



Solvent-free Horner–Wadsworth–Emmons reaction using DBU

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ABSTRACT

The solvent-free Horner–Wadsworth–Emmons reaction with a variety of aldehydes using 1.5 equiv of DBU gave *E*- α,β -unsaturated esters and ketones in high yields. The *E*-selectivity was high and the used DBU was recovered.

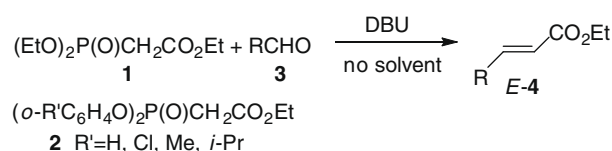
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The Horner–Wadsworth–Emmons modification of the Wittig reaction is a widely used method for the preparation of α,β -unsaturated esters.¹ The phosphonate anions are strongly nucleophilic and react readily with carbonyl compounds under mild conditions to form olefins in good yields. Because of environmental concerns, safety consideration, reduction of the costs, and simplicity of the process, the solvent-free reaction has drawn great attention in recent years.² Furthermore, an increased reactivity is expected due to the intimacy of the reagents. A limited number of reports have appeared on the solvent-free Wittig olefination of phosphorus ylides with carbonyl compounds.³ In these reactions, a mixture of carbonyl compounds and phosphorus ylides or phosphonium salts with a base was milled in a dry mortar or heated under microwave irradiation. As far as we know, only two reports described solvent-free Horner–Wadsworth–Emmons (HWE) reactions.⁴ One is the solid phase reaction by milling a highly π -conjugated solid aldehyde with *p*-Ar-benzylphosphonates using *t*-BuOK^{4a} and the other is the silica gel-catalyzed reaction using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base reported by Inanaga and co-workers.^{4b} In the latter, the *E*- α,β -unsaturated esters were obtained with high selectivity when a mixture of triethyl phosphonoacetate **1**, aldehyde, and silica gel-dispersed DBU was stirred. During the course of our study on the *Z*-selective HWE reagents, ethyl (diarylphosphono)acetates **2**,⁵ we were interested in their solvent-free HWE reaction. When we applied their procedure to our HWE reagent (PhO)₂P(O)CH₂CO₂Et **2a**, that is, a mixture of **2a**, PhCHO, and DBU (1:1:1) was stirred with silica gel (0.6 g/mmol) for 10 h, ethyl cinnamate was obtained in 70% yield. Disappointingly, the *E*-isomer was mainly obtained with 71:29 selectivity. The moderate yield seemed to be mainly due to the inefficient mixing because of the troublesome cases using the heterogenous silica gel. When the reaction of **2a** with PhCHO using DBU was performed in the absence of silica gel, the reaction smoothly proceeded to give ethyl cinnamate in 97% yield within 30 min. Although we could not get the *Z*-isomer selectively, we found that the HWE reaction pro-

ceeded rapidly without silica gel. Furthermore, the reaction of **1** with a variety of aldehydes proceeded in the absence of silica gel to give *E*- α,β -unsaturated esters highly selectively using DBU. Herein, we would like to report a solvent-free HWE reaction by just using phosphonate reagents, aldehydes, and DBU or tetramethylguanidine (TMG) (Scheme 1).

The solvent-free HWE reaction of **1** with benzaldehyde was carried out using several amines. As shown in Table 1, DBU and TMG⁶ were found to be the most effective and the reaction gave *E*-**4a** in 96% and 90% yields, respectively, and 99:1 *E*-selectivity (entries 1 and 2). Trialkylamines, Et₃N, Bu₃N, and *i*-Pr₂NEt, were much less effective (entries 3–5).

