Quantum Mechanical Investigation of the Horner-Wadsworth-Emmons Reaction of Benzyl Pyridyl Ketone

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The Horner-Wadsworth-Emmons (HWE) reaction is one of much versatile tools in syntheses of α,β-unsaturated esters, α,β-unsaturated ketones, and other conjugated systems.[1] Mechanistically, it is generally accepted that the HWE reaction occurs with the addition of enolate derived from phosphonoacetate to aldehyde or ketone, followed by oxaphonphetane formation, pseudorotation, P-C bond cleavage, and then O-C bond cleavage.[2,3] Stereochemically, the general phosphonoacetates with alkyl phosphonate substituents give *E*-olefins, which can be explained as a result of the predominant formation of thermodynamically more stable *threo* adducts. According to an *ab initio* calculation performed by Ando,[2] in the transition states of the nucleophilic addition to the carbonyl group of acetaldehyde with the trimethyl phosphonoaceate enolate, a transition state leading to *Z*-olefin (*erythro*-TS-1) is more stable than *threo*-TS-1 due to a repulsive interaction between the phosphonate moiety and the methyl substituent of aldehyde in *threo*-TS-1 (Fig. 1). On the other hand, the transition state for the oxaphosphetane formation favors a transition state leading to *E*-olefin (*threo*-TS-2) over *erythro*-TS-2 due to the steric hindrance between the ester moiety and the alkyl substituent of the carbonyl compound (Fig. 1). Based on the energy difference calculated, Ando concluded that the rate-determining transition state for the HWE reaction is TS-2 and, therefore, the *threo*-olefin is the product of choice.

In our recent attempt to convert benzyl phenyl ketone (**1**, Table 1) to its corresponding olefinic compound (**3** and **4**, Table 1), the strong preference for *E*-olefin[4] (**3**) was also observed (*E*:*Z* > 99:1, Table 1) regardless of the base used. However, to our surprise, benzyl 2-pyridyl ketone[5] (**2**, Table 1), by the reaction with triethyl phosphonoacetate in the presence of *t*-BuOK, provided a 1:1 mixture of the corresponding *E*- (**5**) and *Z*- (**6**) olefins (Entry 4, Table 1) in fair-to-good yields.[6] Interestingly, the increased *Z*-selectivity was not reproduced by use of NaH or LiHMDS as a base (Entires 5 and 6, Table 1), which indicates that the counter cation of the base plays the key role in determining the stereochemi-

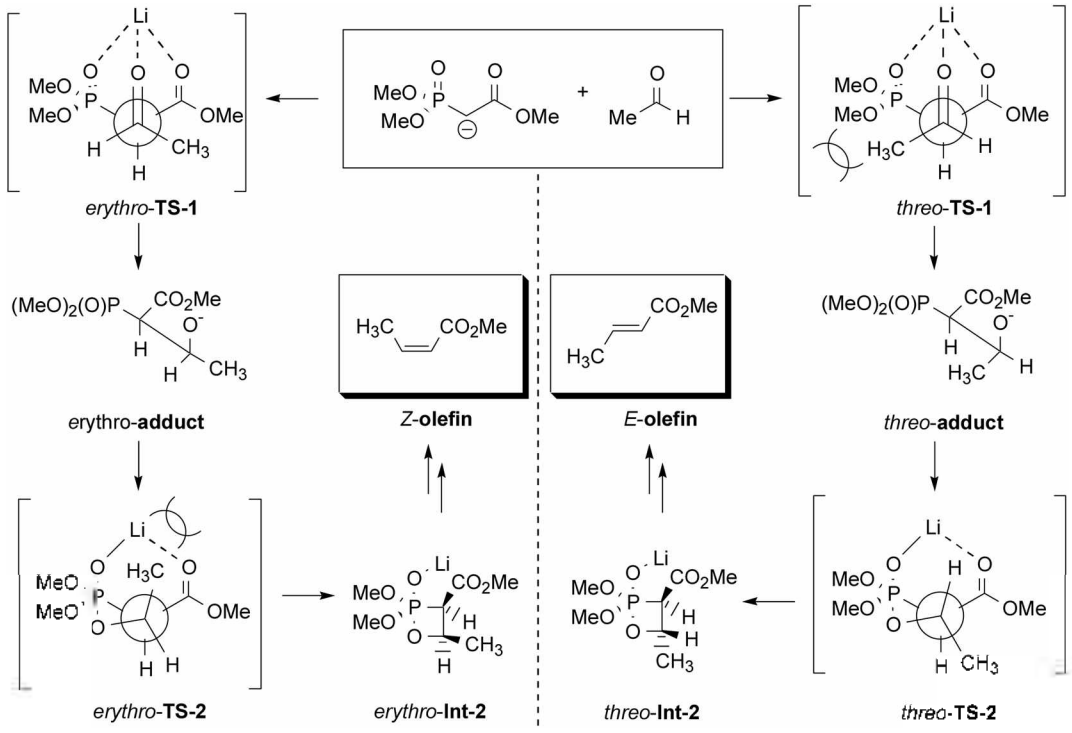
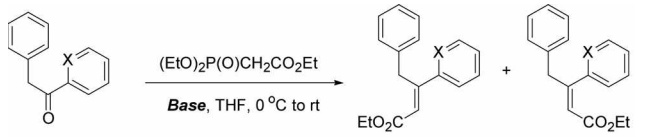


