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Practical Synthesis of Z-Unsaturated Esters by Using a New Horner-Emmons Reagent, Ethyl Diphenylphosphonoacetate

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Abstract : A new Horner-Emmons reagent, ethyl diphenylphosphonoacetate **1** was prepared from triethyl phosphonoacetate, PCl_5, and phenol in 60% overall yield. Horner-Emmons reaction of **1** with aldehydes in the presence of Triton® B or NaH in THF gave the Z-unsaturated esters in 89-93% selectivity in almost quantitative yields. Furthermore, **1** showed up to 99% Z-selectivity under Still's condition (KHMDS/18-crown-6).

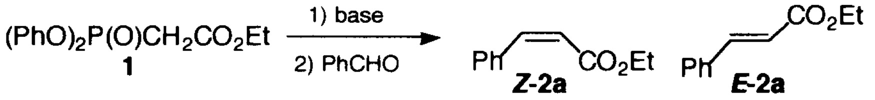
The Horner-Emmons modification of the Wittig reaction is a widely used method for the preparation of unsaturated esters. In contrast to the Wittig reaction of non-stabilized ylides with aldehydes, the Horner-Emmons modification shows a strong preference for formation of the more stable *E*-olefins. Several attempts were made to increase the proportion of Z-olefins by the choice of cation, temperature, solvent, and the structure of phosphonate reagents with a limited success.[1,2] Some reports of getting the Z-olefins as main products by using five-membered cyclic phosphonates,[3] five-membered cyclic phosphonamides,[4] and bis(trifluoroethyl) phosphonates[5] have appeared. Among them, Still's reagent, methyl bis(trifluoroethyl) phosphonoacetate in the presence of KHMDS / 18-crown-6 in THF have been shown to be the most selective and versatile. Although this method had attained widespread recognition in synthesis,[6,7] we felt the need of developing an economical way to the Z-unsaturated esters.

In this paper we report on the Horner-Emmons reaction of our new reagent, ethyl diphenylphosphonoacetate **1**, which shows a high Z-selectivity without use of expensive reagents. The compound **1** was readily prepared from triethyl phosphonoacetate, PCl_5, and phenol via ethyl dichlorophosphonoacetate in 60% overall yield.[8]

$$(EtO)_2P(O)CH_2CO_2Et \xrightarrow[75\ ^\circ C,\ 10\ h]{PCl_5} Cl_2P(O)CH_2CO_2Et \xrightarrow[benzene]{PhOH,\ Et_3N} \underset{\mathbf{1}}{(PhO)_2P(O)CH_2CO_2Et}$$

The reagent **1** was first reacted with benzaldehyde and the results are summarized in Table 1. When the reaction was carried out in tetrahydrofuran (THF) at -78 °C for 30 min using benzyltrimethylammonium hydroxide (40% in MeOH) (Triton® B) as a base, 91% Z-selectivity was obtained (Entry 1). Diluting the reaction medium favored the formation of the Z-isomer and achieved 93% Z-selectivity in 98% chemical yield (Entry 2). Low solubility of **1** to ether

Table 1. Horner-Emmons Reaction of **1** with Benzaldehyde



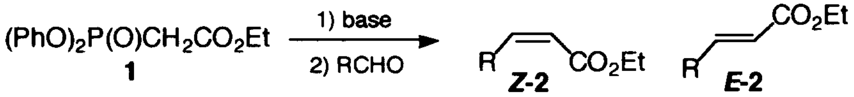
Entry	base	Solvent	Conditions	yield(%)	*Z*/*E* ratio
1	Triton® B	THF (3)[a]	-78 °C, 30 min	96	91 : 9
2	Triton® B	THF (20)	-78 °C, 30 min	98	93 : 7
3	Triton® B[b]	THF (20)	-78 °C, 1 h	71 (24)[c]	91 : 9
4	Triton® B	ether (20)	0 °C, 1 h	67	29 : 71
5	Triton® B	DME (20)	-78 °C, 20 min→-50 °C	63 (34)	79 : 21
6	Triton® B	toluene (20)	-78 °C, 1 h	46 (7)	66 : 34
7	BuLi	THF (3)	-78 °C, 30 min	60 (34)	67 : 33
8	LDA	THF (5)	-78 °C, 1 h	85 (12)	80 : 20
9	NaH	THF (5)	-78 °C, 30 min→-35 °C	100	85 : 15
10	*t*-BuOK	THF (3)	-78 °C, 30 min	94	86 : 14
11	*t*-BuOK	THF (20)	-78 °C, 2.5 h→-50 °C	98	91 : 9
12	*t*-BuOK	DME (20)	-78 °C, 40 min	59 (41)	89 : 11
13	KHMDS	THF (20)	-78 °C, 1 h	93	92 : 8
14	KHMDS	THF (20), 18-crown-6 (5 eq)	-78 °C, 1 h	98	99 : 1

a: The number in parentheses is the quantity of solvent (ml / 1 mmol). b: Methanol of Triton® B was removed by aspirator. c: The number in parentheses is the recovered yield of **1** (%).

and toluene prevented their use and THF turned out to be the best with respect to both the *Z*-selectivity and the chemical yield among the solvents examined (Entries 4-6). The effect of bases on the *Z* / *E* ratio was next studied (Entries 7-13). Moderate to good *Z*-selectivity (67-85%) was obtained when BuLi, LDA, or NaH was employed, while better results were observed with potassium bases, *t*-BuOK and potassium hexamethyldisilazide (KHMDS) (91-92% *Z*-selectivity). Furthermore, when Still's procedure (KHMDS / 18-crown-6) was applied to this reaction, an extremely high *Z*-selectivity (99:1) was attained in 98% chemical yield (Entry 14). This result shows the reagent **1** is as effective as Still's reagent or more for the synthesis of ethyl *cis*-cinnamate. Since the main object of this study is to develop a practical and economical method for the synthesis of *Z*-unsaturated esters, we chose cheap Triton® B as a base.

