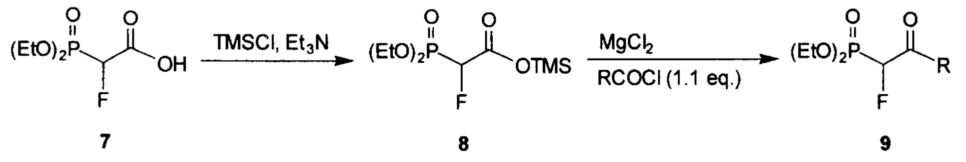
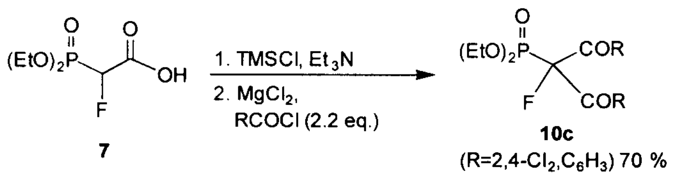


Table 2. Preparation of α-fluoro-β-keto phosphonates 9.

Comp. 9	R	Yield[a](%)	Comp. 9	R	Yield[a](%)
a	C_6H_5	80	**e**	p-CH_3, C_6H_4	85
b	p-Cl, C_6H_4	85	**f**	C_6F_5	71
c	2,4-Cl_2, C_6H_3	83	**g**	cyclo-C_6H_{11}	64
d	p-OCH_3, C_6H_4	84	**h**	n-C_5H_{11}	75

[a] Isolated yields are based on diethyl α-fluorophosphonoacetic acid 7.

Compared with the acylation of triethyl α-fluorophosphonoacetate **1**, leading to diacylated adduct **2** through P-C bond cleavage, the acylation of α-fluoro phosphonoacetic acid **7** afforded monoacylated adduct only. In the case of acylation of **7** with 2.2 equiv. of carboxylic acid chloride under the same reaction conditions, diacylated phosphonates **10c** was obtained as major product, no products through the P-C bond cleavage being detected.



In summary, we have developed a new method for the preparation of α-fluoro-β-keto phosphonates **9** by generating trimethylsilyl diethylphosphonoacetate **8** *in-situ* and treating this species with a carboxylic acid chloride in the presence of $MgCl_2$-triethylamine.

Conclusion

We have described the acylation of α-fluorophosphonoacetate derivatives using $MgCl_2$-triethylamine. Acylations of triethyl α-fluorophosphonoacetate **1** and diethyl α-fluorophosphonoacetic acid **7** provided α-fluoro-β-keto esters **3** and α-fluoro-β-keto phosphonates **9**, respectively, in high yields.

Experimental Section

General. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are measured in part per million(δ) and coupling constants , J, are reported in Hz. Multiplicity was simplified such as s=singlet, bs=broad singlet, d=doublet, t=triplet, dq=double quartet, and m=multiplet. Infrared spectra were measured on a Perkin-Elmer 283B. Mass spectra were determined with a Hewlett-Packard 5985A or Jeol HX 100/110 through EI or FAB method. Toluene was refluxed and distilled from calcium hydride. Column chromatography was performed on Merck silica gel 60(230-400mesh). The triethyl α-fluorophosphonoacetate **1**[22] and diethyl α-fluorophosphonoacetic acid **7**[23] were prepared as reported previously.

Acylation of triethyl α-fluorophosphonoacetate 1 with 1.0 equiv. of benzoyl chloride. Triethylamine (455 mg, 4.5 mmol) and phosphonate **1** (364 mg, 1.5 mmol) were added to a suspension of $MgCl_2$ (143 mg, 1.5 mmol) in dry toluene (5 mL). The resulting heterogeneous mixture was stirred at room temperature for 1 h. A solution of benzoyl chloride (211 mg, 1.5 mmol) in toluene (1 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h and quenched with saturated aqueous NH_4Cl and partitioned with diethyl ether (2X30 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give diacylated adduct **2a** (146 mg, 31 %) and monoacylated adduct **4a** (145 mg, 28 %).

