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# IMPROVED HORNER-WADSWORTH-EMMONS PREPARATION OF $\alpha$ -METHYL- OR $\alpha$ -ETHYL- $\alpha$ , $\beta$ -UNSATURATED ESTERS FROM ALDEHYDES

Richard J. Petroski<sup>a</sup> & David Weisleder<sup>a</sup>

<sup>a</sup> National Center for Agricultural Utilization Research , 1USDA, REE, Agricultural Research Service, Bioactive Agents Research Unit and Analytical Support Unit, 1815 N. University Street, Peoria, IL, 61604, U.S.A. Published online: 09 Nov 2006.

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## IMPROVED HORNER-WADSWORTH-EMMONS PREPARATION OF $\alpha$ -METHYL- OR $\alpha$ -ETHYL- $\alpha$ , $\beta$ -UNSATURATED ESTERS FROM ALDEHYDES

Richard J. Petroski\* and David Weisleder

<sup>1</sup>USDA, REE, Agricultural Research Service, National Center for Agricultural Utilization Research, Bioactive Agents Research Unit and Analytical Support Unit, 1815 N. University Street, Peoria, IL 61604

#### ABSTRACT

The *E*-isomer selectivity of the Horner-Wadsworth-Emmons olefination of aldehydes to form  $\alpha$ -methyl- or  $\alpha$ -ethyl- $\alpha$ , $\beta$ unsaturated esters has been improved by using lithium *tert*-butoxide as the base, triethyl-2-phosphonopropionate or triethyl-2-phosphonobutyrate as the phosphonate, an aldehyde, and hexane as the reaction solvent. Greater *E*-isomer selectivity was observed in the formation of  $\alpha$ -methyl- $\alpha$ , $\beta$ -unsaturated esters than  $\alpha$ -ethyl- $\alpha$ , $\beta$ unsaturated esters. These compounds are useful intermediates for the synthesis of insect pheromones and natural products.

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<sup>\*</sup>Author to whom correspondence should be addressed; fax (309) 681-6693; e-mail: petrosrj@mail.ncaur.usda.gov.

<sup>&</sup>lt;sup>1</sup>Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

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#### PETROSKI AND WEISLEDER



Insect pheromones are currently used as pest management tools. Aggregation pheromones have been identified for nine species of sap beetles, belonging to the genus *Carpophilus* (1). The pheromones are composed of alkyl-branched, conjugated triene or tetraene hydrocarbons having all *E*-double-bond configuration (1). A project was undertaken to improve the synthetic pathway leading to the sap beetle pheromones (2). Robust reactions using mild conditions were sought.

The pheromones have been prepared using Horner-Wadsworth-Emmons (HWE) reactions to build up the carbon chain (2). High yields, and *E*-isomer double-bond configuration, were critical to our efforts.

HWE reactions resulting in the formation of  $\alpha$ -methyl- or  $\alpha$ -ethyl- $\alpha$ , $\beta$ unsaturated esters from aldehydes do not always yield acceptable *E*-isomer selectivity because alkyl substitution on the 2-position of the phosphonate (e.g., triethyl-2-phosphonobutyrate vs triethyl-2-phosphonoacetate) has been linked to increased *Z*-isomer formation in the reaction products (3).

In this paper, we report facile conversion of aldehydes to  $\alpha$ -methyl- or  $\alpha$ -methyl- $\alpha$ , $\beta$ -unsaturated esters with high *E*-isomer selectivity using lithium *tert*-butoxide as the base and hexane as the reaction solvent (Scheme). These compounds can serve as useful synthetic intermediates (1,2).

#### **RESULTS AND DISCUSSION**

Mild HWE reaction conditions for the formation of mainly *E*-isomer  $\alpha,\beta$ unsaturated esters from aldehydes utilizing either barium hydroxide (4,5) or lithium hydroxide (4) as the base and 1,4-dioxane or THF as the reaction solvent have been developed, but our attempts to prepare  $\alpha$ -branched- $\alpha,\beta$ -unsaturated esters using these conditions resulted in the formation of little or none of the desired product when either triethyl-2-phosphonopropionate (TEPP) or triethyl-2-phosphonobutyrate (TEPB) was substituted for triethyl-2-phosphonoacetate (TEPA).

