JOC Note

Temperature Effects on Stereocontrol in the Horner−Wadsworth−Emmons Condensation of α-Phosphono Lactones

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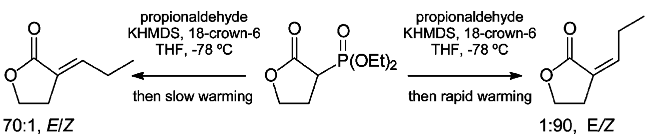
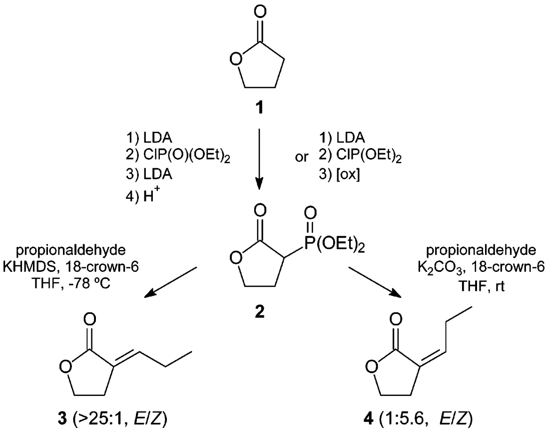


The Horner−Wadsworth−Emmons condensation of some α-phosphono lactones has been examined for conditions that impact product stereochemistry. The temperature employed to quench the reaction was found to be a major factor. For example, after the diethyl phosphonate derivative of γ-butyrolactone was treated with potassium hexamethyldisilazane, 18-crown-6, and propionaldehyde at −78 °C in THF, an aliquot transferred to a flask at ∼30 °C gave almost exclusively the *Z*-olefin product, while one allowed to warm to room temperature over several hours greatly favored the *E*-olefin.

The Horner−Wadsworth−Emmons (HWE) condensation has become an important method for preparation of α,β-unsaturated esters.[1] In its earliest descriptions,[2] this reaction of an α-phosphono ester with an aldehyde or ketone was used to obtain the *E*-olefin isomer, but several more recent studies have revealed strategies that can be employed to favor the *Z*-olefin. The *Z*-selective reactions generally have used carefully chosen phosphonate esters, including trifluoroethyl[3] or substituted phenyl esters,[4,5] but the reaction also is known to be sensitive to the presence of additives that complex with the cation[3,5] among other factors.[1]

Some years ago, we reported the use of electrophilic phosphorus reagents such as diethyl chlorophosphate[6] or diethyl chlorophosphite followed by oxidation[7] to obtain α-phosphono lactones (e.g., **2**) from lactones (**1**) via an intermediate enolate (Scheme 1). In a later study, the α-phosphono lactones were condensed with propionaldehyde under different standard HWE protocols, and conditions were reported that favored formation of either the *E*- or the *Z*-alkylidene product (**3** or **4**).[8] While conditions then reported as *Z*-selective have been applied in other systems,[9] a recent report also found predominance of the *Z*-olefin isomer under what appeared to be the conditions originally reported to favor the *E*-isomer.[10] In the recent case, treatment of the α-phosphono lactone **2** with potassium hexamethyldisilazane (KHMDS), 18-crown-6, and butyraldehyde gave predominant formation of the *Z*-isomer (1:18, *E*/*Z*),[10] while reaction of phosphonate **2** with propionaldehyde had been reported to afford almost exclusively the *E*-isomer **3**.[8] This has prompted us to reexamine the HWE condensations of phosphonate **2** and some closely related compounds in more detail. The results of these studies suggest that it is possible to obtain either olefin isomer **3** or **4** from this condensation with only small changes in the reaction conditions.

SCHEME 1. Prior Syntheses and HWE Condensations of Phosphonate 2[6−8]



Because the ^{1}H NMR spectra of compounds **3** and **4** show significant differences in the resonance of the vinylic hydrogen[11] (δ 6.74 for compound **3** and δ 6.22 for compound **4**), at the outset of these studies it was assumed that in each report the observed products were due to a minor difference in the conditions rather than any incorrect assignment. Because commercial sources of KHMDS provide both toluene and THF solutions, we first examined whether a difference in solvent composition might explain the observed results. As shown in Table 1, in the first trial the α-phosphono lactone **2** in THF at −78 °C was treated with a room-temperature solution of KHMDS in toluene, propionaldehyde was added, and the reaction mixture was forced to warm rather quickly to room temperature (<1 h). These conditions provided almost exclusively the *Z*-isomer **4**, as determined by analysis of the ^{1}H NMR

