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A FACILE P-C BOND CLEAVAGE OF 2-FLUORO-2-PHOSPHONYL-1,3-DICARBONYL COMPOUNDS ON SILICA GEL

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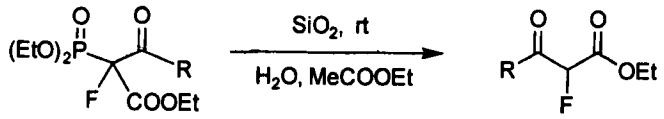
Abstract : α-Fluoro-β-keto esters and α-fluoromalonates were prepared by the P-C bond cleavage of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds on wet silica gel.

Organofluorine compounds have been of importance in organic synthesis because of their use as pharmaceuticals, agrochemicals, and in fundamental studies of biochemical and metabolic process.[1] α-Fluoro-β-keto esters and α-fluoromalonates have been used as valuable intermediates for the preparation of biologically active monofluorinated heterocycles[2,3] and fluorine-substituted building blocks.[4] Although a number of synthetic methods of 2-fluoro-1,3-

dicarbonyl compounds have been developed, they have limitations in terms of the reaction conditions employed and use of toxic and/or hazardous materials. Commonly, 2-fluoro-1,3-dicarbonyl compounds are prepared by the electrophilic fluorination[5] of 1,3-dicarbonyl compounds with various fluorinating agents.

In a continuation of studying the synthetic utility of α-fluoro phosphonoacetate,[6] we recently reported a synthesis of α-fluoro-β-keto esters from α-fluoro phosphonoacetate.[7] Here, we now report a synthesis of 2-fluoro-1,3-dicarbonyl compounds(**2**, **3**) from 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**) with P-C bond cleavage[8] on wet silica gel in ethyl acetate. In this method, P-C bond cleavages of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**) are achieved by the stirring a heterogeneous mixture of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**), wet silica gel in ethyl acetate at room temperature for 12 h. P-C Bond cleavage of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**) proceeds smoothly on wet silica gel in ethyl acetate to give α-fluoro-β-keto esters **2** and α-fluoromalonates **3** in good yields. The wide variety of compounds to which this method applies is illustrated by the list in the Table 1. The starting 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**) were easily prepared from α-fluoro phosphonoacetate and corresponding carboxylic acid chlorides and alkyl chloroformates as described previously.[9]

There are some advantages associated with this procedure. This method offers



1

2, R : alkyl, aryl
3, R : O-alkyl

Table 1. Preparation of α-fluoro-β-keto esters **2** and α-fluoromalonates **3**.

No.	R	% yield[a]	No.	R	% yield[a]
2a	C_6H_5	85	**2f**	cyclohexyl	88
2b	*p*-Me,C_6H_4	92	**3a**	Me	85
2c	*p*-Cl,C_6H_4	88	**3b**	Et	89
2d	*2,4*-Cl_2,C_6H_3	87	**3c**	CHClMe	91
2e	*n*-pentyl	91	**3d**	CH_2CCl_3	89

[a] Isolated yields are based on 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**).

simple and efficient route for P-C bond cleavage of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds. The procedure occurs under neutral and mild conditions, the yields are excellent in all cases tried.

In summary, we have found that P-C bond cleavage of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**) on wet silica gel in ethyl acetate provides a new synthetic route to α-fluoro-β-keto esters **2** and α-fluoromalonates **3**.

Experimental Section

All reactions were carried out under nitrogen atmosphere. ^{1}H and ^{13}C NMR were measured at 200 and 50 MHz, respectively, in $CDCl_3$ with TMS as internal standard. Infrared spectra were measured on a Perkin-Elmer 283B. Mass spectra were recorded on HP 5985A or Jeol HX100/HX110. Elemental analyses were performed on a Carlo Erba EA1108 instrument. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). The 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds(**1**) prepared as reported previously.[9]

The general experimental procedure : To a stirred solution of 2-fluoro-2-phosphonyl-1,3-dicarbonyl compounds (1.0 mmol) in ethyl acetate (3 mL) was added H_2O (0.1 g) and silica gel (230-400 mesh, 1 g) at room temperature. After stirring 16 h, the reaction mixture was filtered. The filterate was dried over anhydrous $MgSO_4$ and concentrated. The residue was chromatographed on silica gel to give 2-fluoro-1,3-dicarbonyl compounds as colorless oils.

Ethyl 2-fluoro-3-oxo-3-(phenyl)propionate (**2a**) [2c, 9a] : yield : 179 mg (85 %); R_F 0.14(EtOAc:hexane= 1: 10) ; IR(cm^{-1}) 3010, 2940, 1750, 1705, 1285, 1105; ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.26(t, 3H, *J*=7.3), 4.31(q, 2H, *J*=7.2), 5.87(d, 1H, *J*=48.7), 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; Anal. Calcd for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.28. Found: C, 62.74; H, 5.34.

Ethyl 2-fluoro-3-oxo-3-(*p*-tolyl)propionate (**2b**) : yield : 206 mg (92 %); R_F 0.82(EtOAc); IR(cm^{-1}) 3060, 1765, 1697, 1285, 1215, 1105; ^1H NMR ($CDCl_3$, 200MHz) δ 1.26(t, 3H, *J*=7.1), 2.43(s, 3H), 4.29(q, 2H, *J*=7.1), 5.87(d, 1H, *J*=49.0), 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; Anal. Calcd for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84. Found: C, 64.20; H, 5.91.

