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ON A SAFE AND PRACTICAL METHOD FOR THE PREPARATION OF β-KETO PHOSPHONATES[1].

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Abstract : Acylations of the magnesium enolate derivatives of trimethyl and triethylphosphonoacetates, using a magnesium chloride-triethylamine system, lead to 2-acylphosphonoacetates which are decarbalkoxylated to give β-keto phosphonates.

Dialkyl 2-oxoalkylphosphonates are useful intermediates for homologations of aldehydes and ketones to α,β-unsaturated carbonyl compounds via the Horner-Wadsworth-Emmons reaction[2] and for liquid-liquid extraction of metals[3]. Many synthetic approaches have been developed, ranging from the direct Arbuzov reaction of trialkylphosphites with 1-haloalkylketones[4] to the more sophisticated methods using organometallic reagents[5]. All of these methods suffer from limitations : the Arbuzov reaction generally leads to a mixture of phosphonates and

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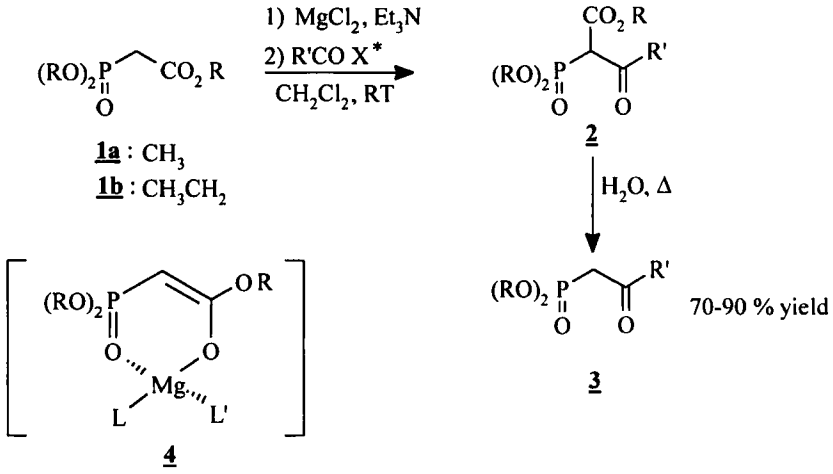
enolphosphates resulting from a Perkow reaction[6]. Other side reactions are observed in the Michaelis-Becker process[7] and the use of masked carbonyl compounds, which has proved to be successful[8], is limited by the restricted availability of starting materials. The Claisen condensation between α-lithioalkylphosphonates and esters[5a] gives a mixture of the desired compounds and alkanephosphonates since β-keto phosphonates are stronger acids than alkane phosphonates. The modified version[5b] using organocopper reagents and acyl chlorides overcomes this acid-base exchange though handling large amounts of the hazardous butyllithium is not very convenient in terms of economical cost and safety.

Our continuing interest in β-keto phosphonate chemistry has lead us to consider a practical approach, related to malonic synthesis, in which the magnesium enolate derivative **4** of trialkylphosphonoacetate **1** is acylated with acyl chlorides, anhydrides or imidazolides. The resulting β-keto esters **2** are decarbalkoxylated[9] to give the title compounds. A recent publication by D.Y. Kim et al.[10] prompts us to report our results.

As mentioned by D.Y. Kim, we found that magnesium enolate **4**, made by proton exchange between triethylphosphonoacetates **1** and magnesium ethoxide in ether or THF, could be acylated by aroyl and acyl chlorides, and the resulting β-keto esters **2** be decarbethoxylated[9] with water to give the β-keto phosphonates **3** (see scheme). The procedure, which was used fifty years ago by N. Kreutzkamp[14] to prepare and acetylate the enolate **4**, is an adaptation of a method described by C.R. Hauser[11] for diethylmalonate. The acylations of sodium[14b] and



* X = Cl, OCOR, imidazolyl

Scheme : Acylation of trialkylphosphonoacetate magnesium enolate

lithium[14c] enolates of **1** were reported too. In our hands, the yields were in the range published by D.Y. Kim[10] : good when aroyl chlorides were used and fair for acyl chlorides[17].

Although this procedure gave good results for aroyl chlorides, it suffered from major drawbacks : the tedious preparation of the magnesium enolate **4**, in anhydrous diethylether or tetrahydrofuran and the poor yields obtained for acyl chlorides.

In 1985, M.W. Rathke et al.[15] reported on an elegant acylation of diethyl malonate and ethyl acetoacetate with acid chlorides using magnesium chloride to enhance the methylene acidity of the reagent to the point that triethylamine or pyridine could be used to generate the magnesium enolate. This procedure, which has

recently been used for large scale production of methyl ketones[16], can also be applied to the synthesis of β-keto phosphonates.

