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The surprising diacylation of diethyl (ethoxycarbonylmethyl)phosphonate

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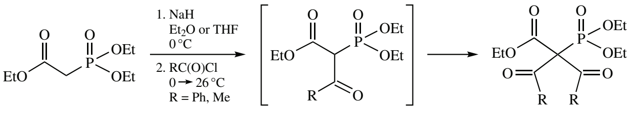
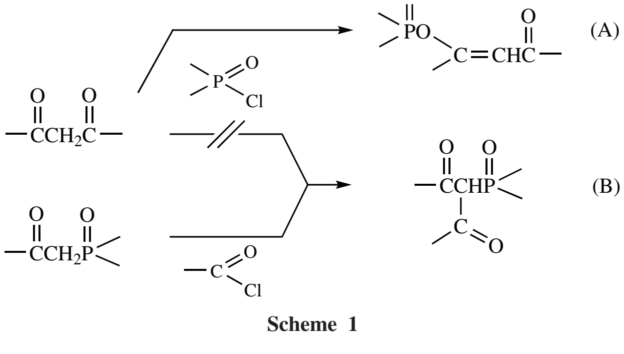
Deprotonation of diethyl (ethoxycarbonylmethyl)-phosphonate with NaH followed by treatment with acyl chlorides affords surprisingly the corresponding C,C-diacylated derivatives as the predominating products.



Keywords: CH-acidic compounds, phosphonates, acylation, diacylation, relative ΔpK_a value.

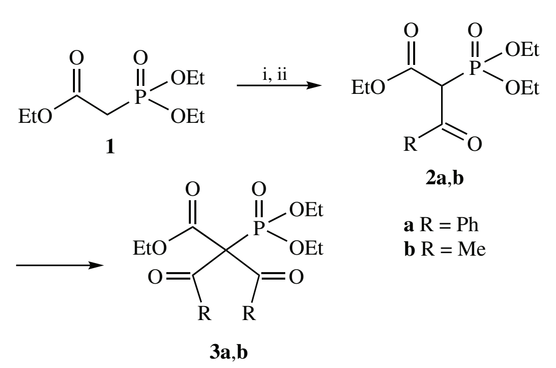
The substitution in active methylene compounds is of interest because it may afford valuable intermediates. The alkylation of CH-acidic substrates is better studied than the acylation.[1] The green chemistry protocols are especially important.[2] It was a challenge for us to synthesize phosphonoylated derivatives of 1,3-dicarbonyl compounds. However, this approach led to the corresponding enol-substituted derivatives as shown by route 'A' in Scheme 1, which is exemplified by the reaction of methyl acetoacetate with diethyl phosphorochloridate in ether after deprotonation with sodium hydride. The corresponding enol phosphate was prepared in 97% yield in a diastereoselective manner.[3] It is noteworthy that the copper-catalyzed radical cross-coupling of dicarbonyl compounds and trialkyl phosphites afforded the corresponding C-phosphonoylated derivatives.[4] We chose another strategy to prepare C-phosphonoylated derivatives of dicarbonyl compounds. According to this, we planned to acylate β-oxo phosphonate derivatives in the fashion shown by route 'B' in Scheme 1, which was successfully applied in earlier studies. One possibility is to carry out the acylation *via* the magnesium derivatives of phosphonoacetates.[5–7] As an alternative method, the treatment of β-oxo phosphonates with sodium hydride followed by acylation of the sodium derivatives so formed was also described.[8] Arbuzov *et al.* elaborated the acylation of trimethyl phosphonoacetate salts obtained by deprotonation with sodium metal or magnesium methoxide.[9]