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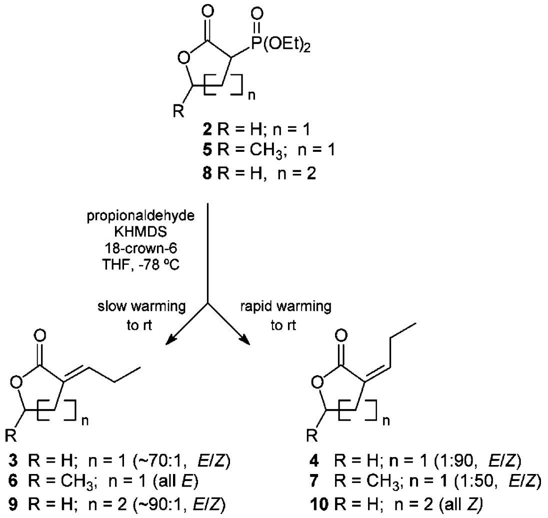
TABLE 1. HWE Condensations of Phosphonate 2

trial	base	18-crown-6	time to reach rt	*E*/*Z*	yield (%)[a]
1	KHMDS/toluene	yes	<1 h	1:30	68
2	KHMDS/THF	yes	<1 h	all *Z*	61
3	KHMDS/THF (cold)	yes	<1 h	1:42	nd
4	KHMDS/THF	no	<1 h	1:20	70
5	KHMDS/THF	yes	immediate	1:90	77
6	KHMDS/THF	yes	≥3 h	all *E*	58

[a] nd = not determined.

SCHEME 2. Temperature Effects on HWE Condensations of Phosphonates 2, 5, and 8



spectrum of the product. When the same conditions of temperature and time were used with addition of a room temperature solution of KHMDS in THF, only the *Z*-isomer was observed (trial 2), and addition of a cold solution of KHMDS in THF did not affect the outcome significantly (trial 3). When the original conditions were employed in the absence of 18-crown-6, once again the *Z*-isomer predominated (trial 4). Because the stereochemistry of the HWE condensation is known to result from a complex set of equilibria,[4c] the effect of temperature also was examined. In the most productive of these experiments, phosphonate **2** was treated with KHMDS and 18-crown-6 in THF at -78 °C and propionaldehyde was added at that temperature, but then the reaction vessel was transferred to a water bath at $\sim$30 °C to promote more rapid warming. This set of conditions gave only the *Z*-product **4** (trial 5). However, when the reaction mixture was allowed to reach room temperature very slowly (over more than 3 h), only the *E*-isomer **3** was observed (trial 6). These two experiments appeared to indicate that the speed with which the reaction mixture reached room temperature was the important variable.

To isolate this variable and verify this conclusion, the reaction was repeated, and phosphonate **2**, KHMDS, and 18-crown-6 were allowed to react at -78 °C in THF for 30 min, propionaldehyde was added, and then the reaction was split into two portions (Scheme 2). One aliquot was transferred by cannula to a flask standing in an $\sim$30 °C water bath, and this sample gave nearly pure *Z*-olefin **4** (1:90, *E*/*Z*, Figure 1). The other half of the same reaction mixture was kept in the -78 °C bath and the solid dry ice was removed, but the reaction flask was kept in the cooling bath and allowed to warm to room temperature over the course of 3 h. This portion of the reaction mixture gave nearly pure *E*-olefin **3** ($\sim$70:1, *E*/*Z*, Figure 1). Thus, the reported difference in the stereochemical outcome of this reaction[8,10] probably was due to different interpretations of the common phrase “allowed to warm to room temperature”.

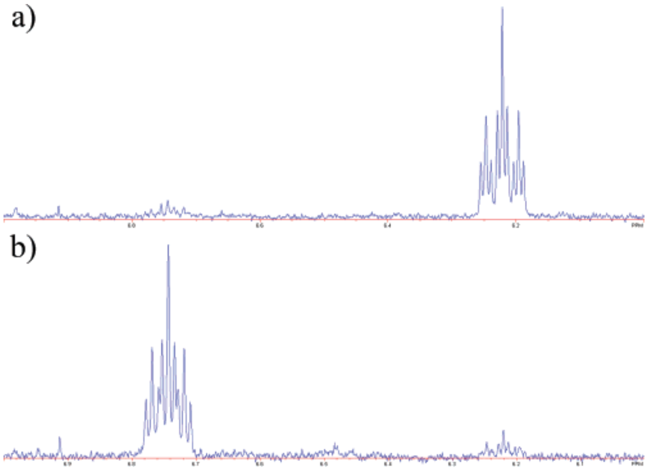


FIGURE 1. Vinylic resonances in the ^{1}H NMR spectra of the products from a single reaction of phosphonate **2** and propionaldehyde, divided and quenched (a) with immediate warming to room temperature (**4**) and (b) with gradual warming (**3**).

To test these reaction conditions with other lactones, phosphonates **5** and **8** were prepared through the methods described earlier.[6−8] After treatment of phosphonate **5** with 18-crown-6 and KHMDS at -78 °C in THF, propionaldehyde was added and the reaction mixture was split into two portions. The aliquot transferred via cannula to a flask at room temperature clearly favored formation of the *Z*-olefin **7** (1:50, *E*/*Z*), while the portion allowed to reach room temperature over the course of about 3 h gave only the *E*-isomer **6**. With the six-membered ring α-phosphono lactone **8**, the same pattern was observed. After phosphonate **8**, 18-crown-6, and KHMDS were allowed to react at -78 °C in THF for 30 min, propionaldehyde was added and the reaction was split. The portion transferred to a flask at room temperature showed only the *Z*-isomer, while the aliquot allowed to warm slowly to room temperature favored the *E*-isomer by a ratio of $\sim$90:1.

