Convenient Preparations of (Diphenylphosphono)acetic Acid Esters and the Comparison of the *Z*-Selectivities of Their Horner−Wadsworth−Emmons Reaction with Aldehydes Depending on the Ester Moiety

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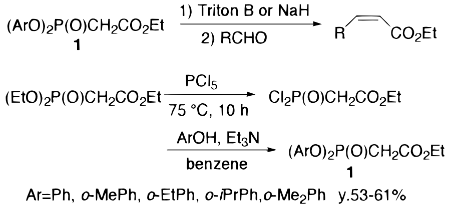
The Horner−Wadsworth−Emmons (HWE) reaction is a widely used method for the preparation of α,*β*-unsaturated esters.[1] Since this reaction preferentially gives more stable *E*-olefins in general,[2] extensive effort has been devoted to the stereoselective construction of *Z*-α,*β*-unsaturated esters.[3] Recently we have reported the preparation of ethyl (diarylphosphono)acetates (**1**) and the HWE reaction of **1** with several kinds of aldehydes to give *Z*-unsaturated esters with high selectivity (Scheme 1).[4] Our method provides a simple, economical, and highly selective route to a wide range of *Z*-unsaturated esters in almost quantitative yields. Since our reagents **1** are useful in synthesis,[5,6] we saw the need to improve the preparation procedure. Originally we prepared **1** from triethyl phosphonoacetate, PCl_5, and the corresponding phenol via ethyl (dichlorophosphono)acetate. Since we could not isolate those reagents by distillation and there were some byproducts with R_f values similar to the reagents, this method required a tedious and careful column chromatography purification. Now we report two new and convenient preparations of ethyl (diphenylphosphono)acetate. These procedures also gave us an opportunity to make other (diphenylphosphono)acetic acid esters. Two decades ago Kishi showed that the ratio of *E*- and *Z*-esters in the HWE reaction is in proportion to the bulkiness of phosphonate reagents.[7] A phosphonate reagent with a larger phosphonate or a larger ester group gave higher *E*-selectivity. To our surprise, the comparison of the HWE reaction of (diphenylphosphono)acetic acid esters showed that a phosphonate reagent with a bulkier ester moiety gave higher *Z*-selectivity.

Scheme 1



Scheme 2

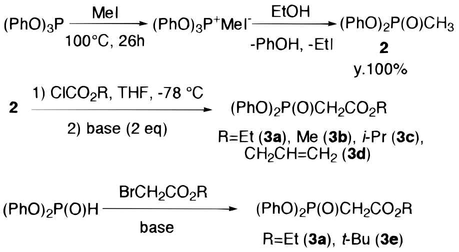


Table 1. Acylation of Diphenyl Methylphosphonate 2

entry	$ClCO_2R$	base	product, % yield
1	$ClCO_2Me$	LDA	**3b**, 76
2	$ClCO_2Me$	LiHMDS	**3b**, 87
3	$ClCO_2Et$	LiHMDS	**3a**, 89
4	$ClCO_2$*i*Pr	LiHMDS	**3c**, 71
5	$ClCO_2CH_2CH{=}CH_2$	LiHMDS	**3d**, 87

Table 2. Reaction of Diphenyl Phosphite with Alkyl Bromoacetate

entry	$BrCH_2CO_2R$	conditions	% yield
1	$BrCH_2CO_2Et$	benzene, Et_3N, 2 h	19
2	$BrCH_2CO_2Et$	benzene, pyridine, 2 d	trace
3	$BrCH_2CO_2Et$	DMSO, NaH, 2 h	trace
4	$BrCH_2CO_2Et$	CH_3CN, Et_3N, 2 h	29
5	$BrCH_2CO_2Et$	CH_2Cl_2, *i*-Pr_2EtN, 40 °C, 4 h	47
6	$BrCH_2CO_2Et$	CH_2Cl_2, Et_3N, 1 h	53
7	$BrCH_2CO_2$*t*-Bu	CH_2Cl_2, Et_3N, 1 h	77

Results

Improved Preparations of (Diphenylphosphono)-acetic Acid Esters. In the first preparation procedure, (diphenylphosphono)acetic acid esters (**3**) were prepared by acylation of diphenyl methylphosphonate (**2**), which was prepared from triphenyl phosphite and methyl iodide in a quantitative yield (Scheme 2).[8] Unlike the anions derived from dialkyl methylphosphonate,[9,10] the anion from **2** is unstable even at −78 °C. When **2** was treated with lithium diisopropylamide (LDA) at −78 °C, followed by methyl chloroformate, only a trace of product was obtained, and decomposition of **2** was the main reaction. Treatment of **2** with base in the presence of acylating reagent circumvented this difficulty. Also, it is essential