Diacylated adduct **2a** : R_F 0.71(EtOAc: hexane = 1:2); IR(neat) 3050, 2970, 1745, 1675, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.33(t, J=7.1, 3H), 4.47(q, J=7.1, 2H), 7.26-8.02(m, 10H); ^{13}C NMR($CDCl_3$, 50MHz) δ 13.9, 62.6, 99.9(d, J=211.1), 128.8, 129.5,129.8, 134.4, 163.9(d, J=20.5), 189,3(d, J=23.7); HRMS: calcd for $C_{18}H_{15}FO_4$ 314.0954, found 314.0961.

Monoacylated adduct **4a** : R_F 0.23(EtOAc: hexane = 1:2); IR(neat) 3030, 2985, 1735, 1675, 1595, 1250, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.22(t, J=7.4, 6H), 1.40(t, J=7.3), 3.95-4.25(m, 4H), 4.38(q, J=7.3, 2H), 7.40-7.46(m, 3H), 7.66-7.71(m, 2H); ^{13}C NMR($CDCl_3$, 50MHz) δ 14.1, 15.9, 61.7, 64.8, 115.1, 118.9, 128.2, 130.5, 164.3, 199.0; HRMS: calcd for $C_{15}H_{20}FO_6P$ 346.0982, found 346.0978.

Typical procedure of acylation of triethyl α-fluorophosphonoacetate 1 : Preparation of Ethyl 2-fluoro-3-oxo-3-(*p*-tolyl)propionate (3b). Triethylamine (304 mg, 3 mmol) and phosphonate **1** (242 mg, 1 mmol) were added to a suspension of $MgCl_2$ (95 mg, 1 mmol) in dry toluene (3 mL). The resulting heterogeneous mixture was stirred at room temperature for 1 h. A solution of *p*-toluoyl chloride (340 mg, 2.2 mmol) in toluene (1 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h and quenched with saturated aqueous NH_4Cl and partitioned with diethyl ether (2X20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated to leave a white solid. This solid was washed with hexane (10 mL). Diacylated adduct **2b** : mp 117 °C; IR(neat) 2970, 1750, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.33(t, J=7.1, 3H), 2.42(s, 6H), 4.41(q, J=7.1, 2H), 7.24-7.29(m, 4H), 7.80-7.86(m, 4H); ^{13}C NMR($CDCl_3$, 50MHz) δ 13.9, 21.8, 63.4, 100.3(d, J=178.0), 129.5, 130.1, 163.9(d, J=20.5); MS(70eV) *m/z* 342(M$^+$, 0.3%), 120(8.2), 119(100), 91(96); HRMS: calcd for $C_{20}H_{19}FO_4$ 342.1261, found 342.1267. A mixture of diacylated product **2b**, ethyl acetate (5 ml), one drop of water and silica gel (1g) was set aside at 40 °C for 24 h. The reaction mixture was filtered. The filtrate was dried over anhydrous $MgSO_4$ and concentrated. The residue was flash chromatographed on silica gel using ethyl acetate/hexane as an eluent to give α-fluoro-β-keto esters **3b** as an oil.

Ethyl 2-fluoro-3-oxo-3-phenylpropionate (**3a**) : R_F 0.14(EtOAc:hexane= 1: 10) ; IR(neat) 3010, 1760, 1700, 1285, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.26(t, *J*=7.3, 3H), 4.31(q, *J*=7.3, 2H), 5.87(d, *J*=48.7, 1H), 7.45-8.10(m, 5H); ^{13}C NMR($CDCl_3$, 50MHz) δ 13.9, 62.7, 90.1(d, *J*=196.6), 128.8, 129.6, 130.0, 134.5; MS(70eV) *m/z* 210(M^+, 0.6%), 176, 105(100), 77; HRMS: calcd for $C_{11}H_{11}FO_3$ 210.0692, found 210.0687.

