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Dae Young Kim [a], Myeon Sik Kong [a] & Taek Hyeon Kim [b]

[a] Department of Chemistry, Soonchunhyang University, Onyang P. O. Box 97, Chungnam, 336-600, Korea

[b] Department of Fine Chemical Technology, Chonnam National University, Kwangju, 500-757, Korea

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A PRACTICAL SYNTHESIS OF β-KETO PHOSPHONATES FROM TRIETHYL PHOSPHONOACETATE

Dae Young Kim,*[a] Myeon Sik Kong[a] and Taek Hyeon Kim[b]

[a]Department of Chemistry, Soonchunhyang University, Onyang P. O. Box 97, Chungnam 336-600, Korea, [b]Department of Fine Chemical Technology, Chonnam National University, Kwangju 500-757, Korea

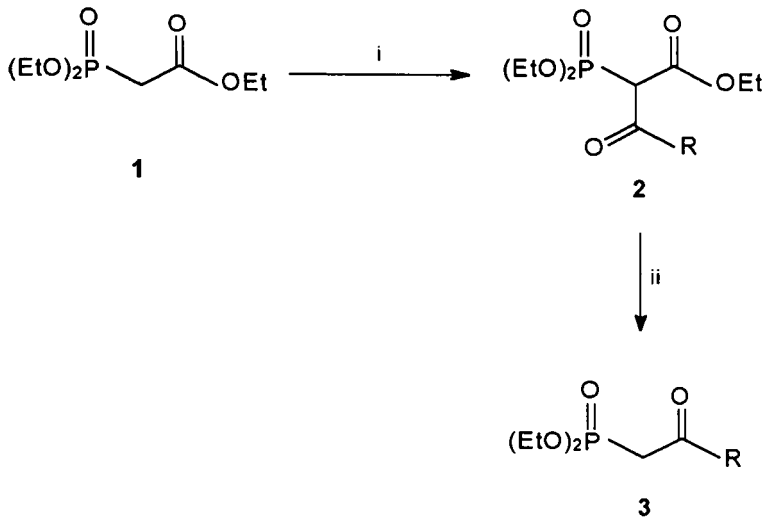
ABSTRACT : An efficient and practical preparation of β-keto phosphonates, *via* acylation reaction of triethyl phosphonoacetate with carboxylic acid chlorides in the presence of magnesium chloride-triethylamine followed by decarbethoxylation, is described.

β-Keto phosphonates are useful intermediates in organic synthesis, especially for the preparation of α,β-unsaturated carbonyl compounds by the Horner-Wadsworth-Emmons condensation.[1] Although a number of synthetic methods of β-keto phosphonates have been developed, they have limitations in terms of the reaction conditions employed and competition from other reactions. Commonly, β-keto phosphonates are prepared by the Arbuzov reaction and acylation of alkylphosphonate anions. The Arbuzov reaction of trialkyl phosphite and α-

* To whom correspondence should be addressed

halogeno ketones leads β-keto phosphonates. The latter method is restricted to highly reactive α-halogeno ketones or α-halogeno ketones containing carbonyl protecting group, because of the nucleophilicity of phosphites and competition from the Perkow reaction to give enol phosphates.[2] The most commonly used method for preparing β-keto phosphonates is acylation of alkylphosphonate α-anions with carboxylic acid esters,[3] carboxylic acid chlorides,[4] or N-methoxy-N-methylcarboxamides.[5] Recently, β-keto phosphonates were also obtained by either base-induced isomerization of enol phosphates or reaction of ketone enolates with dialkylphosphorochloridite followed by aerial oxidation.[6] Other miscellaneous methods include acylation of 1-(trimethylsilyl)vinylphosphonates,[7] hydrolysis of vinylogous phosphoramides,[8] reaction of 2-(diethoxy-phosphinyl)carboxylic acid chlorides with organometallic reagents,[9] the use of (diethoxyphosphoryl)acetonitriles oxides,[10] *via* allen oxide,[11] oxidation of β-hydroxyalkylphosphonates,[12] reaction of silyl enol ethers with phosphite using hypervalent iodine compound,[13] alkylation of β-keto phosphonates,[14] acylation of phosphonoacetate,[15] and reaction of nitroalkenes and α-nitro epoxides with phosphite.[16]

In this paper, we wish to report a practical synthesis of β-keto phosphonates **3** from triethyl phosphonoacetate **1**. (Scheme 1) It was performed by the acylation of triethyl phosphonoacetate with carboxylic acid chlorides in the presence of magnesium chloride-triethylamine and followed by decarbethoxylation. The triethyl phosphonoacetate **1** was treated with triethylamine and $MgCl_2$ in dry toluene at room temperature and to this suspension was added carboxylic acid chloride at 0^{0}C. Acylated adduct **2**, was



Scheme 1 i, $MgCl_2$, Et_3N, RCOCl, room temp. ii, cat. *p*-TsOH, H_2O, reflux

Table 1. Preparation of β–keto phosphonates **3**.