Horner-Emmons reaction of **1** with other types of aldehydes in THF solvent was studied (Table 2).[9] The reaction with α,β-unsaturated aldehyde or aliphatic aldehyde in the presence of Triton® B was not sensitive to the structure of aldehydes and 89-90% *Z*-selectivity was uniformly obtained in an almost quantitative yield (Entries 2,3,7,9,11). The *Z*-selectivities with octyl aldehyde are not changed by using NaH and 90% *Z*-selectivity was obtained irrespective of the concentration (Entries 4,5). Still's procedure (KHMDS / 18-crown-6) again gave a slightly improved selectivity (92:8), which is identical with the result from Still's reagent (The chemical

Table 2. Horner-Emmons Reaction of **1** with Several Types of Aldehydes in THF Solvent



Entry	R	base	THF[a]	Conditions[b]	yield(%)	*Z*/*E* ratio
1	Ph	Triton® B	20	-78 °C, 30 min	98	93 : 7
2	PrCH=CH	Triton® B	20	-78 °C → -35 °C	97	89 : 11
3	*n*-C_7H_{15}	Triton® B	20	-78 °C → -25 °C	99	90 : 10
4	*n*-C_7H_{15}	NaH	20	-78 °C → 0 °C	99	90 : 10
5	*n*-C_7H_{15}	NaH	5	-78 °C → -10 °C	100	90 : 10
6	*n*-C_7H_{15}	KHMDS, 18-crown-6 (5 eq)	20	-78 °C → 0 °C	68 (19)[c]	92 : 8
7	Me_2CHCH_2	Triton® B	20	-78 °C → -25 °C	98	90 : 10
8	Me_2CHCH_2	NaH	5	-78 °C → -25 °C	100	90 : 10
9	EtCHMe	Triton® B	20	-78 °C → -30 °C	84[d]	90 : 10
10	EtCHMe	NaH	5	-78 °C → -10 °C	100	92 : 8
11	BuCHEt	Triton® B	20	-78 °C → -20 °C	100	89 : 11
12	BuCHEt	NaH	5	-78 °C → -10 °C	90	93 : 7
13	Cyclohexyl	NaH	5	-78 °C → -25 °C	97	90 : 10

a: ml / 1 mmol. b: The reaction was warmed over 1-2 h except Entry 1. c: The yield was not optimized and the number in parentheses is the recovered yield of **1** (%). d: This rather low yield is mainly due to the volatility of the products.

yield was not optimized). NaH brought some improvement for *Z*-selectivity in the case of α-branched aldehydes to give 90-93% *Z*-isomer (Entries 10,12,13). We should note **1** is much more selective for the reaction with cyclohexanecarboxaldehyde than Still's reagent (90% vs. 80% *Z*-selectivity).

All Horner-Emmons products **2** described in this paper and the reagent **1** were characterized by 500 MHz ^1H NMR and mass spectroscopy. The *Z* / *E* ratio of **2** was determined by integration of the vinyl proton signals in the 500 MHz ^1H NMR spectrum. In general, the vinyl protons of the *Z*-isomer exhibit upfield signals compared to the vinyl resonance of the *E*-isomer, which were prepared from triethyl phosphonoacetate in more than 97% selectivity. These assignments were confirmed by nuclear Overhouser effect (NOE) experiments.

The methods described above provide simple and economical routes to a wide range of *Z*-unsaturated esters in almost quantitative yields. Our new reagent, ethyl diphenylphosphonoacetate **1** will undoubtedly prove to be of considerable utility in synthesis. Efforts to further expand the scope and utility of **1** are presently under active investigation in this laboratory.

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8. Preparation of **1**: PCl_5 (15.6g, 75 mmol) was added to triethyl phosphonoacetate (5.95 ml, 30 mmol) at 0 °C. When exothermic reaction was completed, the mixture was heated at 75 °C for 10 h. Distillation removed $P(O)Cl_3$ and excess PCl_5 and yielded the dichloride (5.96 g, 3 mmHg/105-110 °C), which was dissolved in benzene (30 ml) and treated with a solution of PhOH (5.65 g, 60 mmol) and Et_3N (10.1 ml, 73 mmol) in benzene (10 ml) at 0 °C. After stirring for 1 h at 25 °C, the mixture was filtered. The filtrate was diluted with AcOEt (30 ml) and washed with 1 N NaOH (3×20 ml), saturated NH_4Cl, brine, and dried ($MgSO_4$), and concentrated. Column chromatography (silica gel / hexane-AcOEt (15:1→ 5:1)) provided **1** (5.80 g, yield 60%) as a colorless oil.
9. Typical procedure-Triton® B: A solution of **1** (0.5 mmol) in 10 ml anhydrous THF was treated with Triton® B (0.55 mmol) at -78 °C for 15 min under an argon atmosphere. The aldehyde (0.55 mmol) was then added and the resulting mixture was gradually warmed to the indicated temperature over 1-2 h. The reaction was quenched with saturated NH_4Cl and the mixture extracted with AcOEt (3×). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. After determining the *Z* / *E* ratio of the crude mixture by 500 MHz ^1H NMR, the product was isolated by flash chromatography. The *Z* / *E* ratio did not changed by flash chromatography.

   Typical procedure-NaH: To a suspension of NaH (0.65 mmol) in 1.5 ml THF was added **1** (0.5 mmol) in 1 ml THF at -78 °C under an argon atmosphere. 15 min later, the aldehyde (0.55 mmol) was added. The following reaction procedure was same as the above.

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