Ethyl 2-fluoro-3-oxo-3-(*p*-chlorophenyl)propionate (**2c**) : yield : 215 mg (88 %); R_F 0.53 (EtOAc: hexane= 1:4); IR(cm^{-1}) 3030, 1766; ^1H NMR ($CDCl_3$, 200MHz) δ 1.27(t, 3H, *J*=7.3), 4.31(q, 2H, *J*=7.1), 5.84(d, 1H, *J*=48.9), 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; Anal. Calcd for $C_{11}H_{10}ClFO_3$: C, 54.00; H, 4.12. Found: C, 53.94; H, 4.14.

Ethyl 2-fluoro-3-oxo-3-(2,4-dichlorophenyl)propionate (**2d**) : yield : 243 mg (87 %); R_F 0.22(EtOAc: hexane = 1:10); IR(cm^{-1}) 3010, 1760, 1700; ^1H NMR ($CDCl_3$, 200MHz) δ 1.20(t, 3H, *J*=7.3), 4.23(q, 2H, *J*=7.9), 5.83(d, 1H, *J*=48.0), 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^++2, 0.4) 177. 175, 173(100), 147, 145, 105; Anal. Calcd for $C_{11}H_9Cl_2FO_3$: C, 47.34; H, 3.25. Found: C, 47.30; H, 3.31.

Ethyl 2-fluoro-3-oxo-octanoate (**2e**)[5b] : yield : 186 mg (91 %); R_F 0.46 (EtOAc:hexane =1:10); IR(cm^{-1}) 2975, 1770, 1730(C=O); ^1H NMR ($CDCl_3$, 200MHz) δ 1.20-1.48(m, 7H), 1.55-1.70(m, 2H), 2.60-2.75(m, 2H), 4.31(q, 2H, *J*=7.3), 5.22(d, *J*=42.7); ^{13}C NMR ($CDCl_3$, 50MHz) δ 13.8, 14.0, 22.3, 31.0, 38.4, 62.6, 91.4(d, *J*=196.7), 163.9, 201.4(d, *J*=22.7); MS(70eV) *m/z* 204(M^+, 2.7%), 194, 179, 159, 148, 125, 99(100); HRMS calcd for $C_{10}H_{17}FO_3$ 204.1162, found 204.1150; Anal. Calcd for $C_{10}H_{17}FO_3$: C, 58.81; H, 8.39. Found: C, 58.74; H, 8.44.

Ethyl 2-fluoro-3-oxo-3-(cyclohexyl)propionate (**2f**)[5b, 5c] : yield : 190 mg (88 %); R_F 0.12(EtOAc;hexane = 1:10); IR(cm^{-1}) 2970, 1775, 1740(C=O), 1128; ^1H NMR ($CDCl_3$, 200MHz) δ 1.10-1.55(m, 9H), 1.95-1.60(m, 4H), 2.80-2.98(m, 1H), 4.31(q, 2H, *J*=7.3), 5.29(d, 1H, *J*=49.2); ^{13}C NMR ($CDCl_3$, 50MHz) δ 14.4, 25.2, 25.4, 27.4, 28.0, 28.6, 46.4, 62.4, 90.6(d, *J*=197.3), 164.3(d, *J*=23.9), 203.7(d, *J*=21.6); MS(70eV) *m/z* 216(M^+, 0.8%); Anal. Calcd for $C_{11}H_{17}FO_3$: C, 61.10; H, 7.92. Found: C, 61.06; H, 8.01.

Ethyl methyl fluoromalonate (**3a**)[2b] : yield : 140 mg (85 %); IR (cm^{-1}) 2980, 1770, 1750(C=O), 1020(C-O); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.34(t, *J*=4.9, 3H), 3.88(s, 3H), 4.34(q, *J*=14.3, 2H), 5.31(d, *J*=47.9, 1H) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.54(s), 52.90(s), 62.45(s), 84.94(d, *J*=194.5), 163.90(dd, *J*=23.95, *J*=29.55) %); Anal. Calcd for $C_6H_9FO_4$: C, 43.91; H, 5.53. Found: C, 43.88; H, 5.55.

Diethyl fluoromalonate (**3b**)[2b] : yield : 159 mg (89 %); IR(cm^{-1}) 2980, 1775, 1750 (C=O), 1025 (C-O); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33(t, *J*=7.0, 6H), 4.30(q, *J*=7.1, 4H), 5.28(d, *J*=48.3, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.93(s),

62.67(s), 85.31(d, J=195.3), 163.70(d, J=24.0); Anal. Calcd for $C_7H_{11}FO_4$: C, 47.19; H, 6.23. Found: C, 47.12; H, 6.28.

Ethyl (1-chloro)ethyl fluoromalonate (**3c**) : yield : 193 mg (91 %); IR(cm^{-1}) 2980, 1780, 1750 (C=O), 1020(C-O), 680(C-Cl); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35(t,J=13.6, 3H); 1.90(m, 3H), 4.30(m, 2H), 5.40(d, J=55.7, 1H), 6.60(m, 1H);^{13}C NMR ($CDCl_3$, 50MHz) δ 15.18(s), 23.28(s), 63.02(s), 81.61(s), 84.935(d, J=196.5), 161.5(dd, J=19.4, J=54.25); Anal. Calcd for $C_7H_{10}ClFO_4$: C, 39.55; H, 4.74. Found: C, 39.51; H, 4.76.

Trichloroethyl fluoromalonate (**3d**) : yield : 251 mg (89 %); IR(cm^{-1}) 2980, 1775, 1750, (C=O), 1020(C-O), 740(C-Cl); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.35(t, J=11.0, 3H), 4.34(q, J=16.6, 2H), 4.67-4.95(ABq, J=33.8, 2H), 5.39(d, J=47.8, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.86(s), 63.04(s), 74.53(s), 84.70(d, J=195.2), 161.50(t, J=12.05); Anal. Calcd for $C_7H_8Cl_3FO_4$: C, 29.87; H, 2.86. Found: C, 29.82; H, 2.90.

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