3	R	Yield (%)[a]	**3**	R	Yield (%)[a]
3a	Ph	88	**3f**	*trans*-PhCH=CH	74
3b	4-Cl, C_6H_4	83	**3g**	$PhOCH_2$	80
3c	C_6F_5	98	**3h**	Et	61
3d	4-Me, C_6H_4	92	**3i**	$MeOCH_2$	56
3e	3-Br, C_6H_4	75			

[a] Isolated yields are based on triethyl phosphonoacetate.

formed after stirring for 6 h at room temperature, hydrolysed with catalytic amount of *p*-TsOH in water affording β-keto phosphonates **3** in good yields. The results are summurized in Table 1. The use of LiCl in the place of $MgCl_2$ gave a reduced yield. (61% yield for **3a**)

Compared with general synthetic route for the preparation of β-keto phosphonates by the acylation of alkylphosphonate,[3-5] which use strong bases such as n-BuLi, the present procedure is inexpensive, safe and convenient. And also, the present procedure has some advantages of good yields and mild reaction conditions. So, the present synthetic route is good candidate for the practical preparation of β-keto phosphonates.

Experimental Section

NMR spectra were obtained on a Bruker AC200 (200 MHz) spectrometer using and tetramethylsilane as internal standard. Mass spectra were recorded on Hewlett Packard 5985A instrument operating at 70 eV. Triethyl phosphonoacetate, magnesium chloride, and all carboxylic acid chlorides were obtained from commercial suppliers and were used without further purification. Toluene was distilled from sodium and stored under nitrogen. Triethylamine was distilled from calsium hydride and stored over 4A° molecular sieves.

The general experimental procedure :

Triethylamine (607 mg, 6 mmol) and triethyl phosphonoacetate **1** (448 mg, 2 mmol) were added to a flask containing $MgCl_2$ (190 mg, 2 mmol) in dry

toluene (6 ml). The resulting heterogeneous mixture was stirred at room temperature for 2 h. A solution of carboxylic acid chloride (2.4 mmol) in toluene (1 ml) was added dropwise at 0 ^{0}C. The reaction mixture was stirred at room temperature for 6 h, quenched with aqueous solution of 10 % sulfuric acid under ice-cooling, and partitioned with ethyl acetate (2X20 ml). The organic layer was separated, washed with water and concentrated *in vacuo*. A solution of *p*-TsOH (10 mg) in water (10 ml) was added to the residue, and then the mixture was refluxed for 4h. After cooling, and mixture was extracted with ethyl ether (2X20 ml). 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 2-phenyl-2-oxoethylphosphonate (**3a**) : R_F 0.46(ethyl acetate); ν_{max}/ cm^{-1} 2980, 1675(C=O), 1260(P=O), 1060, 1025(P-O) and 970 ; δ_H ($CDCl_3$, 200 MHz) 1.28(t, 6H, J=7.0Hz), 3.65(d, 2H, J=22.7), 4.07-4.22(dq, 4H), 7.44-7.65(m, 3H), 7.99-8.04(m.2H) ; δ_C ($CDCl_3$, 50 MHz) 16.21(d, J=6.05), 38.51(d, J=129.1), 62.63(d, J=6.38), 128.58, 129.03, 133.61, 136.60 and 191.93(d, J=5.52) ; *m/z* (70eV) 256(M^+, 0.7%), 151(5.4) and 105(100).

Diethyl 2-(*p*-chlorophenyl)-2-oxoethylphosphonate (**3b**) : R_F 0.62(ethyl acetate); ν_{max}/ cm^{-1} 2990, 1675(C=O), 1255(P=O), 1129 and 970 ; δ_H ($CDCl_3$, 200 MHz) 1.29(t, 6H, J=6.0Hz), 3.61(d, 2H, J=22.8), 4.06-4.22(m, 4H), 7.40-7.48(m, 2H), 7.90-7.99(m.2H) ; δ_C ($CDCl_3$, 50 MHz) 16.30(d, J=5.75), 38.71(d, J=128.6), 62.80(d, J=6.15), 128.98, 130.58 and 190.73 ; *m/z* (70eV) 292(M+2, 1.2%), 290(M^+, 0.7), 180(7.1), 154(19.5) and 139(100).

Diethyl 2-(pentafluorophenyl)-2-oxoethylphosphonate (**3c**) : R_F 0.53(ethyl acetate); ν_{max}/ cm^{-1} 2995, 1705(C=O), 1321(P=O), 1035 and 990 ; δ_H ($CDCl_3$, 200 MHz) 1.30(t, 6H, J=7.1Hz), 3.60(d, 2H, J=22.4), 4.00-4.30(m, 4H) ; δ_C ($CDCl_3$, 50 MHz) 16.13(d, J=6.15), 44.49(d, J=127.0), 62.98(d, J=5.20), 135.10, 140.08, 140.51, 142.02, 145.81, 147.08, 185.21 ; *m/z* (70eV) 346(M^+, 7.7%), 291(17.5), 270(24.7), 210(20.2), 195(100), 188(33.7), 168(48.2), 149(41.4), 123(63.6) and 109(36.2).