We chose diethyl (ethoxycarbonylmethyl)phosphonate **1** as the starting material in our acylation reactions in order to prepare new diacyl-phosphonoylmethyl derivatives. The deprotonation was performed with 60% sodium hydride / paraffin in ethereal or THF solution at 0 °C. This was followed by the addition of acyl chlorides (Scheme 2). To our surprise, in all experiments the expected monoacylated products **2** were only minor components, while the diacylated ones **3** predominated.[†] The molar ratios and the solvent had only a small effect on the outcome (Table 1). When 1.1 equiv. of NaH in Et_2O and 1.2 equiv. of PhC(O)Cl were used, the resulting mixture contained 35% of the starting material **1** along with 14% of the monobenzoyl derivative **2a** and 51% of the dibenzoyl compound **3a** (see Table 1, entry 1). Changing for THF led to a 25–37% proportion of **2a** and **3a** (entry 2). With the use of 1.5 equiv. of NaH and the similar amount of PhC(O)Cl, the crude composition was 22% of **1**, 19% of **2a** and 59% of **3a** (entry 3). In this case, dibenzoyl compound **3a** was isolated in a 44% preparative yield after column chromatography. The similar reaction with MeC(O)Cl furnished diacetyl product **3b** in a proportion of 77%, and in a preparative yield of 58% (entry 4).



Scheme 1

This is a new observation revealing that despite the 1.1–1.5 : 1.2–1.5 molar ratios of NaH / **1** and PhC(O)Cl / **1**, the disubstituted product **3a** predominated. It was impossible to achieve predomination of the mono-acylated compound **2a**. It is of note that according to the observation of Arbuzov *et al.*, the reaction between trimethyl phosphonoacetate [deprotonated with Na or $(MeO)_2Mg$] and aroyl chlorides [PhC(O)Cl and $4\text{-}O_2NC_6H_4C(O)Cl$] also gave bis-aroyl products along with the monoacylated ones.[9]



Scheme 2 *Reagents and conditions*: i, NaH (1.2–1.5 equiv.), THF or Et_2O, 0 °C; ii, RC(O)Cl (1.2–1.6 equiv.), 0 → 26 °C.

Table 1 The effect of the reagent molar ratios on the outcome of the acylation of diethyl (ethoxycarbonylmethyl)phosphonate **1**.

Entry	NaH (equiv.)	RC(O)Cl		Solvent	Product composition^a (%)		
		R	equiv.		**1**	**2**	**3**
1	1.1	Ph	1.2	Et_2O	$35^{b,c}$	$14^{b,d}$	$51^{b,e}$
2	1.2	Ph	1.2	THF	$38^{b,c}$	$25^{b,d}$	$37^{b,e}$
3	1.5	Ph	1.5	THF	$22^{b,c}$	$19^{b,d}$	$59^{b,e}$
4	1.5	Me	1.6 or 2.2	Et_2O	$17^{b,c}$	$6^{b,f}$	$77^{b,g}$

^{a} From ^{31}P NMR of the crude product. ^{b} LC–MS: ^{c} **1**, M + H = 225 Da, ^{d} **2a**, M + H = 329 Da, ^{e} **3a**, M+ H = 433 Da, ^{f} **2b**, M + H = 267 Da, ^{g} **3b**, M + H = 309 Da.

The minor mono-acylated species **2a** and **2b** were detected by ^{31}P NMR and HR-MS. The benzoyl product **2a** was known from earlier studies,[4] when its keto–enol tautomerism was assumed. The diacylated species **3a** and **3b** isolated were characterized by ^{31}P, ^{13}C and ^{1}H NMR, as well as HR-MS.[†] For comparison, the δ_P shift of the starting material **1** in this work was measured as 19.9 ppm ($CDCl_3$) (*cf.* 19.5 ppm in ref. 10 and 21.0 ppm in ref. 11).

The reason for the lack of selectivity for the monoacylation of (ethoxycarbonylmethyl)phosphonate **1** can be attributed to the higher acidity of the monoacyl products **2** compared to the starting substrate **1**. Apparently, the ΔpK_a values (criteria for the relative acidities estimated by the Gaussian method[12]) of the starting material **1** and the monoacyl intermediates **2a**,**b** are equal to 10.034, 0 and 1.362, respectively.

In summary, acylation of the sodium salt obtained from diethyl (ethoxycarbonylmethyl)phosphonate **1** afforded surprisingly the diacyl derivatives as predominated products regardless of the amounts of the base and acyl chlorides having been applied. The reason for the rather selective formation of the diacylated products is the greater CH-acidity of the monoacylated intermediates.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.033.