The results of our synthetic study (Table 1) show that the reaction conditions afford high yields (86–98%) of the desired products. The reactions are facilitated by the fact that lithium *tert*-butoxide is commercially available as a 1.0 M solution in hexane (Aldrich Chemical Co., St. Louis, MO). Longer reaction times (4 h) are required when triethyl-2-phosphonobutyrate (TEPB) is used to prepare  $\alpha$ -ethylbranched- $\alpha$ , $\beta$ -unsaturated esters. The workup is straightforward.

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#### ESTER PREPARATION

*Table 1.* Preparation of  $\alpha$ -branched- $\alpha$ , $\beta$ -unsaturated Esters from Aldehydes<sup>a</sup>

Entry	Structure	Phosphonate	Product	Time (h)	Isolated Yield (%) <sup>b</sup>	E/ZRatio
1	СНО	TEPP	CO <sub>2</sub> Et	1	93	140
2	СНО	TEPB	CO2Et	4	95	25
3	СНО	TEPP		1	86	8.6
4	СНО	TEPB		4	90	1.7
5	СНО	TEPP	CO2Et	1	98	44
6	СНО	TEPB	CO <sup>2</sup> Et	4	92	8.0

<sup>a</sup>Reaction conditions: phosphonate (20 m moles), Li OtBu (20 m moles), aldehyde (13.3 m moles), hexane (60 mL), 25°C.

<sup>b</sup>Kugelrohr distillation.

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Double-bond configurations were assigned by NMR spectroscopy. Brouwer and Stothers reported that the olefinic protons of *E*- and *Z*-methyl-2-methyl-2butenoate were found at  $\delta$  6.745 and  $\delta$  5.978, respectively (7). The *E*-isomer olefinic proton is downfield when compared to the *Z*-isomer olefinic proton. We prepared ethyl-2-ethyl-2-hexenoate as a mixture of *E*- and *Z*-isomers in a ratio of 1.7 to 1.0 (Entry 4, Table 1). The olefinic protons of *E*-ethyl-2-ethyl-2-hexenoate and *Z*-ethyl-2-hexenoate were found at  $\delta$  6.91 and  $\delta$  5.72, respectively, in the integrated ratio of 1.7 to 1.0. The olefinic protons at the 3-position of all the compounds encountered in our study were observed at a chemical shift of at least  $\delta$ 6.91, which partially justifies our assignment of the *E*-double-bond configuration for the major isomer produced by synthesis.

Further confirmation of our assigned double-bond geometry was acquired with the use of nOe difference NMR spectra. When the protons of the 2-methyl or 2-methylene (of ethyl branch) were irradiated, very small nOe's for the olefinic proton at the 3-position were observed. The very small nOe's obtained by NMR analysis confirm the *E*-configuration. If the olefinic proton was cis to the irradiated methyl or methylene protons, then an easily noticeable nOe effect would be expected.

The minor isomer of all compounds was assigned the Z double-bond configuration on the basis of nearly identical mass spectra to the major product isomer and earlier GC retention times. In the case of ethyl-2-ethyl-2-hexenoate (entry 4, Table 1), we could determine the double-bond configuration for both isomers directly by NMR analysis because both isomers were abundant in the NMR sample.

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The E/Z isomeric ratio was higher in the case of  $\alpha$ -methyl- $\alpha$ , $\beta$ -unsaturated esters (8.6–140 to 1) than for the corresponding  $\alpha$ -methyl- $\alpha$ , $\beta$ -unsaturated esters (1.7–25 to 1). Our results suggest that the E/Z isomeric ratio is enhanced when  $\alpha$ - $\alpha$ , $\beta$ -unsaturated aldehydes are used in HWE reactions instead of aliphatic aldehydes. Very high E/Z isomeric ratios (at least 25 to 1) were observed when benzaldehyde was used in the reaction.

