Preparations of Z-α,β-Unsaturated Amides by Using Horner-Wadsworth-Emmons Reagents, (Diphenylphosphono)acetamides

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Abstract: New Horner-Wadsworth-Emmons reagents, (diphenylphosphono)acetamides **2** react with a variety of aldehydes to give the corresponding Z- α , β -unsaturated amides stereoselectively (up to Z:E = 98: 2).

Key words: amides, alkenes, aldehydes, Horner-Wadsworth-Emmons reaction, *Z*-selective

 α , β -Unsaturated amides are useful synthetic intermediates in organic synthesis. They can not only be transformed to a variety of compounds, but also have been used as Michael acceptors or Diels-Alder dienophiles. Stereo-defined synthesis of carbon-carbon double bonds with high selectivity is critically important for the stereoselective reactions. The Wittig reaction,¹ the Horner-Wadsworth-Emmons (HWE) reaction,²⁻⁴ and the Peterson olefination⁵ have been used for the synthesis of α,β -unsaturated amides. While it is rather easy to obtain thermodynamically favored E isomers, only one direct preparation of Z-isomers has been reported by Peterson olefination.^{5b} Since more general and practical methods are desirable, we studied Z-selective synthesis of α,β -unsaturated amides as an extension of our HWE reaction using (diarylphosphono)acetate reagents 1.6 We prepared (diphenylphosphono)acetamide reagents 2 and performed the HWE reaction with representative aldehydes under various conditions.⁷ Herein we report our results.

The N,N-dimethyl(diphenylphosphono)acetamide 2a was prepared by acylation of diphenyl methylphosphonate as shown in Scheme in 55% yields (not optimized). The results of the HWE reaction of 2a with aldehydes were summarized in Table 1. When Triton B (40% benzyltrimethylammonium hydroxide in MeOH) was used as base for the reaction with benzaldehyde, only a low yield of the olefin products was obtained along with a large quantity of phenol (entry 1). Treating 2a with tBuOK at 0 °C also caused partial decomposition of 2a (entry 2). These results show that the anion from 2a is labile and easily decomposes. The reaction successfully gave 3a in 95% Z-selectivity and in 90% yield by treating 2a with tBuOK at -78 °C before the addition of PhCHO (entry 3). Furthermore, 98% Z-selectivity was obtained in the presence of 18-crown-6 (1 equiv) (entry 5). In the same condition, 2E-hexenal gave Z-olefin in 88% selectivity (entry 8). Disappointingly, the reaction of 2a with aliphatic aldehydes showed only moderate Z-selectivities (entries 9-14). The best Z-selectivities were obtained when



 Table 1
 The HWE reaction of 2a with aldehydes in THF

Entry	RCHO	base	yield(%) ^a	3 (Z:E)
1	PhCHO	Triton B	23	88:12
2	PhCHO	<i>t</i> BuOK ^b	70	93:7
3	PhCHO	<i>t</i> BuOK	90 (8)	95:5
4	PhCHO	<i>t</i> BuOK ^e	90 (7)	96:4
5	PhCHO	<i>t</i> BuOK ^d	98	98:2
6	2E-hexenal	<i>t</i> BuOK	97	79:21
7	2E-hexenal	NaHMDS	95	83:17
8	2E-hexenal	tBuOK ^e	100	88:12
9	n-C ₇ H ₁₅ CHO	<i>t</i> BuOK	95	63:37
10	n-C7H15CHO	NaHMDS	89 (6)	77:23
11	<i>n</i> -C ₇ H ₁₅ CHO	LDA	89 (8)	60:40
12	2-Et-hexanal	<i>t</i> BuOK	84 (5)	63:37
13	2-Et-hexanal	NaHMDS	97	75:25
14	2-Et-hexanal	LDA	93 (7)	75:25

The reaction was carried out at -78 °C (entries 1-5) and from -78 to 0 °C (entries 6-14). a: The number in parentheses is the recovered yield of **2a**, b: **2a** was treated with base at 0 °C, c: HMPA(2 eq), d: 18-crown-6 (1 eq), e: 18-crown-6 (2 eq).

NaHMDS⁸ was used as base (77% and 75% Z, entries 10 and 13).