Ethyl 2-fluoro-3-oxo-3-(*p*-tolyl)propionate (**3b**) : R_F 0.82(EtOAc); IR(neat) 3060, 1765, 1697, 1285, 1215, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.26(t, *J*=7.1, 3H), 2.43(s, 3H), 4.29(q, *J*=7.1, 2H), 5.87(d, *J*=49.0, 1H), 7.24-7.33(m, 2H), 7.95-8.02(m, 2H) ; ^{13}C NMR($CDCl_3$, 50MHz) δ 14.0, 21.8, 63.4, 90.0(d, *J*=196.2), 128.8, 129.1, 129.4, 129.6, 129.9, 130.9, 165.0(d, *J*=23.8), 189.0(d, *J*=19.6); MS(70eV) *m/z* 224(M^+, 0.8%), 179, 123, 120, 119(100), 105, 91; HRMS: calcd for $C_{12}H_{13}FO_3$ 224.0849, found 224.0845.

Ethyl 2-fluoro-3-oxo-3-(*p*-chlorophenyl)propionate (**3c**) : R_F 0.53 (EtOAc: hexane= 1:4); IR(neat) 3030, 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.27(t, *J*=7.3, 3H), 4.31(q, *J*=7.3, 2H), 5.84(d, *J*=48.9, 1H), 7.45-7.50(m, 2H), 7.98-8.02(m, 2H) ; ^{13}C NMR($CDCl_3$, 50MHz) δ 14.1, 62.8, 90.1(d, J=196.8), 129.2, 130.8, 130.9, 131.1, 141.1, 164.6(d, *J*=24.1), 188.5(d, *J*=32.5); MS(70eV) *m/z* 244(M^+, 0.3%), 199, 149, 139(100), 111; HRMS: calcd for $C_{11}H_{10}ClFO_3$ 244.0303, found 244.0310.

Ethyl 2-fluoro-3-oxo-3-(m-bromophenyl)propionate (**3d**) : R_F 0.42 (EtOAc:hexane =1:4); ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.28(t, *J*=7.3, 3H), 4.32(q, *J*=7.3, 2H), 5.84(d, *J*=49.0), 7.36-8/17(m, 4H); ^{13}C NMR($CDCl_3$, 50MHz) δ 13.9, 62.8, 90.9(d, *J*=197.0), 128.0, 128.1, 130.3, 132.3, 164.5(d, *J*=24.0), 188.4(d, *J*=20.5); MS(70eV) *m/z* 289(M^+, 0.3%), 185, 183(100), 157, 155, 76, 75; HRMS: calcd for $C_{11}H_{10}BrFO_3$ 287.9797, found 287.9791.

Ethyl 2-fluoro-3-oxo-3-(2,4-dichlorophenyl)propionate (**3e**) : R_F 0.22(EtOAc: hexane = 1:10); IR(neat) 3010, 1760, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.20(t, *J*=7.3, 3H), 4.23(q, *J*=7.3, 2H), 5.83(d, *J*=48.0, 1H), 7.26-7.52(m, 3H); ^{13}C NMR($CDCl_3$, 50MHz) δ 13.9, 62.9, 90.4(d, *J*=199.0), 127.4, 130.1, 130.7, 133.1, 139.0; MS(70eV) *m/z* 280(M^++2, 0.2%), 278(M^+, 0.4) 177. 175, 173(100), 147, 145, 105; HRMS: calcd for $C_{11}H_9Cl_2FO_3$ 277.9913, found 277.9909.

Ethyl 2-fluoro-3-oxo-3-(2,4-dichloro-5-fluorophenyl)propionate (**3f**) : R_F 0.49(EtOAc;hexane = 1:4); ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.30(t, *J*=7.3, 3H), 4.3(q, *J*=7.3, 2H), 5.90(d, *J*=48.2, 1H), 7.4-7.6(m, 2H); ^{13}C NMR($CDCl_3$, 50MHz) δ 13.9, 63.0, 90.3(d, *J*=198.9), 117.9, 118.3, 131.3, 131.9, 132.4, 163.6(d, *J*=23.9), 190.3(d, *J*=23.7); MS(70eV) *m/z* 296(M^+, 0.8%), 195, 193, 191(100), 165, 163, 105; HRMS: calcd for $C_{11}H_8Cl_2F_2O_3$ 295.9819, found 295.9821.