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This is an improved HWE preparation of  $\alpha$ -branched- $\alpha$ , $\beta$ -unsaturated esters from aldehydes because of higher yields and greater selectivity in terms of *E*double-bond configuration in the reaction products. When compounds **3**, **5**, and **6** were prepared using n-BuLi as the base and THF as the reaction solvent, the yields were 83%, 82%, and 87%, respectively, and the E/Z isomeric ratios were 5.9, 38, and 6.0, respectively (Bartelt, personal communication). Our yields were slightly higher and a greater proportion of the desired *E*-double-bond isomer was obtained. Also, it was previously necessary to heat the reaction mixture to THF reflux temperature when TEPB was used as the phosphonate (2). Preparation of  $\alpha$ branched- $\alpha$ , $\beta$ -unsaturated esters from aldehydes using alkoxide bases in alcohols resulted in lower yields of the desired products (2).

#### **EXPERIMENTAL**

#### General Synthetic Procedure Using Triethyl-2-phosphonopropionate (TEPP)

TEPP (4.76 g, 20 mmol) was added to 35 mL of hexane. A nitrogen atmosphere was introduced and the mixture was stirred at room temperature. Lithium *tert*-butoxide (20 mL of a 1.0 M solution in hexane) was added in one portion via syringe. The solution became turbid, but no significant heating of the solution was observed. After stirring for 15 min, the aldehyde (13.3 mmol in 5 mL of hexane) was added dropwise over the course of 10 min. The solution clarified as aldehyde was added, but no heating of the solution was observed. The solution was allowed to stir for an additional hour before it was transferred to a separatory funnel and washed with 100 mL of water (4×). The hexane phase, containing the product, was dried over anhydrous MgSO<sub>4</sub>. After filtration and rotary evaporation of the solvent, the product was distilled (Kugelrohr), to afford a colorless liquid. Purity was checked by gas chromatography (GC) and found to be 94%, 98%, and 95% for products 1, 3, and 5, respectively. Products are composed of both *E*- and *Z*-isomers (Table 1).

#### General Synthetic Procedure Using Triethyl-2-phosphonobutyrate (TEPB)

TEPB (5.04 g, 20 mmol) was added to 35 mL of hexane. A nitrogen atmosphere was introduced and the mixture was stirred at room temperature. Lithium

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tert-butoxide (20 mL of a 1.0 M solution in hexane) was added in one portion via syringe. No significant heating of the solution was observed. After stirring for 15 min, the aldehyde (13.3 mmol in 5 mL of hexane) was added dropwise over the course of 10 min. The solution was allowed to stir for an additional 4 h before it was transferred to a separatory funnel and washed with 100 mL of water (4 $\times$ ). The hexane phase, containing the product, was dried over anhydrous MgSO<sub>4</sub>. After filtration and rotary evaporation of the solvent, the product was distilled (Kugelrohr), to afford a colorless liquid. Purity was checked by GC and found to be 99%, 99%, and 98%, for products 2, 4, and 6, respectively. Products are composed of both Eand Z-isomers (Table 1).

#### **Analysis of Reaction Products**

All reactions were monitored by GC using a Hewlett-Packard (HP) 5890 Series II instrument equipped with flame ionization detector, splitless injector, and an HP 7673 autosampler and interfaced to a HP ChemStation data system. The oven temperature was programmed from 50° to  $250^{\circ}$ C at 10°C/min; the injector temperature was 250°C and the detector temperature was 250°C. A DB-1 capillary column (15 m  $\times$  0.25 mm, 1.0-mm film thickness, J&W Scientific, Folsom, CA) was used with 1-ml sample injections.

Electron impact mass spectra (70 eV) were obtained with an HP 5970 MSD instrument, with a DB-1 capillary GC column as described above. Proton NMR spectra (C<sub>6</sub>D<sub>6</sub>) were obtained on a Bruker (Bellerica, MA) Advance 400 spectrometer at 400-MHZ. Chemical shifts are referenced to tetramethylsilane; J is in Hertz. Standard Bruker software was used to obtain the nuclear Overhauser enhancement (nOe) difference spectra.

