Pergamon

*Tetrahedron Letters*, Vol. 37, No. 5, pp. 653-654, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02224-4

# Acylation of Diethyl (Ethoxycarbonyl)fluoromethylphosphonate using Magnesium Chloride-Triethylamine : A Facile Synthesis of α-Fluoro β-Keto Esters

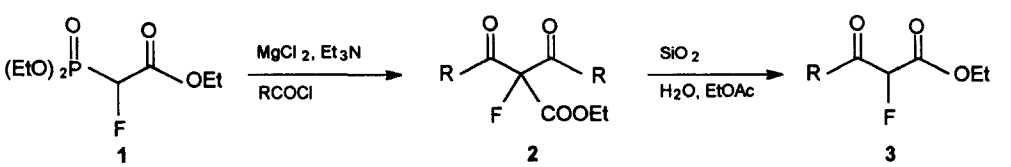
**Dae Young Kim,[a,*] Dae Yong Rhie[a] and Dong Young Oh[b]**

[a]Department of Chemistry, Soonchunhyang University, Onyang P. O. Box 97, Chungnam 336-600, Korea
[b]Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

**Abstract** : A facile synthesis of α-fluoro β-keto esters, *via* diacylation reaction of diethyl (ethoxycarbonyl)fluoromethylphosphonate with aromatic carboxylic acid chlorides in the presence of magnesium chloride-triethylamine followed by deacylation, is described.

Organofluorine compounds have been of importance in organic chemistry because of their use as medicinals, as tools in medical diagnosis, 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 $FClO_3$,[5] $C_{19}XeF_6$,[6] *N*-fluorobis[(perfluoroalkyl)sulfonyl]imides[7] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate).[8] α-Fluoro β-keto esters are also obtained by Claisen and crossed Claisen condensation of fluoroacetate,[9] reaction of trifluoroethene with acid chlorides under Fridel-Crafts conditions,[10] acylation of (ethoxycarbonyl)fluoro-substituted phosphonium ylide with acid chloride followed by hydrolysis under basic conditions,[11] and oxidation of fluoroalkyl-substituted carbinols by the Dess-Martin reagent.[12]

Herein, we now report a synthesis of α-fluoro β-keto esters *via* acylation of diethyl (ethoxycarbonyl)-fluoromethylphosphonate[4] **1** using $MgCl_2$-triethylamine. The phosphonate **1** was treated with $MgCl_2$-triethyl-amine in dry toluene at room temperature and to this suspension was added 2.2 equiv. of aromatic carboxylic acid chloride at 0°C. Diacylated adduct **2** formed after stirring for 6 h at room temperature 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.[13] Acylation of **1** with aliphatic carboxylic acid chlorides such as propionyl chloride and pivaloyl chloride did not proceed cleanly and gave complex mixture. A possible explanation of reaction pathway (**1** to **2**)




**1** **2** **3**

involves cleavage of P-C bond and formation of magnesium enolate **5**.[14] We have shown that acylation of diethyl (ethoxycarbonyl)fluoromethylphosphonate **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 product and the mild reaction conditions.

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

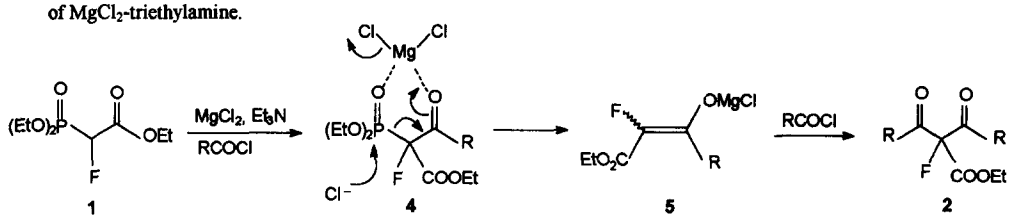
| Comp. **3** | R | Yield[a](%) | Comp. **3** | R | Yield[a](%) |
|---|---|---|---|---|---|
| a | $C_6H_5$ | 78 | d | *m*-Br, $C_6H_4$ | 83 |
| b | *p*-$CH_3$, $C_6H_4$ | 88 | e | 2,4-$Cl_2$, $C_6H_3$ | 94 |
| c | *p*-Cl, $C_6H_4$ | 82 | f | 2,4-$Cl_2$, 5-F, $C_6H_2$ | 81 |

[a] Isolated yields are based on diethyl (ethoxycarbonyl)fluoromethylphosphonate **1**.