Figure 1. Reaction mechanism of HWE reaction.

Table 1. Stereoselectivity of the HWE reactions of benzyl phenyl ketone (**1**) and benzyl 2-pyridyl ketone (**2**) in the presence of various bases



1 X = CH, **2** X = N; **3** X = CH, **5** X = N; **4** X = CH, **6** X = N

Entry	Ketone	Base	*E*-olefin:*Z*-olefin
1		*t*-BuOK	> 99:1
2	1	NaH	> 99:1
3		LiHMDS	> 99:1
4		*t*-BuOK	50:50
5	2	NaH	> 99:1
6		LiHMDS	> 99:1

stry of the HWE reaction of the benzyl 2-pyridyl ketone (**2**).

Thus, in order to understand the increased *Z*-stereoselectivity of the benzyl 2-pyridyl ketone (**2**) in the presence of a potassium counter cation, we investigated which factor could stabilize the *erythro*-TS-2 by using the Ando protocol[2] (*ab initio* calculations in the RHF/6-31+G* level). Briefly, the reaction pass was first followed using *ab initio* RHF (restricted Hartree-Fock) calculations with the 3-21+G basis set incorporated in the GAUSSIAN 98 program.[7] All the reaction intermediates and transition structures were re-optimized by RHF/6-31+G*, and those energies were calculated by the B3LYP hybrid functional together with the 6-31+G* basis set. Vibrational frequency calculations (RHF/6-31+G*) gave only one imaginary frequency for all transition structures and confirmed that those structures are authentic transition structures. The transition state of the rate-determining oxaphosphetane formation step of benzyl phenyl ketone (**1**) was found to favor *threo*-TS-2 over *erythro*-TS-2 by 2.2 kcal/mol due to the steric repulsion between the ester moiety and the phenyl ring of the ketone in the *erythro*-TS-2 (Figs. 2a and 2b). Specifically, distances between the ester carbonyl oxygen (O) and C1 of phenyl ring (2.93 Å) are closer than the sum of their van der Waals radii (3.22 Å) (Fig. 2a). By the same token, the *erythro*-TS-2 of benzyl 2-pyridyl ketone (**2**) in the presence of lithium or sodium counter cation is less stable than *threo*-TS-2 (Fig. 2c). However, the 2-pyridyl nitrogen atom of benzyl 2-pyridyl ketone (**2**) is involved in the coordination of the potassium ion in the transition state of the oxaphosphetane formation step (*erythro*-TS-2. Fig. 2d). It seems like that the small lithium and sodium ions form tight transition states, and thus, involvement of nitrogen atom in coordination of the metal ion destabilizes the transition states by making the distance between O and C1 shorter than the sum of their van der Waals radii (2.75 and 2.90 Å for Li^+ and Na^+, respectively). On the other hand, the larger potassium ion sits on the top of the rectangle composed of three oxygen atoms and a nitrogen atom (Fig. 2d). As a result, the 2-pyridyl ring is located away from the ester carbonyl group and O and C1 acquire enough distance from each other (3.26 Å). Taken together, the quantum mechanical calculation shows that the lack of steric repulsion between ester moiety and phenyl ring conferred by involvement of the 2-pyridyl nitrogen atom in the coordination of the potassium ion stabilizes the *erythro*-TS-2 of the benzyl 2-pyridyl ketone (**2**) leading to formation of the *Z*-olefin: energy difference between *erythro*-TS-2 and *threo*-TS-2 is only 0.17 kcal/mol.