In order to see the substituent effect of 2, N-phenyl(diphenylphosphono)acetamide 2b and N-methoxy-N-methyl(diphenylphosphono)acetamide 2c were prepared by the reaction of diphenyl phosphite, bromoacetyl bromide, and the corresponding amines in one pot. The results of the reaction of **2b** are given in Table 2. When **2b** was treated with tBuOK at -78 °C and the reaction with benzaldehyde was performed at -78 °C, 90% Z-selectivity was obtained in 98% yield (entry 1). At -95 °C, slightly better selectivity of 92% was attained (entry 2). In the presence of 18-crown-6 (1 equiv), the selectivity increased to 94% (entry 3). The reaction with 2E-hexenal was also found to be Z-selective, although the selectivity was not quite high (85%, entry 4). The HWE reactions with n-octanal, 2-ethylhexanal, and pivalaldehyde were carried out using NaHMDS⁸ (entries 5-7). The resulting olefin products contain 91-94% Z-isomers in almost quantitative yields. Thus, the reagent **2b** gives a wide range of Z- α , β -unsaturated amides in high selectivities.9

Table 2 The HWE reaction of 2b with aldehydes in THF

Entry	RCHO	base	yield(%) ^a	3 (Z:E)
1	PhCHO	<i>t</i> BuOK	98	90:10
2 ^b	PhCHO	<i>t</i> BuOK	91 (9)	92:8
3	PhCHO	<i>t</i> BuOK ^c	78 (22)	94:6
4	2E-hexenal	<i>t</i> BuOK	95	85:15
5	<i>n</i> -C ₇ H ₁₅ CHO	NaHMDS	90 (4)	91:9
6	2-Et-hexanal	NaHMDS	96	93:7
7	<i>t</i> BuCHO	NaHMDS	95	94:6

The reaction was carried out at -78 °C (entries 1-3) and from -78 to 10 °C (entries 4-7). a: The number in parentheses is the recovered yield of **2b**, b: at -95 °C, c: 18-crown-6 (1 eq)

Further, we studied the HWE reaction of the reagent 2c. Since the initial report from Weinreb group,¹⁰ the *N*-methoxy-N-methylamides (Winreb amides) have served as valuable intermediates in organic synthesis. The Wittig or HWE reagents containing this amide moiety were reported.^{1,3} These reagents are useful for converting aldehydes into α,β -unsaturated N-methoxy-N-methylamides with high *E*-selectivity. Hoping **2c** gives *Z*-isomers selectively, the HWE reaction of 2c with benzaldehyde, 2-ethylhexanal, and n-octanal was performed (Table 3). Since the anion derived from 2c is stable at 0 °C, 2c was treated with *t*BuOK at 0 °C and the reaction with benzaldehyde was carried out at -78 °C. Disappointingly, 66% Z-selectivity was obtained in 94% yield (entry 1). The use of LDA instead of *t*BuOK slightly improved the Z-selectivity (77%). The HWE reaction of **2c** with 2-ethylhexanal was also performed using NaH, tBuOK, and LDA (entries 4-6). NaH gave a highest selectivity (79%). In the presence of MgBr₂ (0.1 equiv.), the Z-selectivity slightly increased to 81%. Increasing the quantity of MgBr₂ (1 equiv.) only caused a diminished yield (63%, 81% Z). The reaction with *n*-octanal using NaH gave the olefin products with 75% Z-selectivity. Although these selectivities are just moderate, the Z-olefins can be easily obtained in pure form by column chromatography or recrystallization.

Table 3 The HWE reaction of 2c with aldehydes in THF

Entry	RCHO	base	yield(%) ^a	3 (Z:E)
1	PhCHO	tBuOK	94	66:34
2	PhCHO	NaH	94	70:30
3	PhCHO	LDA	67 (28)	77:23
4	2-Et-hexanal	NaH	99	79:21
5	2-Et-hexanal	tBuOK	94	69:31
6	2-Et-hexanal	LDA	84 (14)	70:30
7	2-Et-hexanal	NaH ^b	83 (14)	81:19
8	n-C ₇ H ₁₅ CHO	NaH	98	75:25

The reaction was carried out at -78 °C(entries 1-3) and from -78 to 0 °C (entries 4-8). a: The number in parentheses is the recovered yield of **2c**, b: MgBr₂ (0.1 eq)

All new compounds described here were characterized by ¹H NMR, mass, and high-resolution mass spectrum. The *Z*:*E* ratios of **3** were determined by integrating the vinyl proton signals in the 500 MHz ¹H NMR spectra. These assignments were confirmed by NOE experiments.

In summary, the HWE reaction described above provides a direct route to a wide range of Z- α , β -unsaturated amides. Further efforts to expand the scope and utility of the reagents **2** are in progress in this laboratory.

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- (9) The typical procedure of the HWE reaction of **2b** with pivalaldehyde (entry 7 in Table 2): After a solution of

TMS₂NH (0.45 mmol) in THF (1 mL) was treated with NaH (0.45 mmol) for 30 min, the resulting suspension was added to a solution of **2b** (0.3 mmol) in THF (5 mL) at -78 °C. 20 min later, pivalaldehyde (0.33 mmol) was added and the resulting mixture was gradually warmed to 10 °C over 2.5 h. After the usual workup and chromatographic purification, *N*-phenyl-4,4-dimethyl-2-pentenoamide was obtained in 95% yield (*Z*:*E* = 94:6).

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