**Acknowledgements :** We thank the Soonchunhyang University (Grant No. 95-1905) for financial support.

**References and Notes :**

1. Schlosser, M. *Tetrahedron* **1978**, 34, 3. Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of FluorineChemistry*, Kodansha Ltd., Elsevier Biochemical Press, Tokyo, New York, 1982.
2. Bergman, E. D.; Cohen, S.; Shahak, I. *J. Chem. Soc.* **1959**, 3278.
3. Montellano, P. R. O.; Vinson, W. A. *J. Org. Chem.* **1977**, 42, 2013.
4. Patois, C.; Savignac, P. *Synth. Commun.* **1994**, 24, 1317. Elikik, E.; Imbeaux, M. *Synthesis* **1989**, 861.
5. Takeuchi, Y.; Ogura, H.; Kanada, A.; Koizumi, T. *J. Org. Chem.* **1992**, 57, 2196.
6. Yemul, S. S.; Kagan, H. B.*Tetrahedron Lett.* **1980**, 21, 277.
7. DesMarteau, D. D. ; Gotoh, Y. *J. Fluorine Chem.* **1992**, 58, 71. DesMarteau, D. D. ; Gotoh, Y. *J. Chem. Soc. Chem. Commun.* **1991**, 179. Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, 60, 6730.
8. Bank, R. E.; Lawrence, N. J.; and Popplewell, A. L. *J. Chem. Soc. Chem. Commun.* **1994**, 343.
9. McBee, E. T.; Pierce, O. R.; Kilbourne, H. W.; Wilson,E. R. *J. Am. Chem. Soc.* **1953**, 75, 3152.
10. Ishikawa, N.; Takaoka, A.; Iwakiri,H.;Kubota, S.; Kagaruki, S. R. F. *Chem. Lett.* **1980**, 1107. Ishikawa, N.; Takaoka, A.; Ibrahim, K. J. *J. Fluorine Chem.* **1984**, 25, 203.
11. Thenappan, A.; Burton, D. J. *Tetrahedron Lett.* **1989**, 30, 6113. Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1991**, 56, 273.
12. Linderman, R. J.; Graves,D. M. *J. Org. Chem.* **1989**, 54, 661
13. *General Experimental Procedure;Ethyl 2-fluoro-3-oxo-3-(p-tolyl)propionate* (**3b**). Triethylamine (304g, 3 mmol) and phosphonate **1** (242mg, 1 mmol) were added to a flask containing $MgCl_2$ (95mg, 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 (340mg, 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). Compound **2b**: m.p. 117°C; $^1H$ NMR ($CDCl_3$, 200MHz) δ 1.30(t, 3H, *J*=6.8), 2.42(s, 6H), 4.41(q, 2H, *J*=6.8), 7.24-7.29(m, 4H), 7.80-7.86(m, 4H) ; MS(70eV) *m/z* 342($M^+$, 0.3%), 120(8.2), 119(100) and 91(19.6). 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 24h. The reaction mixture was filtered. The filterate was dried over anhydrous $MgSO_4$ and concentrated. The residue was flash chromatographed on silica gel using ethyl acetate/hexane (1/1) as an eluent to give ethyl 2-fluoro-3-oxo-3-(*p*-tolyl)propionate **3b** (197 mg, 88 %) as an oil. Compound **3b**: $R_F$ 0.82; IR($cm^{-1}$ ) 3060, 1765, 1697, 1285, 1215 and 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(s), 21.8(s), 63.4(s), 90.0(d, J=196.2), 128.8(s), 129.1(s), 129.4(s), 129.6(s), 129.9(s), 130.9(s), 165.0(d, J=23.8), 189.0(d, J=19.6); MS(70eV) *m/z* 224($M^+$, 0.8%), 179(1.3), 123(2.7), 120(9.3), 119(100), 105(2.6) and 91(24.1).
14. 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.




(*Received in Japan* 6 *October* 1995; *revised* 10 *November* 1995; *accepted* 24 *November* 1995)