The specific role of the 2-pyridyl nitrogen atom in coordinating the potassium ion in the oxaphosphetane step was further investigated by a comparison with the HWE reactions of 3-pyridyl and 4-pyridyl benzyl ketones of which pyridyl nitrogen atoms cannot be involved in coordination of the counter cations (Table 2).

As expected, neither **7** nor **8** gave *Z*-olefins regardless of the counter cations used in the HWE reactions (Table 2). Transition state geometries optimized by *ab initio* calcu-

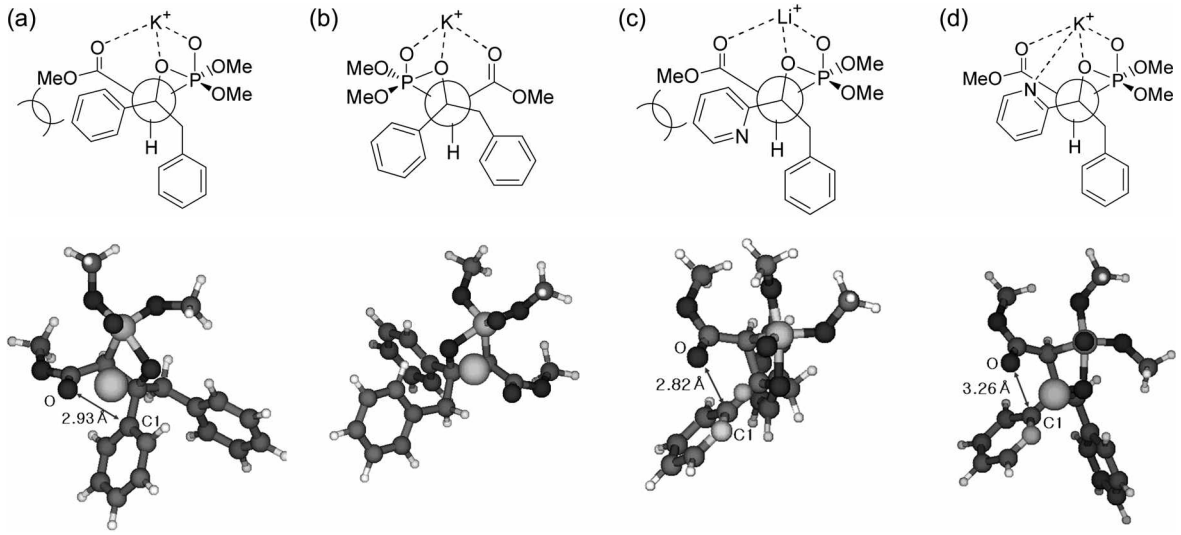
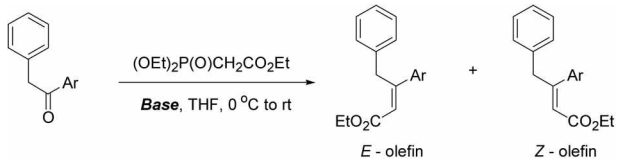


Figure 2. Transition state geometries optimized by *ab initio* calculations of (a) **1** with K^+ leading to *erythro*-TS-2; (b) **1** with K^+ leading to *threo*-TS-2; (c) **2** with Li^+ leading to *erythro*-TS-2; (d) **2** with K^+ leading to *erythro*-TS-2.

