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Heterogeneous mediated Alkylation of Ethyl Diethylphosphonoacetate. A "One Pot" Access to α-Alkylated Acrylic Esters

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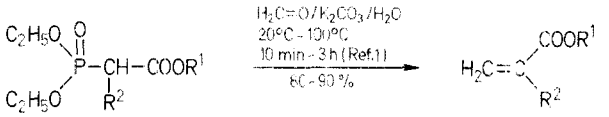
Ethyl diethylphosphonoacetates are α-alkylated in high yield in a heterogeneous reaction with solid potassium carbonate as base. A "one pot" synthesis of α-alkylated acrylic esters is achieved in a PO-activated olefination reaction aqueous media, when aqueous potassium carbonate and formaldehyde are added directly to the above reaction mixture.

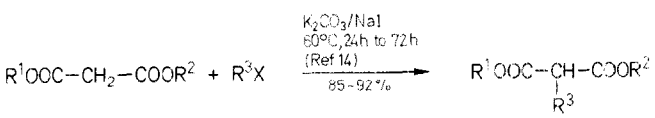
α-Alkylated acrylic esters **3** are potential intermediates in synthesis of some natural products, especially when R^2 is an allyl group. A very attractive route for their preparation has been described[1] from α-substituted alkyl diethylphosphonoacetates using a PO-activated olefination reaction in aqueous media with mild base (potassium carbonate) and aqueous formaldehyde.



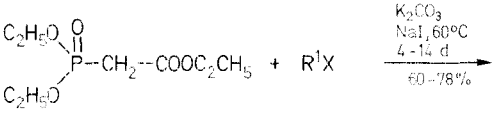
2 **3**

Access to **2** has been made by Arbuzov reaction between triethylphosphite and the appropriate α-bromoester[2-3,4]. Another method is the alkylation of metallated alkyl dialkylphosphonoacetates in anhydrous media (xylene, benzene, ether, tetrahydrofuran) with lithium sodium, potassium, or sodium hydride as metallating agent[5-10]. Yields are generally not so good (30% to 75%) due to simultaneous mono- and dialkylation giving product mixtures, which are difficult to separate. Ion pair extraction is very attractive, but gives poor yields (30%) with alkyl dialkylphosphonoacetates[11]. Recently α-substituted phosphonoacetates had been synthesized from dimethyl-1-diazo-2-oxoalkylphosphonates by a Wolf rearrangement on direct irradiation[12] and from diethyl 1-lithioethylphosphonate by condensation with diethylcarbonate[13].

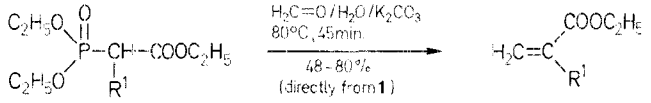
In a previous publication[14] we give a simplified procedure for high yield, selective, mono C-alkylation of active methylene compounds in heterogeneous media using potassium carbonate as base and small amount of sodium iodide to generate an iodide derivative *in situ*, which favors alkylation.



Now we apply these reaction conditions to the alkylation of phosphonic ester **1**. Despite the lower acidity of the methylene group, we found that **1** can be alkylated in good yields with high mono-C-alkylative selectivity. Phosphonic ester **1** is simply mixed with an alkyl bromide or chloride, potassium carbonate, sodium iodide, and stirred at 60°C.



1



2a-g **3a-h**

Due to the lower acidity of the methylene group in **1**, total reaction requires longer time (4 to 14 days) and a larger amount of sodium iodide. Results are summarized in Table 1.

Surprisingly with alkyl iodide used without sodium iodide no alkylation of **1** occurs, as it does with acetoacetic or malonic esters. Allyl and propargyl halides are known to favor dialkylation; mild reaction conditions generally minimize this lack of selectivity with allylic derivatives (**2a, 2b**), but the method fails with propargyl bromide (**2d**) which is completely consumed after five days giving a 16:58:26 mixture of starting material, monoalkylated, dialkylated compounds. Using classical methods (potassium in xylene and sodium hydride in tetrahydrofuran), results are quite identical, in contradiction with a recent report[15], which gives a 71% yields of ethyl 2-diethylphosphono-4-pentynoate (**2d**).