A final experiment shed some light on the mechanistic basis for the observed selectivity. For this experiment, phosphonate **2** was treated with KHMDS, 18-crown-6, and propionaldehyde at -78 °C (-76 °C by internal thermometer) as described above, and aliquots were removed at 30, 60, 90, and 120 min and quickly brought to room temperature. In each case, the *Z*-olefin isomer greatly predominated, and even the last aliquot gave an *E*/*Z* ratio of 1:70. By analogy to the equilibria described for α-phosphono ester condensations,[12] this suggests that formation of an erythro adduct (or cis disubstituted oxaphosphetane) is favored under the initial reaction conditions and that this species does not equilibrate appreciably within this time span at this low temperature. When aliquots are brought to room temperature quickly, phosphate elimination is rapid, irreversible, and gives the *Z*-olefin. In contrast, when the reaction mixture is allowed to warm to room temperature slowly, equilibration of an erythro adduct to a threo adduct (or trans disubstituted oxaphosphetane) and subsequent phosphate elimination would afford the *E*-olefin isomer.

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In conclusion, these studies of HWE condensations of α-phosphono lactones have determined that the specific strategy employed under the phrase “allowed to warm to room temperature” is a variable that plays a key role in the stereochemical course of the reaction. Either the *Z*- or the *E*-olefin product can be obtained with high selectivity depending upon whether the reaction is brought to room temperature quickly or allowed to warm slowly. This suggests that there may be more flexibility in controlling the stereochemical outcome of HWE reactions with lactones than previously recognized and further enhances the importance of this condensation.[13]

Experimental Section

(*E*)-3-Propylidenedihydrofuran-2(3*H*)-one (3). To a solution of α-phosphono lactone **2** (285 mg, 1.3 mmol) in THF (30 mL) at room temperature was added 18-crown-6 (1.70 g, 6.4 mmol). The reaction mixture was cooled to −78 °C in an acetone/dry ice bath and allowed to stir for an additional 5 min before KHMDS (1.60 mL, 0.91 M in THF, 1.4 mmol) was added. A pale yellow solution was formed immediately, and this solution was stirred for 30 min before propionaldehyde (0.12 mL, 1.5 mmol) was added dropwise via syringe over 2 min. Immediately after the aldehyde addition, the remaining solid dry ice was removed from the bath and the cold acetone was allowed to warm gradually to room temperature over the course of 3 h. After addition of saturated NH_4Cl, the aqueous layer was extracted with ether, the combined ether extract was washed with water (50 mL) and brine (50 mL) and then dried ($MgSO_4$). Removal of solvent under reduced pressure afforded a yellow oil that was purified via flash chromatography (silica gel, 25% EtOAc in hexanes) to yield pure lactone **3** (92 mg, 58%). The ^{1}H NMR data for compound **3** was identical with that previously reported.[11]

(*Z*)-3-Propylidenedihydrofuran-2(3*H*)-one (4). To a solution of α-phosphono lactone **2** (264 mg, 1.2 mmol) in THF (30 mL) at room temperature was added 18-crown-6 (1.58 g, 5.9 mmol). The reaction mixture was cooled to −78 °C and allowed to stir for an additional 5 min before KHMDS (1.50 mL, 0.91 M in THF, 1.3 mmol) was added. A pale yellow solution was formed immediately. After this solution was stirred for 30 min, propionaldehyde (0.11 mL, 1.4 mmol) was added dropwise via syringe over 2 min. Immediately after addition of the aldehyde, the reaction flask was placed in an ~30 °C water bath and allowed to stir for an additional 3 h. After addition of saturated NH_4Cl, the reaction mixture was extracted with ether, and the combined organic layer was washed with water and brine and then dried ($MgSO_4$). Removal of solvent *in vacuo* gave a mixture of compounds **4** and **3** in a ratio of ~90:1. Purification by flash chromatography (silica gel, 25% EtOAc in hexanes) afforded pure compound **4** (115 mg, 77%). The ^{1}H NMR data for compound **4** was identical with that previously reported.[11]

General Procedure for Split Reactions. After preparation of the reaction as described above, and immediately following addition of the aldehyde, a portion of the cold reaction mixture was transferred via cannula to a flask under argon in an ~30 °C water bath. This aliquot of the reaction mixture then was allowed to react for an additional 3 h, while the remainder of the reaction mixture was allowed to gradually warm to room temperature over 3 h. After saturated NH_4Cl was added to both reaction mixtures, each was extracted by the same method. Following removal of solvents from both fractions, the olefin isomer ratio was determined via integration of the ^{1}H NMR resonance of each vinylic hydrogen.

Acknowledgment. This note is dedicated to the memory of Prof. Leopold Horner, 1911−2005. We thank Prof. Michael E. Jung for disclosing the results of his recent work prior to publication. Financial support from the Roy J. Carver Charitable Trust is gratefully acknowledged.

Supporting Information Available: General experimental procedures and complete ^{1}H NMR spectra for compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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