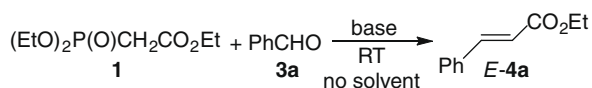
We examined the solvent-free HWE reaction of **1** with a variety of aldehydes using DBU. The results are summarized in Table 2.^{7,9} The reaction with benzaldehyde using 1.1 equiv of DBU gave *E*-**4a** in 92% yield after 1 h, and the reaction proceeded within 0.5 h using 1.5 equiv of DBU to give 96% yield (entries 1 and 2). The reaction of **1** with *p*-chloro- and *p*-methoxybenzaldehyde, furfural, and 4-(1*H*-imidazo-1-yl)benzaldehyde using 1.5 equiv of DBU also gave *E*-olefins in 95–98% yields with 98:2–99:1 *E*-selectivity (entries 3–6). The reaction with *E*-cinnamaldehyde gave **4f** in 86% yield with slightly lower 96:4 selectivity. The reaction with *n*-octanal gave **4g** in 85% yield with 98:2 selectivity. TMG gave a slightly higher 87% yield (entry 9). For the most of the reaction described in Table 2, TMG can replace DBU as a base. Generally, slightly lower yields were obtained except for the reaction with *n*-octanal. We also performed the reaction in THF (0.5 mol/L), which gave much lower 64% yield after 4 h (entry 10). The reaction of α -branched aldehydes, cyclohexancarboxaldehyde, and 2-ethylhexanal also gave *E*-olefins in higher 99:1 selectivity in 90–92% yields (entries 11 and 12). Although the reaction of bulkier pivalaldehyde proceeded slowly, *E*-**4j** was obtained in 91% yield with >99:1 selectivity



Scheme 1.

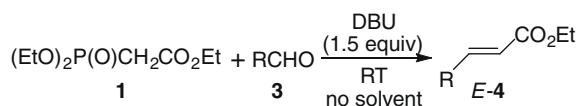
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Table 1
Effect of a base on the solvent-free HWE reaction of **1** with benzaldehyde^a



Entry	Base (equiv)	Time (h)	Yield%	E:Z
1	DBU (1.5)	0.5	96	99:1
2	TMG (1.5)	2	90	99:1
3	Et ₃ N (1.5)	30	5	99:1
4	Bu ₃ N (1.5)	32	10	>99:1
5	<i>i</i> -Pr ₂ NEt (1.5)	24	15	97:3

Table 2
The solvent-free HWE reaction of **1** with various aldehydes using DBU^a



Entry	R	Time (h)	Product	Yield%	E:Z
1	Ph	1	4a	92	99:1
2	Ph	0.5	4a	96	99:1
3	<i>p</i> -ClC ₆ H ₄	2	4b	98	98:2
4	<i>p</i> -MeOC ₆ H ₄	2	4c	95	98:2
5	Furfural	3	4d	97	98:2
6	<i>p</i> -Imid-C ₆ H ₄	3	4e	98	99:1
7	<i>E</i> -PhCH=CH	3	4f	86	96:4
8	<i>n</i> -C ₇ H ₁₅	4	4g	85	98:2
9 ^b	<i>n</i> -C ₇ H ₁₅	4	4g	87	97:3
10 ^c	<i>n</i> -C ₇ H ₁₅	4	4g	64	98:2
11	<i>c</i> -C ₆ H ₁₁	3	4h	90	99:1
12	2-EtPentyl	7	4i	92	99:1
13	<i>t</i> -Bu	24	4j	91	>99:1
14	BnOCHMe	3	4k	91	97:3

^a 1.0 mmol of **1** and 1.1 mmol of **3** were used except for entry 1, where 1.0 mmol of **1**, 1.0 mmol of **3**, and 1.1 mmol of DBU were used.

^b TMG (1.5 equiv) was used instead of DBU.

^c The reaction was performed in THF (0.5 mol/L).