Hydrolysis of diacylated adduct 2a with *p*-TsOH. A mixture of diacylated adduct **2a** (314 mg, 1.0 mmol) and *p*-TsOH (19 mg, 0.1 mmol) in water (5 mL) was refluxed for 4 h. The reaction mixture was extracted with ethyl acetate (3X20 mL) and combined organic extracts were dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography to give **3a** (113 mg, 54 %) and **6a** (43 mg, 31 %).

α-Fluoroacetophenone (**6a**) : IR (neat) 3053, 2920, 1700, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 5.53 (d, *J*=46.8, 2H), 7.45-7.96(m, 5H);^{13}C NMR ($CDCl_3$, 50MHz) δ 83.48(d, *J*=217.7), 127.81, 128.87, 133.68, 134.07, 193.38 (d, *J*=18.6); MS(70eV) *m/z* 138(M^+, 35%), 105(100), 77(97); HRMS: calcd for C_8H_7FO 138.0481, found 138.0477.

General procedure of acylation of diethyl α-fluorophosphonoacetic acid 7. To a stirred solution of diethyl phosphonoacetic acid (392 mg, 2.0 mmol) in toluene (5 mL) was added triethylamine (1.12 mL, 8.0 mmol) and trimethylsilyl chloride (0.38 mL, 3.0 mmol) at 0 °C. After stirring for 1 h at room temperature, magnesium chloride (190 mg, 2.0 mmol) was added and the heterogeneous mixture was stirred for 1h. Carboxylic acid chloride (2.4 mmol) was added dropwise and the solution was stirred for 6 h at room temperature. The reaction was quenched by adding a saturated NH_4Cl solution and the resilient mixture was extracted with ethyl ether. The organic layer was dried over $MgSO_4$ and concentrated. The residual oil was purified by silica gel column chromatography using ethyl acetate as an eluent.

Diethyl 1-fluoro-2-phenyl-2-oxoethylphosphonate (**9a**)

IR (neat) 2980,1680(C=O), 1265(P=O), 1095,1020 (P-O), 970cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.31(t, *J*=7.1, 6H), 4.20(m, 4H), 5.99(dd, *J*=47.3, *J*=13.4, 1H), 7.45-7.66(m, 3H), 7.94-8.11(m, 2H);^{13}C NMR ($CDCl_3$, 50MHz) δ 16.18(d, *J*=5.1), 64.14(d, *J*=6.6), 90.28(dd, *J*=196.1, *J*=152.5), 128.55, 129.26, 129.31, 134.19, 191.03; HRMS: calcd for $C_{12}H_{16}FO_4P$ 274.0770, found 274.0775.

Diethyl 1-fluoro-2-(*p*-chlorophenyl)-2-oxoethylphosphonate (**9b**)

1H NMR ($CDCl_3$, 200MHz) δ 1.33(t, *J*=7.1, 6H), 4.20(m, 4H), 5.91(dd, *J*=47.6, *J*=13.1 1H), 7.47(d, *J*=*8.7*, 2H), 8.00(d, *J* =8.5, 2H) ;^{13}C NMR ($CDCl_3$, 50MHz) δ 16.22(d, *J*=4.1), 64.35(d, *J*=6.55), 90.4(dd, *J*=195.65, *J*=151.5, 128.93, 130.82,132.37; HRMS: calcd for $C_{12}H_{15}ClFO_4P$ 308.0381, found 308.0375.

Diethyl 1-fluoro-2-(2,4-dichlorophenyl)-2-oxoethylphosphonate (**9c**)

IR (neat) 2980, 1710 (C=O), 1265(P=O), 1025, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.31(t, *J*=7.1, 6H), 4.22(m, 4H), 5.94(dd, *J*=46.7, *J*=15.3, 1H), 7.34(dd,1H), 7.47-7.48(d, 1H), 7.58(d, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.25(d, *J*=5.4), 64.38(d, *J*=6.4), 91.1(dd, *J*=198.9, *J*=154.5), 127.30, 130.37, 131.16, 198.24; HRMS: calcd for $C_{12}H_{14}Cl_2FO_4P$ 341.9991, found 342.0014.

