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Acylation of Diethyl Phosphonoacetic Acid Via the $MgCl_2/Et_3N$ System: A Practical Synthesis of β-Keto Phosphonates

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SYNTHETIC COMMUNICATIONS, 30(4), 609–618 (2000)

ACYLATION OF DIETHYL PHOSPHONOACETIC ACID VIA THE $MgCl_2/Et_3N$ SYSTEM: A PRACTICAL SYNTHESIS OF β-KETO PHOSPHONATES

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Abstract: A one pot simple procedure for the synthesis of β-keto phosphonates has been developed using the $MgCl_2/Et_3N$ base system to generate the magnesium enolate of diethyl phosphonoacetic acid. This intermediate reacts with acid chlorides or imidazolides to give, after workup, the title compounds in good yields.

β-keto phosphonates are important compounds in organophosphorus chemistry. They are not only used to prepare α,β-unsaturated carbonyl derivatives *via* the Horner-Wadsworth-Emmons reaction[1], but also as ligands in liquid-liquid extraction of metal ions[2a] or as starting material to synthesize either β-amino-phosphonates or β-hydroxy derivatives[2b] endowed with interesting biological properties. Several synthesis approaches have been reported in the literature[3-9], but none is fully satisfactory.

Our continuing interest in β-keto phosphonate chemistry has led us to recently propose, a new and general pathway[10] taken from malonic synthesis according to Rathke[11]; it relies on the acylation between an acid chloride, imidazolide or

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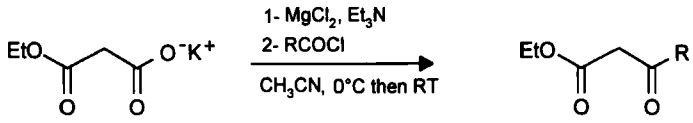
anhydride, and the magnesium enolate of a trialkyl phosphonoacetate. After a thermal decarbalkoxylation, the intermediate β-keto-β'-phosphono-ester gives the expected β-keto phosphonate in good yields (70-98%). A characteristic feature of this reaction stands in the chelation of phosphonic and carboxylic esters with a magnesium salt: this process lowers the pKa of adjacent methylene and makes easier the formation of the carbanion α to the phosphoryl. As demonstrated by Kim[10] and our team it is a general method with advantages such as low-cost, base-safety and easy-implementation.

However, the thermal decarbalkoxylation required in the second step of this procedure can slow down its development. This problem, already met in the malonic synthesis[12] of β-ketoesters, has led chemists to use malonates carrying either an acid-labile function, *e.g.* tert-butyl ester[13a], tetrahydropyranyl ester[13b] and Meldrum's acid[13c], or malonic hemiesters[13d]. After acylation, room temperature hydrolysis is accompanied with spontaneous decomposition with carbon gas evolution.

In a recent paper Kim[14] applied this idea to prepare β-keto phosphonates and proposed a synthesis procedure via an acid chloride acylation of the diethyl-phosphono acetic acid lithio dianion. Even though the decarbalkoxylation step is avoided, the use of two equivalents of n-butyllithium is, once again, a limitation to the applicability of the method.

In 1993 Wemple[15] described the use of Rathke's $MgCl_2/R_3N$ protocol[11] in a large-scale production of β-keto esters from potassium ethylmalonate. This operationally-simple procedure was also applied by Krysan[16] to synthesize α-acylamino-β-keto esters (See scheme 1) :



1993 WEMPLE 83-94 % yield

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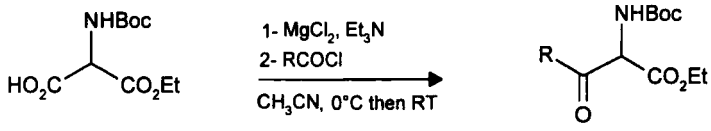


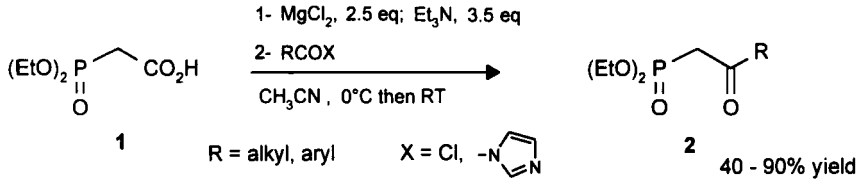
1996 KRYSAN

65-92 % yield

Scheme 1

Results and discussion

In this paper we wish to report that the Wemple procedure was successfully applied to the diethylphosphonoacetic acid substrate **1** to prepare β-keto phosphonates **2** (Scheme 2):



Scheme 2

This method was tested with different alkoyl-, aroyl-chlorides and imidazolides. A short study of reaction parameters enabled us to optimize them (Table).

Acylation yields were comparable to those obtained with carboxylic derivatives when starting from diethyl phosphonoacetic acid potassium salt or acid. So, for practical reason, to carry out these syntheses we chose the acid as substrate; this compound, indeed, gives triethylammonium acetate via an acid-base exchange.