Table 2. Stereoselectivity of the HWE reactions of benzyl 3-pyridyl ketone (**7**) and benzyl 4-pyridyl ketone (**8**) in the presence of various bases



7 Ar = 3-pyridyl
8 Ar = 4-pyridyl
9 Ar = 3-pyridyl **10** Ar = 3-pyridyl
11 Ar = 4-pyridyl **12** Ar = 4-pyridyl

Entry	Ketone	Base	*E*-olefin:*Z*-olefin
1		*t*-BuOK	> 99:1
2	**7**	NaH	> 99:1
3		LiHMDS	> 99:1
4		*t*-BuOK	> 99:1
5	**8**	NaH	> 99:1
6		LiHMDS	> 99:1

lations of **7** and **8** leading to *erythro*-TS-2 show that the nitrogen atoms are not involved in coordination of the counter cations and, as a result, the *erythro*-TS-2 is destabilized by unfavorable steric interactions (2.89 Å and 2.90 Å for 3-pyridyl and 4-pyridyl, respectively, Fig. 3).

In summary, quantum mechanical investigation of the HWE reaction of benzyl 2-pyridyl ketone suggests a possible role of the potassium counter cation in stabilizing the transition state (*erythro*-TS-2) leading to the formation of a *Z*-olefin through coordination of the nitrogen atom in benzyl 2-pyridyl ketone.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Bruker 400 AMX spectrometer (Karlsruhe, Germany) at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR with tetramethylsilane as an internal standard. Chemical shifts (d) are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). TLC was performed on silica gel 60 F_{254} purchased from Merck. Column chromatography was performed using either silica gel-60 (220-440 mesh) for flash chromatography.

General procedure for preparation of benzyl pyridyl ketones. Preparation of 2-phenyl-1-pyridin-2-yl-ethanone (2) is representative. To a stirred solution of benzyl magnesium chloride (1.0 M in diethyl ether) (9.3 mL, 9.3 mmol, 2 eq) in anhydrous THF (18 mL) was slowly added 2-pyridine carboxaldehyde (500 mg, 4.66 mmol) at −78 °C. After 6 h, the mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. After a filtration, the organic solvent was concentrated under reduced pressure and purified by flash column chromatography on silica gel (Hexane:EtOAc = 3:1) to yield 2-phenyl-1-pyridin-2-yl-ethanol (417 mg, 45%) as a dark yellow oil, which was used for the next step without further purification. To a stirred solution of oxalyl chloride (0.35 mL, 4 mmol) in anhydrous CH_2Cl_2 (20 mL), DMSO

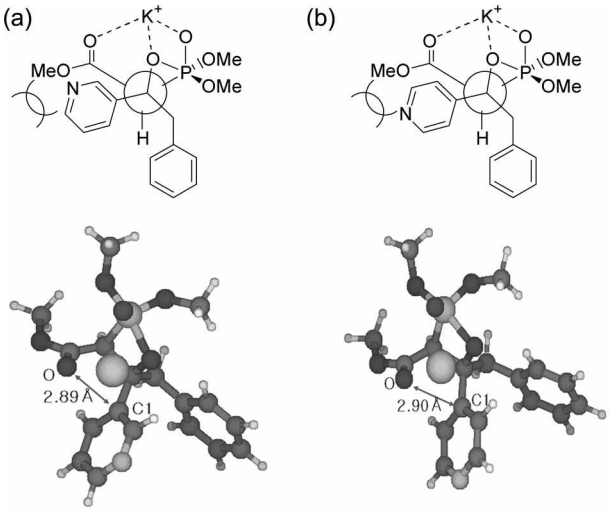


Figure 3. Transition state geometries optimized by *ab initio* calculations of (a) **7** with K^- leading to *erythro*-TS-2; (b) **8** with K^- leading to *erythro*-TS-2.

(0.95 mL, 13.5 mmol) was slowly added at −78 °C. After 15 min, 2-phenyl-1-pyridin-2-yl-ethanol (538 mg, 2.7 mmol) obtained above was added in a dropwise fashion. The reaction mixture was stirred for additional 30 minutes at −78 °C and then TEA (1.9 mL, 13.5 mmol) was slowly added. After 30 min, the mixture was poured into water and extracted by EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure to give a yellow residue which was purified by column chromatography on silica gel (Hexane:EtOAc = 5:1) to afford **2** (530 mg, 97%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (d, J = 4.8 Hz, 1H.), 8.01 (d, J = 7.9 Hz, 1H), 7.77 (td, J = 7.6, 1.6 Hz, 1H), 7.44-7.27 (m, 6H), 4.55 (s, 2H).