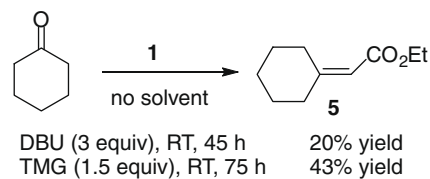
(entry 13). The reaction of 2-benzyloxypropanal gave **E-4k** in 91% yield with 97:3 selectivity. The same reaction in DME using BuLi as a base gave *E/Z* = 90:10 selectivity.^{5b} The *E*-selectivity of the HWE reaction with aldehydes having α -oxygen functional group is generally not high and the HWE reaction with those aldehydes occasionally gave *Z*-olefins selectively.¹⁰ These solvent-free HWE reactions gave *E*- α,β -unsaturated esters just by stirring **1**, aldehyde, and DBU, and almost pure products were obtained by aqueous work-up using a small quantity of organic solvent or direct flash chromatography after the reaction was completed. In addition, the *E*-selectivity is very high. Although 1.1 equiv of aldehydes was used for most of the reactions in this study, excess quantity of aldehydes was not needed. Actually, the main impurities after the work-up are the excess amount of aldehydes and trace amount of phosphonate reagent **1**.

The recovery of the used DBU was next examined. The reaction of **1**, benzaldehyde, and DBU (1:1:1.5) was performed in a 10 mmol scale and the mixture was stirred for 3 h and then **E-4a** was isolated by flash chromatography (*E/Z* = 99:1, 93% yield). The eluate with methanol was treated with 8 mol/L NaOH to give the recovered DBU in 90% yield.¹¹

We further tried to apply this solvent-free HWE reaction to ketones. Unfortunately, ketones reacted very slowly under the identical mild conditions with **1**. For example, the reaction of **1** with cyclohexanone gave **5** in 20% yield after 45 h using DBU and in 43% yield after 75 h using TMG (Scheme 2).

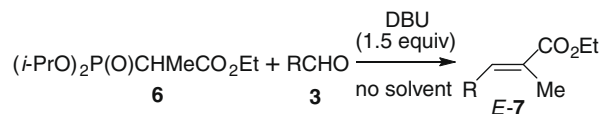
The solvent-free HWE reactions of the α -Me-substituted phosphonate reagent **6** with aldehydes were also performed using 1.5 equiv of DBU (Table 3). The reaction of **6** with benzaldehyde proceeded smoothly at room temperature to give **E-7a** in 96% yield with 87:13 selectivity (entry 1). Change of the reaction temperature from room temperature to 120 °C has almost no effect on the stereochemical outcomes (entries 1–3). The reaction of **6** with *n*-octanal proceeded slowly at room temperature to give **E-7b** in 73% yield after 24 h with 67:33 selectivity together with the recovered **6** (22%) (entry 4). When the reaction was performed at 70 °C, **7b** was obtained in 77% yield with 75:25 *E*-selectivity together with the recovered **6** (17%). Furthermore, 92:8 selectivity was obtained at 120 °C in 31% yield (entry 6). Although the *E*-selectivity of the reaction with *n*-octanal increased at higher temperature, the reaction was not much accelerated and slow decomposition of **6** and/or **7b** occurred at 120 °C. When **7b** (*E/Z* = 17:83)¹² was heated at 70 °C for 6 h, neither the isomerization nor the decomposition was observed. However, the isomerization did occur in the presence of DBU at 70 °C to give *E/Z* = 50:50 and 60:40 mixture after 6 h and 9 h later, respectively. Thus slow isomerization occurred at 70 °C, but noticeable decomposition was not detected. At higher temperature, the volatile aldehyde evaporated and stuck to the upper wall of the reaction flask, therefore the reaction did not proceed well. The reaction of **6** with α -branched aldehyde, cyclohexancarboxaldehyde also proceeded slowly at room temperature to give **E-7c** in 64% yield with 73:27 selectivity after 4 days. Although the reactions with aliphatic aldehydes were slow, the present protocol can be applied for the synthesis of trisubstituted olefins especially from aromatic aldehydes.

The solvent-free HWE reaction using DBU was also applied for the ethyl ketone-type reagent **8**.¹³ The results are summarized in Table 4. The reaction of **8** with benzaldehyde using 1.5 equiv of DBU gave **E-9a** in 91% yield with 99:1 selectivity. The reaction with *n*-octanal is also highly selective and gave **E-9b** in 78% yield with >99:1 selectivity. The reaction with α -branched aldehyde, 2-ethylhexanal gave **E-9c** in 89% yield with >99:1 selectivity. Thus the synthesis of *E*- α,β -unsaturated ketones was performed using solvent-free condition very efficiently.