After the end of the alkylation reaction, a PO-activated olefination reaction can be achieved by adding two equivalents of potassium carbonate (aqueous solution) and two equivalents of formaldehyde (35% aqueous solution) directly to the reaction mixture, and stirring for approximatively forty five minutes at 80°C. The α-alkylated acrylic ester is easily extracted with ether and purified by distillation. Results are summarized in Table 2.

3 is sometimes obtained with by-products: **3a** and **3d** with α-disubstituted phosphonic esters, **3h** with acrylic or α-hydroxyacrylic ester due to PO-activated olefination reaction on remaining starting phosphonoacetate[16,17].

Since phosphonoacetate **1** is synthesized by Arbuzov reaction from ethyl bromoacetate in almost quantitative yield, this method offers a useful way for tandem alkylation and methylenation of this ester in 50–80% overall yield.

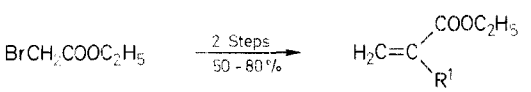


Table 1. Ethyl 2-Diethylphosphonoalkanoates **2** Prepared

Product **2**	R^1X	Reaction Time [days]	Yield [%]	b.p. [°C] (10^{-2} torr)	Molecular Formula[a] n_D^{20} (Lit. data)	^{13}C-NMR[b] 1 2 3 7 8 $(CH_3CH_2O)_2P(O)CH(CH_2R)$ 4 5 6 $COOCH_2CH_3$
a	$CH_2=CHCH_2Br$	5	70 (dialkylation 10%)	85	$C_{11}H_{21}O_5P$ (264.2)	δ: 16.4 (62.7, 62.6); 45.6; 168.4; 61.2; 14.2; 31.2, 134.9; 117 J: C_3P = 130.9; C_7P = 4.4; C_8P = 16.2
b	$CH_3CH=CHCH_2Cl$	5	77	90	$C_{12}H_{23}O_5P$ (278.3) 1.4471	δ: 16.4; (62.7, 62.5); 46.2; 168.4; 61.2; 14.2; 30.2; 127.4; 127.8; 17.8 J: C_3P = 130.9; C_7P = 4.4; C_8P = 16.2
c	$CH_2=C(CH_3)CH_2Cl$	5	60	90	$C_{12}H_{23}O_5P$ (278.3) 1.4453	δ: 16.5; (62.8, 62.6); 44.5; 168.7; 61.3; 14.2; 34.7; 142.2; 22.3; 111.9 J: C_3P = 130.9; C_7P = 4.4; C_8P = 16.2
d	$HC\equiv CCH_2Br$	5	[c]			
e	C_4H_9Br	10	77	100	1.4370 (1.4322[6])	δ: 14.4; (60.5, 60.6); 44; 166.9; 59.1; 12.3; 28.7; 25; 20.4; 11.8 J: C_3P = 131.3; C_7P = 14.4; C_8P = 3.7
f	Me_3SiCH_2Cl	8	64	95	$C_{12}H_{27}O_5PSi$ (310.4)	δ: 16.4; 62.6; 41.1; 169.4; 61.1; 14.2; 13.3; 0.5
g	$C_6H_5CH_2Cl$	4	78	135	1.4873 (1.4832[6])	δ: 16.5 (62.8, 62.6); 47.8; 168.4; 61.2; 14; 133; 138.7 J: C_3P = 128; C_7P = 4.4; C_8P = 16.2

[a] Satisfactory microanalyses obtained: C ±0.09, H ±0.09.
[b] Spectra obtained on a WH90 Bruker spectrometer at 22.63 MHz ($CDCl_3$/TMS): δ[ppm]; J(CP) [Hz].
[c] Mixture of 16% starting material, 58% mono *C*-alkylation and 26% di *C*-alkylation compounds.