Diethyl 1-fluoro-2-(*p*-methoxyphenyl)-2-oxoethylphosphonate (**9d**)

IR(neat) 2980, 1725 (C=O), 1255(P=O), 1025, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.24(t, *J*=7.1, 6H), 3.89(s, 3H), 4.17(m, 4H), 5.96(dd, *J*=47.3, *J*=12.9, 1H), 6.92-7.04(m, 2H), 8.01-8.08(m, 2H);^{13}C NMR ($CDCl_3$, 50MHz) δ 16.16(d, *J*=4.1), 55.45, 64.16(d, *J*=5), 90.06(dd, *J*=195.8, *J*=152.2), 113.78, 131.76, 189.66; HRMS: calcd for $C_{13}H_{18}FO_5P$ 304.0876, found 304.0871.

Diethyl 1-fluoro-2-(*p*-tolyl)-2-oxoethylphosphonate (**9e**)

IR(neat) 2980, 1680 (C=O), 1265 (P=O), 1020, 970 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.26(t, *J*=7.1, 6H), 2.42(s, 3H), 4.18(m, 4H), 6.01(dd, *J*=47.2, *J*=13.2), 7.24-7.30(m, 2H), 7.81-8.01(m, 2H);^{13}C NMR ($CDCl_3$, 50MHz) δ 16.19(d, *J*=5.1), 21.67, 64.25(d, *J*=6.7), 90.10(dd, *J*=195.9, *J*=152.5), 129.40, 129.46, 130.83, 190.37; HRMS: calcd for $C_{13}H_{18}FO_4P$ 288.0927, found 288.0930.

Diethyl 1-fluoro-2-pentafluorophenyl-2-oxoethylphosphonate (**9f**)

IR(neat) 2990, 1720(C=O), 1270(P=O), 1030, 970 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.35(t, *J*=7.1, 6H), 4.26(m, 4H), 5.79(dd, *J*=46.2, *J*=15.4, 1H);^{13}C NMR ($CDCl_3$, 50MHz) δ 16.22(d, *J*=5.1), 64.62(d, *J*=6.55), 91.61(dd, *J*=201.4, *J*=152.1), 136.8, 141.1, 146.7, 184.96; HRMS: calcd for $C_{12}H_{11}F_6O_4P$ 364.0299, found 364.0303.

Diethyl 1-fluoro-2-cyclohexyl-2-oxoethylphosphonate (**9g**)

IR(neat) 2980, 1715(C=O), 1265(P=O), 1025, 970 cm^{-1}; ^{1}H NMR($CDCl_3$, 200MHz) δ 1.12-1.87(m, 16H), 2.85-2.94(m, 1H), 4.25(m, 4H), 5.28(dd, *J*=47.7, *J*=14.5, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.27(d, *J*=5.6), 25.27, 25.54, 27.51, 28.43, 46.73, 64.06(d, *J*=5.3), 90.71(dd, *J*=198.8, *J*=153.1), 179.37(d, *J*=39.9); HRMS: calcd for $C_{12}H_{22}FO_4P$ 280.1240, found 280.1229.

Diethyl 1-fluoro-2-oxoheptylphosphonate (**9h**)

IR (neat) 2960,1720(C=O),1265(P=O),1025,970cm^{-1}; ^{1}HNMR($CDCl_3$, 200MHz) δ 1.35 (m, 15H), 2.69(m, 2H), 4.26(m, 4H), 5.15(dd, *J*=47.9, *J*=14.2, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 13.81, 16.3(d, *J*=5.6), 22.29, 29.65, 31.09, 38.93, 64.08(d, *J*=6.2), 91.55(dd, *J*=197.7, *J*=152.7), 202.97(d, *J*=19.1) ; HRMS: calcd for $C_{11}H_{22}FO_4P$ 268.1240, found 268.1246.

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