Scheme 2.

Table 3
The solvent-free HWE reaction of the α -Me reagent **6** with various aldehydes using DBU



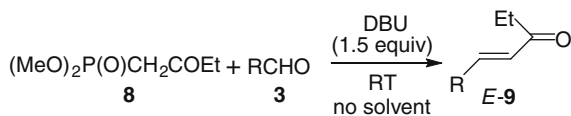
Entry	R	Conditions ^a	Yield% ^b	E:Z
1	Ph	RT, 3 h	7a 96	87:13
2	Ph	70 °C, 2 h	7a 92	87:13
3	Ph	120 °C, 2 h	7a 99	87:13
4	<i>n</i> -C ₇ H ₁₅	RT, 24 h	7b 73(22)	67:33
5	<i>n</i> -C ₇ H ₁₅	70 °C, 11 h	7b 77(17)	75:25
6	<i>n</i> -C ₇ H ₁₅	120 °C, 6 h	7b 31(38)	92:8
7	<i>c</i> -C ₆ H ₁₁	RT, 4 d	7c 64(34)	73:27

^a 0.5 mmol of **6** and 0.55 mmol of **3** were used.

^b The number in parentheses is the recovered yield of **6** (%).

Table 4

The solvent-free HWE reaction of the ketone reagent **8** with various aldehydes using DBU^a



Entry	R	Time (h)	Product	Yield%	E:Z
1	Ph	3	9a	91	99:1
2	<i>n</i> -C ₇ H ₁₅	6	9b	78	>99:1
3	2-EtPentyl	8	9c	89	>99:1

^a 0.5 mmol of **8** and 0.55 mmol of **3** were used.

In summary, we showed that a solvent-free HWE reaction of **1** with a variety of aldehydes can be performed by just using 1.5 equiv of DBU as a base to give the *E*-olefins in high yields with 96:4 to >99:1 selectivity. The reaction of the ethyl ketone-type reagent **8** with aldehydes is also highly *E* selective to give α,β -unsaturated ketones in high yields. Furthermore, the used DBU can be recovered easily in a high yield. This method also can be applied to the synthesis of trisubstituted olefins especially from aromatic aldehydes. This method is simple, environmentally friendly, and safe, and it does not require any expensive catalysts or bases. The additional advantages of workup simplicity and high *E*-selectivity make this methodology a serious candidate for not only laboratory use but also widespread industrial applications.

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- A typical procedure of the solvent-free HWE reaction: (entry 12 in Table 2): To a mixture of **1** (0.224 g, 1.0 mmol) and 2-ethyl hexanal (0.172 mL, 1.1 mmol) was added DBU (0.223 mL, 1.5 mmol), and the resulting mixture was stirred for 7 h at room temperature under Ar atmosphere. The reaction was quenched with water (5 mL) and the reaction mixture was extracted with AcOEt (5 mL). The extract was washed with brine, dried (MgSO₄), and concentrated to give **4i** in >90% purity. The product was isolated by flash chromatography (hexane/AcOEt = 30:1) as colorless oil (0.183 g, 92% yield).
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- Recovery of DBU: After a mixture of **1** (2.242 g, 10.0 mmol), benzaldehyde (1.01 mL, 10.0 mmol), and DBU (2.30 mL, 15.0 mmol) was stirred for 3 h, **4a** was isolated by flash chromatography (silica gel 10 g) as a colorless oil (*E/Z* = 99:1, 93% yield). The eluate with MeOH was treated with 8 mol/L NaOH (2 mL) and extracted with CH₂Cl₂ (3 mL × 2). The organic phase was dried (MgSO₄) and concentrated to give the recovered DBU in 90% yield.
- Compound **7b** (*E/Z* = 17:83) was prepared from (PhO)₂P(O)CHMeCO₂Et.^{5c}
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