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10.1021/jo9907181 CCC: $18.00

Table 3. HWE Reaction of 3a−e with Aldehydes in THF

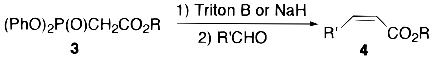
entry	reagent	R′CHO	conditions[a]	yield (%)	**4** (*Z*:*E*)
1	**3b**(Me)	PhCHO	Triton B, −78 °C, 1 h	94	91:9
2	**3d**(allyl)	PhCHO	Triton B, −78 °C, 1 h	88	91:9
3	**3a**(Et)	PhCHO	Triton B, −78 °C, 30 min	98	93:7
4	**3c**(*i*-Pr)	PhCHO	Triton B, −78 °C, 1 h	95	94:6
5	**3e**(*t*-Bu)	PhCHO	Triton B, −78 °C, 1 h	100	94:6
6	**3b**(Me)	*t*-2-hexenal	Triton B, −78 °C → −20 °C	89	87:13
7	**3d**(allyl)	*t*-2-hexenal	Triton B, −78 °C → 0 °C	90	87:13
8	**3a**(Et)	*t*-2-hexenal	Triton B, −78 °C → −35 °C	97	89:11
9	**3c**(*i*-Pr)	*t*-2-hexenal	Triton B, −78 °C → −20 °C	100	90:10
10	**3e**(*t*-Bu)	*t*-2-hexenal	Triton B, −78 °C → −20 °C	95	91:9
11	**3b**(Me)	*n*-$C_7H_{15}CHO$	NaH, −78 °C → 0 °C	94	86:14
12	**3d**(allyl)	*n*-$C_7H_{15}CHO$	NaH, −78 °C → 0 °C	100	88:12
13	**3a**(Et)	*n*-$C_7H_{15}CHO$	NaH, −78 °C → −10 °C	100	90:10
14	**3c**(*i*-Pr)	*n*-$C_7H_{15}CHO$	NaH, −78 °C → 0 °C	98	90:10
15	**3e**(*t*-Bu)	*n*-$C_7H_{15}CHO$	NaH, −78 °C → 0 °C	99	91:9
16	**3b**(Me)	BuCHEtCHO	NaH, −78 °C → 0 °C	92	93:7
17	**3d**(allyl)	BuCHEtCHO	NaH, −78 °C → 0 °C	93	93:7
18	**3a**(Et)	BuCHEtCHO	NaH, −78 °C → −10 °C	100	94:6
19	**3c**(*i*-Pr)	BuCHEtCHO	NaH, −78 °C → 0 °C	94	95:5
20	**3e**(*t*-Bu)	BuCHEtCHO	NaH, −78 °C → 0 °C	92	95:5

[a] **3** was treated with Triton B at −78 °C for 10 min, and NaH at 0 °C for 15 min, respectively. The reaction mixture was warmed over 1−2 h except for the reaction with benzaldehyde.

to use 2 equiv of base to get optimized yields. The results are summarized in Table 1. When LDA was used as a base, methyl (diphenylphosphono)acetate (**3b**) was obtained in 76% yield (entry 1). We noticed some impurity derived from LDA, whose R_f value was similar to the product and which was difficult to remove from the product by distillation. The use of lithium hexamethyldisilazide (LiHMDS) suppressed the formation of this byproduct and gave a higher yield (87%) (entry 2). Ethyl, isopropyl, and allyl chloroformate gave the corresponding (diphenylphosphono)acetic acid esters, **3a**, **3c**, and **3d** in 71−89% yields (entries 3−5). These reactions were clean, and the products were easy to purify. This method gives convenient access to a variety of (diphenylphosphono)acetic acid esters.

As an alternative procedure, we examined nucleophilic substitution of ethyl bromoacetate with commercially available diphenyl phosphite in the presence of base. This is a promising candidate since it is well-known that the anion of dialkyl phosphite reacts readily with alkyl halides to give high yields of phosphonates.[11−13] When diphenyl phosphite was treated with ethyl bromoacetate and triethylamine in benzene for 2 h, **3a** was obtained in 19% yield (entry 1 in Table 2). Although the extension of reaction time was not advantageous, changing the solvent to CH_2Cl_2 improved the yield dramatically. Now **3a** is obtained in 53% yield by a simple procedure (entry 6). Although the yield is not great, this procedure uses only commercially available and inexpensive reagents and does not require any hazardous chemicals. The product is also easily isolated by either column chromatography or distillation.[14] *tert*-Butyl (diphenylphosphono)acetate (**3e**) was also prepared by the same procedure in 77% yield.