The E/Z-isomeric ratio of all reaction products was calculated by gas chromatography/mass spectrometry and the stereochemistry of the major isomer was confirmed by NMR analysis. The *E*-isomer of all the products had a greater GC retention time than the corresponding Z-isomer. Compound names, boiling point data, MS data, and NMR spectral data ( $C_6D_6$ ) follow:

#### Ethyl- $\alpha$ -methylcinnamate

B.p. 70°C, 1.1 Torr, MS m/z (% base) 190 (M<sup>+</sup>, 51), 161 (17), 145 (54), 133 (6), 115 (100), 91 (35), 77 (7), <sup>1</sup>H NMR  $\delta$  1.07 (3H, t, J = 7.1), 2.11 (3H, br s), 4.13 (2H, q, J = 7.1), 7.1 (1H, m), 7.1 (2H, m), 7.2 (2H, m), 7.92 (1H, br s).

#### Ethyl- $\alpha$ -ethylcinnamate

B.p. 69°C, 1.0 Torr, MS m/z (% base) 204 (M<sup>+</sup>, 50), 175 (9), 158 (43), 147 (7), 131 (100), 115 (59), 91 (64), 77 (18). <sup>1</sup>H NMR  $\delta$  1.06 (3H, t, J = 7.1), 1.21



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(3H, t, J = 7.4) 2.65 (2H, q, J = 7.4), 4.13 (2H, q, J = 7.1), 7.1 (1H, m), 7.1 (2H, m), 7.3 (2H, m), 7.92 (1H, br s).

Ethyl-2-methyl-2-hexenoate

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B.p. 34°C, 1.2 Torr, MS m/z (% base) 156 (M<sup>+</sup>, 44), 141 (4), 128 (13), 111 (60), 102 (16), 95 (16), 87 (53), 83 (32), 55 (100). <sup>1</sup>H NMR  $\delta$  0.78 (3H, t, J = 7.4), 1.04 (3H, t, J = 7.1), 1.3 (2H, m), 1.87 (3H, br s), 1.9 (2H, m), 4.09 (2H, q, J = 7.1), 6.9 (1H, m).

Ethyl-2-ethyl-2-hexenoate

B.p.  $34^{\circ}$ C, 1.0 Torr, MS m/z (% base) 170 (M<sup>+</sup>, 41), 155 (20), 141 (14), 125 (45), 101 (19), 95 (22), 81 (23), 67 (20), 55 (100). <sup>1</sup>H NMR  $\delta$  0.79 (3H, t, J = 7.4), 1.04 (3H, t, J = 7.1), 1.11 (3H, t, J = 7.5), 1.3 (2H, m), 1.9 (2H, m), 2.41 (2H, q, J = 7.5), 4.10 (2H, q, J = 7.1), 6.91 (1H, m).

Ethyl-2,4-dimethyl-2,4-heptadienoate

B.p. 48°C, 1.0 Torr, MS m/z (% base) 182 (M<sup>+</sup>, 22), 153 (65), 137 (17), 125 (100), 109 (49), 93 (22), 79 (18), 67 (25). <sup>1</sup>H NMR  $\delta$  0.86 (3H, t, J = 7.5), 1.07 (3H, t, J = 7.1), 1.63 (3H, br s), 1.9 (2H, m), 2.12 (3H, br s), 4.12 (2H, q, J = 7.1), 5.5 (1H, m), 7.44 (1H, br s).

Ethyl-2-ethyl-4-methyl-2,4-heptadienoate

B.p.  $52^{\circ}$ C, 1.0 Torr, MS m/z (% base) 196 (M<sup>+</sup>, 23), 167 (70), 151 (14), 139 (100), 123 (37), 107 (20), 91 (19), 81 (25), 67 (12). <sup>1</sup>H NMR  $\delta$  0.86 (3H, t, J = 7.5), 1.06 (3H, t, J = 7.1), 1.20 (3H, t, J = 7.4), 1.66 (3H, br s), 1.9 (2H, m), 2.66 (2H, q, J = 7.4), 4.13 (2H, q, J = 7.1), 5.6 (1H, m), 7.4 (1H, m).

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