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[†] *General procedure for the acylation of diethyl (ethoxycarbonylmethyl)phosphonate* **1**. To diethyl (ethoxycarbonylmethyl)phosphonate **1** (4.0 mmol, 0.80 ml, 0.90 g) in dry diethyl ether or THF (20 ml), sodium hydride (60% dispersion in mineral oil, 4.4–6.0 mmol, 0.18–0.24 g) was added at 0 °C on stirring. After the evolution of hydrogen gas ceased, benzoyl chloride (4.8–6.0 mmol, 0.56–0.70 ml, 0.67–0.84 g) or acetyl chloride (8.8 mmol, 0.63 ml, 0.69 g) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 24 h, then filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by repeated column chromatography on silica gel using dichloromethane–methanol (97 : 3) as the eluent to afford products **3a** and **3b**.

Diethyl (1,1-dibenzoyl-1-ethoxycarbonylmethyl)phosphonate **3a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.13 (t, 3H, $COCH_2CH_3$, *J* 7.1 Hz), 1.31 (t, 6H, $POCH_2CH_3$, *J* 7.1 Hz), 4.14–4.26 (m, 6H, OCH_2), 7.29–8.21 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 13.7 ($C–OCH_2CH_3$), 16.2 ($P–OCH_2CH_3$, *J* 6.9 Hz), 62.0 ($C–OCH_2$), 62.9 ($P–OCH_2$, *J* 5.4 Hz), 117.4 (CP, *J* 176.5 Hz), 161.3 (C=O, *J* 3.1 Hz), 163.8 (C=O, *J* 1.8 Hz), 164.9 (CO_2Et, *J* 9.3 Hz); aromatic signals: C_α: 128.76, 133.93 (*J* 12.5 Hz); C_β: 128.54*, 130.35*; C_γ: 127.56*, 128.68*; C_δ: 130.83, 133.92. * tentative assignments; ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 8.9; HRMS (ESI), *m*/*z*: 455.1230 $[M + Na]^+$ (calc. for $C_{22}H_{25}O_7PNa$, *m*/*z*: 455.1236).

Diethyl (1,1-diacetyl-1-ethoxycarbonylmethyl)phosphonate **3b**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.30 (t, 6H, $POCH_2CH_3$, *J* 7.0 Hz), 1.31 (t, 3H, $COCH_2CH_3$, *J* 6.8 Hz), 2.15 (s, 3H, $C(O)CH_3$), 2.21 (bs, 3H, $C(O)CH_3$), 4.03–4.16 (m, 4H, $POCH_2$), 4.23–4.30 (m, 2H, $COCH_2$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 13.9 ($C–OCH_2CH_3$), 16.0 ($P–OCH_2CH_3$, *J* 6.8 Hz), 20.2 (CH_3, *J* 10.9 Hz) and 20.9 (CH_3), 61.7 ($C–OCH_2$), 62.5 ($P–OCH_2$, *J* 5.4 Hz), 116.3 (CP, *J* 180.2 Hz), 164.8 (CO_2Et, *J* 9.3 Hz), 165.3 (C=O, *J* 2.7 Hz), 167.9 (C=O, *J* 1.9 Hz); ^{31}P NMR ($CDCl_3$, 125.5 MHz) δ: 8.7; HRMS (ESI), *m*/*z*: 331.0919 $[M + Na]^+$ (calc. for $C1_2H_{21}O_7PNa$, *m*/*z*: 331.0923).

The minor monoacylated products **2a** and **2b** were identified in the crude mixtures.

Diethyl (1-benzoyl-1-ethoxycarbonylmethyl)phosphonate **2a**. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 13.9 (lit.[5] 13.4, lit.[4] 14.3); HRMS (ESI), *m*/*z*: 351.0967 $[M + Na]^+$ (calc. for $C_{15}H_{21}O_6PNa$, *m*/*z*: 351.0973).

Diethyl (1-acetyl-1-ethoxycarbonylmethyl)phosphonate **2b**. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 13.3; HRMS (ESI), *m*/*z*: 289.0823 $[M + Na]^+$ (calc. for $C_{10}H_{19}O_6PNa$, *m*/*z*: 289.0817).