Horner−Wadsworth−Emmons Reaction of (Diphenylphosphono)acetic Acid Esters with Aldehydes. The results of the HWE reaction of **3b−e** with aldehydes were summarized along with the data of **3a**[4b] in Table 3. When **3** were treated with benzyltrimethylammonium hydroxide (40% in MeOH) (Triton B) followed by addition of benzaldehyde in tetrahydrofuran (THF) at −78 °C, 91−94% *Z*-selectivities were obtained (entries 1−5). The selectivity is highest with the large ester moieties, with **3c** (*i*-Pr) and **3e** (*t*-Bu) being greater than **3b** (Me) and **3d** (allyl). The same trend was observed in the reaction with *trans*-2-hexenal (entries 6−10, 87−91% *Z*-selectivity), *n*-octyl aldehyde (entries 11−15, 86−91% *Z*-selectivity), cyclohexanecarboxaldehyde (90−94% *Z*-selectivity, see Supporting Information), and 2-ethylhexanal (entries 16−20, 93−95% *Z*-selectivity).[15] For the aliphatic saturated aldehydes, NaH was used as a base. The *Z*:*E* ratios of all the HWE products **4** were determined by integrating the vinyl proton signals in the 500 MHz ^1H NMR spectra.[16] The signal assignments were confirmed by nuclear Overhauser effect (NOE) experiments.



Note that the products from the reaction of allyl[17] and *tert*-butyl ester reagents, **3d** and **3e**, can be transformed

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(14) There is a byproduct which cannot be removed by distillation from **3a**. This byproduct gradually decomposes to PhOH and nonvolatile compounds, which can be removed by distillation. Although acid (2 mol/L HCl) or base (2 mol/L NaOH) treatment of the crude mixture did not promote the decomposition of this byproduct, keeping the crude mixture in the air for a few days and bulb-to-bulb distillation (250 °C/3 mmHg) gave ∼95% pure **3a**.

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to the corresponding α,*β*-unsaturated acid[12,18] under mild conditions. The easy availability of many kinds of *Z*-α,*β*-unsaturated esters will increase the value of our diphenyl reagents **3** as useful synthetic tools.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone just before use. All reactions were conducted under an argon atmosphere. Column chromatography was performed on silica gel (Wakogel C-300).

Ethyl Diphenylphosphonoacetate (3a) from 2. To a solution of hexamethyldisilazane (7.33 mL, 34.5 mmol) in THF (10 mL) was added *n*-butyllithium (21.56 mL, 34.5 mmol) at 0 °C, and 15 min later, this solution was added to a solution of diphenyl methylphosphonate **2** (3.72 g, 15.0 mmol) and ethyl chloroformate (1.47 mL, 15.0 mmol) in THF (40 mL) at −78 °C. After stirring for 1 h at −78 °C, the mixture was quenched with saturated NH_4Cl and extracted with AcOEt (20 mL × 2). The combined extracts were washed with water (20 mL × 2) followed by brine, dried ($MgSO_4$), and concentrated to a pale yellow residue. Column chromatography (silica gel 80 g/hexane−AcOEt (5:1 to 3:1)) provided **3a** (4.27 g, yield 89%) as a colorless oil. The above method was applied for the preparation of **3b**−**d**.

Ethyl Diphenylphosphonoacetate (3a) from Diphenyl Phosphite. To a solution of diphenyl phosphite (2.25 mL, 85∼90%, ∼10.0 mmol) in CH_2Cl_2 (10 mL) were added ethyl bromoacetate (1.16 mL, 10.0 mmol) and then triethylamine (1.97 mL, 14.0 mmol) at 0 °C. After stirring for 15 min at 0 °C, the mixture was stirred for 1 h at room temperature, quenched with water, and extracted with AcOEt−hexane (3:1) (30 mL). The extract was washed with water (20 mL) followed by brine, dried ($MgSO_4$), and concentrated to a pale yellow residue. Column chromatography (silica gel 30 g/hexane−AcOEt (5:1 to 3:1)) provided **3a** (1.70 g, yield 53%) as a colorless oil. The above method was applied for the preparation of **3e** (yield 77%).

HWE Reaction of 3 with Aldehydes. See Experimental Section in ref 4b.

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Supporting Information Available: Characterization data and ^{1}H NMR spectra for compounds **3b**−**e** and the olefin products **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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