General procedure and discussion :

To a suspension of 10 mmoles of magnesium chloride (Aldrich Chem. Co) in 10 ml of anhydrous dichloromethane is added, under nitrogen, a 10 mmoles solution of trialkylphosphonoacetate **1** in 5 ml of the same solvent. To this mixture is added 20 mmoles of triethylamine. After 30 minutes, at room temperature, 11 mmoles of acid chloride, anhydride or imidazolide are introduced while maintaining the temperature around 20°C by external cooling (water bath). The resulting mixture is stirred and, after 15 minutes, an aliquot is removed, acidified and checked by ^{31}P NMR spectroscopy. The spectrum exhibits two signals (enol and keto forms) for aroyl derivatives indicative of a quantitative acylation reaction and the remaining signal of the starting material (10 - 20 %) when acyl chlorides are used. A second addition of 0,5 eq. of triethylamine and acyl chloride brings the reaction to completion as shown by NMR. The reaction is quenched with 20 ml of 1M HCl and extracted with methylene chloride. The solvent is removed and 2 molar equivalents of water are added to the oily residue. This mixture is heated (oil bath, 120 - 140°C) for 2-3 hours. 20 ml of water are added at room temperature and the title compound is extracted with methylene chloride. The organic layer is dried over sodium sulfate and concentrated. The β-keto phosphonates are purified by flash chromatography on silica gel or distilled under reduced pressure, to give **3** in good overall yields (see Table).

Table: Acylation-decarbalkoxylation of trialkylphosphonoacetates magnesium enolates **4**

Entry	R	R'	X	**2** ^{31}P NMR δ (ppm)	**3** ^{31}P NMR δ (ppm)	overall yield (%)*
1	CH_3	CH_3	Cl	keto : 16 enol : 28,5	22,4	70
2	CH_3	C_5H_{11}	Cl	keto : 16,6 enol : 28,6	22,7	70
3	C_2H_5	CH_3	Cl	keto : 13,4 enol : 25,4	19,7	80
4	C_2H_5	CH_3	$OCOCH_3$			82
5	C_2H_5	C_2H_5	Cl	keto : 13,4 enol : 25,4	19,9	98
6	C_2H_5	C_2H_5	imidazolyl			80
7	C_2H_5	$PhtNCH_2$	Cl	keto : 12,3 enol : 24,8	18,5	84
8	C_2H_5	$PhtNCH(iC_4H_{10})$	Cl	keto : 13,2 enol : 25,3	19,1	90
9	C_2H_5	$PhtNCH(CH_2Ph)$	Cl	keto : 13,5 enol : 25,1	18,9	75
10	C_2H_5	Ph	Cl	keto : 13,4 enol : 25,4	20,1	75
11	C_2H_5	Ph	imidazolyl			72
12	C_2H_5	4-ClPh	Cl	keto : 13,4 enol : 23,4	19,6	75
13	C_2H_5	2-NO_2Ph	Cl	keto : 13 enol : 23,8	18,6	79
14	C_2H_5	2-furanyl	Cl	keto : 13,1	19,6	64

*Yields are reported on purified compounds and based on trialkylphosphonoacetate.

Trimethylphosphonoacetate **1a**, which is sensitive to nucleophilic demethylation, gives lower yields (entries 1,2 vs 3,5) and the triethylphosphonoacetate **1b** is preferred.

Replacing $MgCl_2$ with $MgBr_2$ gives the same results but is less practical[18]. However, it is the method of choice if there is any doubt about the quality of $MgCl_2$.

Regarding the acylating reagents, acyl chlorides are more reactive than aroyl counterparts but are sensitive to 1,2-eliminations leading to ketene[13] by products. A second addition of reagents overcomes this drawback but is restricted to cheap acid chlorides. The use of N-acyl or N-aroyl imidazoles[19] is a good alternative (entries 6,11) especially when R' is sensitive to HCl (from the thionylchloride preparations of acyl or aroyl chlorides).

Phthaloyl derivatives of α-amino acids (entries 7,8,9) can also be made this way and works are in progress to apply this procedure to the preparation of polyfonctional β-keto phosphonates.

In conclusion, we have developed a safe and economical procedure for the preparation of 2-aryl and 2-alkyl-2-oxoalkylphosphonates based on the acylation of magnesium enolate derivative of trialkylphosphonoacetate using magnesium chloride-triethylamine in methylene chloride. This salt-base system can substitute the hazardous bases, including butyllithium, Grignard reagents or ethoxide, in anhydrous diethylether or tetrahydrofuran and presents significant advantages in terms of cost and simplicity over previously reported syntheses of β-keto phosphonates.

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17. The magnesium ethoxide procedure to make **4** is an adaptation of the C.R. Hauser's method[11]. A few minutes after benzoyl chloride was added, ^{31}P NMR analysis showed a 100 % aroylation reaction. When propanoyl chloride was used 30 to 50 % starting material were left. But, the successive additions of 0.5 eq. of magnesium ethoxide (Aldrich) and acyl chloride eventually led to the complete transformation of the starting material. (R' = C_2H_5, 80 % yield ; R' = Ph, 75 % yield after distillation).
18. To the magnesium bromide-ether complex, made by reacting Br_2 and magnesium turnings in ether, are added successively trialkyl phosphonoacetates **1** (1 eq.) in CH_2Cl_2 followed by triethylamine (2 eq.). After 30 minutes the acylating agent (1.1 eq.) is added dropwise. The resulting solution is checked by ^{31}P NMR and worked up as described before. (R' = C_2H_5, 85 % yield ; R' = Ph, 75 % yield after distillation).
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