Method **A** used twice the amount of phosphonoacetic substrate (see Table) and gave high yields (72-77%) with aliphatic imidazolides and aromatic acid chlorides (77-90%). On the other hand, yields were low (40%) with aliphatic acid chlorides. This result may be due to the formation of both ketene-derived by-products and β,β-diketo phosphonate **3a** which was isolated after workup. This diacylation reaction has been also mentioned by several authors[13d,e,f] when carrying out the

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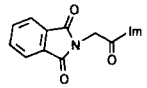
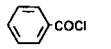
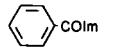
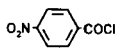
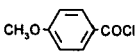
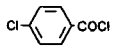
Table: Scope of β-keto phosphonates synthesis using the diethylphosphonoacetic acid/ $Et_3N/MgCl_2$/RCOX system

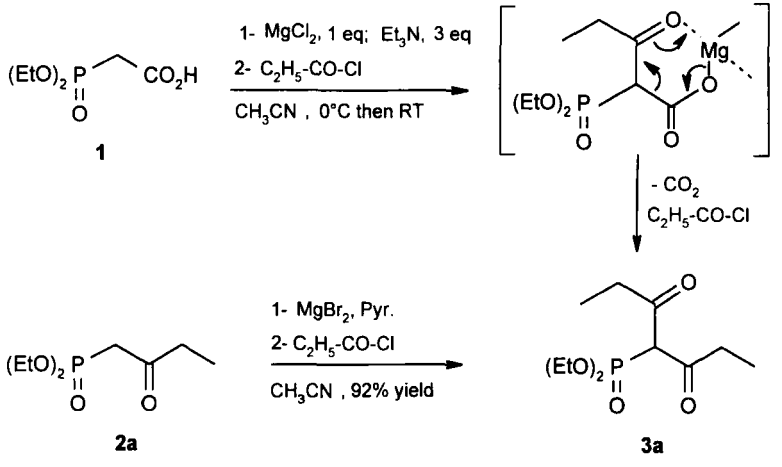
Products	Method[a] (Reaction time)	R-CO-X	Yield[b] %	Literature[c]
2a	**A** (2 days, RT)	C_2H_5- CO-Cl	40 (+ **3a**, 15%)	(4a), (7b), (10a), (5d)
	A (1 day, RT)	C_2H_5- CO-Im	75	
	B (1 day, RT, 2 h reflux)	id	35 (+ **3a**, 30%)	
2b	**A** (1 day, RT)	CH_3-CO-Im	77	(5d), (6f), (7b), (10a)
2c	**A** (1 day, RT)	C_5H_{11}-CO-Im	72	(7b), (8a), (10a)
2d	**A** (2 days, RT)		63	(10a)
	C (15 h, RT)	id	57	
2e	**A** (15 h, RT)		77	(4a), (7b), (10a)
	C (15 h, RT)	id	83	
	A (15 h, RT)		10	
	A (2 h, reflux)	id	15 (+ **3e**, 35%)	
	B (2 h, reflux)	id	0 (**3e**, 40%)	
2f	**A** (15 h, RT)		90	(3c,d)
	B (15h, RT)	id	47	
2g	**A** (15 h, RT)		77	(4b), (7b), (10b)
2h	**A** (15 h, RT)		81	(10c)

a) Method **A**: 1.2 eq $MgCl_2$, 2 eq Et_3N, 0.5 eq R-CO-X; Method **B**: 1 eq $MgCl_2$, 3 eq Et_3N, 1 eq R-CO-X; Method **C**: 2.5 eq $MgCl_2$, 3.5 eq Et_3N, 1 eq R-CO-X.

b) Yields are reported on distilled or chromatographied diethyl 2-oxoalkylphosphonates.

c) Diethyl 2-oxoalkylphosphonates were fully characterized by physicochemical methods (IR, ^{31}P and ^{1}H NMR).

acylation of malonic hemiesters magnesium salts. To avoid this side reaction and obtain β-keto esters in good purity, Bram and Vilkas[13d] have suggested to substitute an imidazolide for the more reactive acid chloride. The same procedure was applied here to get mono-ketonic derivatives (**2**, R = alkyl). However, one should note that heating the reaction mixture speeds up the substrate transformation, but entails the formation of a side product, the diketone **3a**, which can be explained as follows (Scheme 3) :



Scheme 3

For benzoic acid derivatives, acid chlorides should be preferred to the less reactive imidazolides (See **2e**) which, further to reaction mixture heating, give a 50/50 mixture of the expected β-keto phosphonate **2e** and diketonic derivative **3e**.