Table 2. α-Alkylated Acrylic Esters **3** Prepared

Product **3**	R^1X	Yield [%]	b.p. [°C]/torr	n_D^{20}	Molecular Formula or Lit. data: b.p. [°C]/torr or n_D	^{1}H-NMR[a] (Lit. data) (*Z*)-β-H	(*E*)-β-H	δ[ppm] α-CH_2–
a	$CH_2=CHCH_2Br$	53	60°/17	1.4390	155–6°[18] 103°/140[19] n_D^{15} 1.4407[19]	6.07	5.46	2.96
b	$CH_3CH=CHCH_2Cl$	59	74°/17	1.4450	104–106°/45[21] n_D^{23} 1.4434[21]	5.95	5.36	2.90
c	$CH_2=C(CH_3)CH_2Cl$	58	70°/15	1.4412	160–161°[20]	5.97	5.33	2.87
d	$ClCH=CHCH_2Cl$	56	90–95°/10	1.4522	$C_8H_{11}O_2Cl$[b] (174.5)	6.03	5.47	3.03
e	C_4H_9Br	56	70–75°/8	1.4283	82–84°/30[22] 88°/31[21]	6.07 (6.06[23])	5.47 (5.45[23])	2.27 (–)
f	$C_6H_5CH_2Cl$	80	70–75°/1	1.5072	71°/0.3[1] 134°/15[18] 106°/3[21]	6.03 (6.16[23])	5.23 (5.35[23])	3.50 (–)
g	$C_7H_{15}Br$	65	65–69°/0.5	1.4555	87°/2[1]	5.95	5.36	2.23
h	$(CH_3)_3SiCH_2Cl$	48	78°/17	1.4383	50°/10[24]	5.97 (5.97[24])	5.27 (5.23[24])	1.90 (1.80[24])

[a] Spectra obtained on an R24 Hitachi spectrometer at 60 MHz (CCl_4/TMS).
[b] Calc. C 55.02 H 6.35 Cl 20.30
found 55.23 6.47 20.52

The method presented here to prepare **3** complements the syntheses of alkylated acrylic previously reported[1,25]. In one case[25], the synthesis of ethyl 2-butylpropenoate **3e** was also achieved from ethyl diethylphosphonoacetate in a two step, one-pot, alkylation-olefination sequence, but with sodium hydride as base in dimethoxyethane as solvent. In our opinion potassium carbonate in water is a more convenient system and can be used advantageously if short reaction times are not requires for the total sequence **1** → **3**.

Ethyl 2-methylene-4-hexenoate (3b); Typical Procedure:
Ethyl diethylphosphonoacetate (22.4 g, 0.1 mol and crotyl chloride (10.9 g, 0.12 mol) are mixed with potassium carbonate (28 g,

0.2 mol) – dried by storage in a drying oven – and sodium iodide (7.5 g, 0.05 mol), then stirred magnetically at 60°C during five days.

Isolation of Ethyl 2-Diethylphosphono-4-hexenoate (**2b**):
The above mixture is diluted with water, extracted with ether (2 × 50 ml); the organic phase is washed with saturated aqueous sodium chloride solution and dried with magnesium sulfate. Removal of ether and distillation of the residue *in vacuo* give pure **2b**; yield: 21.4 g (77%).

"One pot" Synthesis of Ethyl 2-Methylene-4-hexenoate (**3b**):
Potassium carbonate (28 g, 0.2 mol) diluted in water (50 ml) and formaldehyde (40 ml of 35% aqueous solution, 0.4 mol) are added to the reaction mixture obtained in the alkylation step, and the resultant mixture is stirred at 80°C during 45 min. After cooling, the organic phase is extracted with ether, washed with saturated aqueous sodium chloride solution, and dried with magnesium sulfate. Removal of ether and distillation afford pure **3b**; yield: 18.2 g (59%).

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