Diethyl 2-(*p*-tolyl)-2-oxoethylphosphonate (**3d**) : R_F 0.32(ethyl acetate: hexane=2:1); ν_{max}/ cm^{-1} 2930, 1670(C=O), 1260(P=O), 1029 and 970 ; δ_H ($CDCl_3$, 200 MHz) 1.28(t, 6H, J=7.1Hz), 2.42(s,3H), 3.61(d, 2H, J=22.7), 4.06-4.21(m, 4H), 7.24-7.30(m, 2H), 7.80-7.94(m, 2H) ; δ_C ($CDCl_3$, 50 MHz) 16.38, 21.86, 38.62(d, J=129.0), 62.73, 129.41 ; *m/z* (70eV) 268(M^+, 2.1%) and 119(100).

Diethyl 2-(*m*-bromophenyl)-2-oxoethylphosphonate (**3e**) : R_F 0.72(ethyl acetate:hexane=2:1); ν_{max}/ cm^{-1} 2990, 1679(C=O), 1255(P=O), 1025 and 970 ; δ_H ($CDCl_3$, 200 MHz) 1.30(t, 6H, J=7.0Hz), 3.65(d, 2H, J=22.8), 4.01-4.26(m, 4H), 7.30-8.18(m, 4H) ; δ_C ($CDCl_3$, 50 MHz) 16.00(d, J=6.15), 38.37(d, J=128.9), 62.63(d, J=6.35), 127.47, 130.00, 131.72, 136.22 and 190.38(d, J=6.55) ; *m/z* (70eV) 336(M+2, 1.5), 334(M^+, 1.6%), 224(6.5) and 183(100).

Diethyl (4-phenyl-2-oxobut-3-en-1-yl)phosphonate (**3f**) : R_F 0.76(ethyl acetate) ; δ_H ($CDCl_3$, 200 MHz) 1.34(t, 6H, J=7.1Hz), 3.33(d, 2H, J=22.7), 4.09-4.25(m, 4H), 6.90(d, 1H, 16.1), 7.30-7.70(m, 6H) ; δ_C ($CDCl_3$, 50 MHz) 16.27, 41.08(d, J=127.1), 62.57, 125.74, 128.59, 128.98, 130.88 and 144.75.

Diethyl 3-phenoxy-2-oxopropylphosphonate (**3g**) : R_F 0.43(ethyl acetate: hexane=2:1); ν_{max}/ cm^{-1} 2992, 1725(C=O), 1250(P=O), 1025 and 965 ; δ_H ($CDCl_3$, 200 MHz) 1.33(t, 6H, J=7.1Hz), 3.28(d, 2H, J=22.8), 4.05-4.25(m, 4H), 4.71(s, 2H), 6.85-7.10(m, 3H), 7.21-7.35(m, 2H) ; δ_C ($CDCl_3$, 50 MHz) 16.44(d, J=6.0), 38.82 (d, J=127.0), 62.99(d, J=6.2), 114.80, 122.04 and 129.84.

Diethyl 2-oxobutylphosphoante (**3h**) : R_F 0.32(ethyl acetate); ν_{max}/ cm^{-1} 2990, 1710(C=O), 1255(P=O), 1036 and 970 ; δ_H ($CDCl_3$, 200 MHz) 1.07(t, 3H, 7.23), 1.34(t, 6H, J=7.0Hz), 2.65(q, 2H, J=7.3), 3.08(d, 2H, 22.8), 4.07-4.23(m, 4H) ; δ_C ($CDCl_3$, 50 MHz) 7.54, 16.27(d, J=5.93), 37.35(d, J=129.1), 42.12(d, 126.7) and 62.50(d, J=6.24) ; *m/z* (70eV) 208(M^+, 10.3%), 180(11.5), 179 (100) and 151(52.5).

Diethyl 3-methoxy-2-oxopropylphosphonate (**3i**) : R_F 0.26(ethyl acetate); ν_{max}/ cm^{-1} 2980, 1705(C=O), 1250(P=O), 1025 and 970 ; δ_H ($CDCl_3$, 200 MHz) 1.35(t, 6H, J=7.1Hz), 3.15(d, 2H, J=22.8), 3.44(s, 3H), 4.08-4.25(m, 6H) ; δ_C ($CDCl_3$, 50 MHz) 16.23(d, J=6.40), 38.38(d, J=127.3), 59.23, 62.59, 62.72 and 199.86(d, J=6.40) ; *m/z* (70eV) 224(M^+, 14.7%), 209(24.9), 179(53.8), 153(42.3), 151(81.4), 137(27.0), 123(100) and 109(65.0).

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