In two sets of experiments we investigated the possibility of reducing the substrate/acylating reagent ratio, using equimolecular amounts (Methods **B**, **C**). In method **B**, when using one equivalent of magnesium chloride the yield was cut by two (See **2a**, **2e**) and diketo phosphonates were always present. Using 2.5 equivalents of magnesium chloride restored good yields (See **2d**, **2e**) highlighting, thus, that it was crucial to use more than 2 equivalents of magnesium chloride.

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In conclusion, we have developed a simple and practical procedure to prepare β-keto phosphonates based on a one-pot acylation of magnesium enolate derivative of diethyl phosphonoacetic acid, the magnesium chloride-triethylamine system favorably replacing strong bases like BuLi and $(EtO)_2Mg$ usually used to prepare these compounds.

Experimental section

Magnesium chloride was purchased from Aldrich Chem. Co and used as is. It can be dried by chlorotrimethylsilane treatment[11]. Prior to their use acetonitrile was distilled from phosphoric anhydride, and triethylamine from sodium. The preparation of diethyl phosphonoacetic acid was adapted from a procedure developed by Strube[17] for potassium ethyl malonate: KOH saponification of triethyl phosphonoacetate in a 1/1: THF/H_2O mixture of solvents followed by an acid-base workup. Acyl imidazolides were prepared by the method of Staab[18]. ^1H, and ^{31}P NMR spectra were recorded on a BRUKER AC 300 spectrometer.

General procedure for the acylation of diethyl phosphonoacetic acid:

Method A :Diethyl phosphonoacetic acid (1.96 g, 10 mmol) was placed under nitrogen in a 100 mL three-neck flask. Acetonitrile (15 mL) was added, then the mixture was stirred and cooled to 10°C. Triethylamine (2.8 mL, 20 mmol) was first added, then magnesium chloride (1.14 g, 12 mmol), and stirring continued at room temperature for two hours. The slurry was cooled down to 0°C and an acetonitrile solution (5 mL) of the acid chloride (5 mmol) or imidazolide[18] was added dropwise. The reaction mixture was allowed to stir for 15 to 48 hours at room temperature before removing acetonitrile under vacuum. Aqueous HCl 1 M was added and the organic material extracted with methylene chloride (3 x 20 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and dried with Na_2SO_4. The organic phase was concentrated under vacuum to give the β-keto phosphonate **2** which was purified by distillation or liquid chromatography.

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Method **B**: The procedure was the same as above except for magnesium chloride, triethylamine and acylating reagent amounts which were 1/3/1 equivalent(s) respectively.

Method **C**: Equimolecular amounts of diethyl phosphonoacetic acid and acylating reagent, 2.5 equivalents of magnesium chloride and 3.5 equivalents of triethylamine were used.

Diethyl 3,5-dioxo-4-heptylphosphonate 3a:

To a magnesium bromide etheral solution (0.27 g Mg, 11 mmol; 1.75 g Br_2; 10 mL ether) a methylene chloride solution of diethyl 2-oxobutylphosphonate (10 mmol in 10 mL CH_2Cl_2) and 2 mL of pyridine (25 mmol.) was added. The mixture was cooled down to 0°C before the dropwise addition of propanoyl chloride (1.1 eq in 5 mL CH_2Cl_2). After 15 hours at room temperature, the reaction was quenched with 20 mL of 1 M HCl and extracted with methylene chloride. The organic phase was dried over Na_2SO_4. The solvent was removed under vacuum to give 2.5 g (crude yield: 94%) of **3a** as an oil.

Analytical data: $C_{11}H_{21}O_5P$, MW: 264.25; calc: C (50.00%), H (8.01%), found: C (49.81%), H (7.88%); δ ^{31}P NMR ($CDCl_3$): 13.6 (Keto form, 40%); 20.1 (Enol form, 60%). δ ^1H NMR ($CDCl_3$): 1.15 (bt, 6 H, J_{HH} = 7 Hz); 1.34 (t, 6 H, J_{HH} = 7 Hz); 2.5-3 (m, 4 H); 4.07 (qn, 4 H, $J_{HH} = J_{PH}$ = 7 Hz); 4.5 (d, 0.4 H, J_{PH} = 23 Hz, keto form).

Diethyl 1,3-dioxo-1,3-diphenyl-2-propylphosphonate 3e was prepared from diethyl 2-oxo-2-phenylethylphosphonate and benzoyl chloride in 92% crude yield. **3e** was also obtained as by-product using method **A** and method **B** (PhCOIm, reflux).

Analytical data: $C_{19}H_{21}O_5P$, MW: 360.34; calc: C (63.33%), H (5.87%), found: C (63.05%), H (5.68%). δ ^{31}P NMR ($CDCl_3$): 14.4 (Keto form, 100%) . δ ^1H NMR ($CDCl_3$): 1.22 (t, 6H, J_{HH}=7 Hz) ; 4.22 (qn, 4 H, $J_{HH} = J_{PH}$ = 7 Hz); 6.15 (d, 1 H, J_{PH} = 21 Hz); 1-8.1 (m, 10 H).

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