1-Phenyl-2-pyridin-3-yl-ethanone (7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (1H, s), 8.66 (1H, d, J = 5.1 Hz), 7.20-7.39 (4H, m), 7.14-7.17 (3H, m), 4.46 (2H, s).

1-Phenyl-2-pyridin-4-yl-ethanone (8). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (2H, d, 4.5 Hz), 7.77 (2H, dd, J = 4.3, 1.6 Hz), 7.24-7.36 (5H, m), 4.28 (2H, s).

General procedure of HWE reaction. Base (0.5-1.5 eq) was slowly added to a stirred solution of triethyl phosphonoacetate (1.5-2.0 eq) in anhydrous THF (5 mL) at 0 °C. After 30 min, a solution of ketone (1.0 eq) in anhydrous THF was added to the reaction mixture in a dropwise fashion. The reaction mixture was allowed to slowly warm up to room temperature and stirred overnight. The reaction mixture was poured into water and extracted by EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. After a filtration, organic solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (Hexane:EtOAc = 5:1) to afford the desired compounds.

(*E*)-3,4-Diphenyl-but-2-enoic acid ethyl ester (3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.38 (m, 2H), 7.29 (t, J = 3.2 Hz, 3H), 7.22-7.15 (m, 4H), 7.14-7.08 (m, 1H), 6.23 (s, 1H), 4.51 (s, 1H), 4.22 (quart, J = 7.2 Hz, 2H), 1.30 (t, J =

7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 157.6, 141.4, 139.1, 129.9, 129.3, 129.0, 128.9, 128.8, 128.7, 127.4, 126.4, 119.2, 60.5, 36.9, 14.7.

(*Z*)-3,4-Diphenyl-but-2-enoic acid ethyl ester (4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (dd, J = 7.1 Hz, 1.4 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.50 (dd, J = 9.6 Hz, 2.1 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.40-7.35 (m, 3H), 6.50 (s, 1H), 4.07 (quart, J = 7.1 Hz, 2H), 1.57 (s, 2H), 1.11 (t, J = 7.1 Hz, 3H).

(*E*)-4-Phenyl-3-pyridin-2-yl-but-2-enoic acid ethyl ester (5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (d, J = 4.8 Hz, 1H), 7.58 (td, J = 7.7 Hz, 1.6 Hz, 1H), 7.29-7.08 (m, 7H), 5.82 (s, 1H), 3.98 (quart, J = 7.1 Hz, 2H), 3.85 (s, 2H), 1.08 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 158.4, 157.2, 149.4, 137.4, 135.9, 129.9, 129.0, 127.1, 123.9, 122.9, 120.3, 60.5, 44.8, 14.3.

(*Z*)-4-Phenyl-3-pyridin-2-yl-but-2-enoic acid ethyl ester (6). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 8.61 (d, J = 4.7 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H) 7.32-6.98 (m, 6H), 6.75 (s, 1H), 4.67 (s, 2H), 4.24 (quart, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 157.5, 155.4, 149.7, 149.6, 139.3, 137.0, 129.0, 128.7, 126.4, 122.4, 121.0, 62.2, 34.4, 14.5.

(*E*)-4-Phenyl-3-pyridin-3-yl-but-2-enoic acid ethyl ester (9). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, J = 7.0 Hz, 3H), 4.09 (s, 2H), 4.26 (q, J = 7.0, Hz, 2H), 6.41 (d, J = 16.0 Hz, 1H), 7.01 (s, 1H), 7.13 (d, J = 7.3 Hz, 2H), 7.24-7.32 (m, 3H), 7.95 (d, J = 16.0 Hz, 1H), 8.48 (s, 1H), 8.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 204.7, 189.0, 186.8, 186.5, 177.5, 176.4, 168.4, 167.4, 165.3, 163.3, 160.2, 99.2, 76.9, 52.6.

(*E*)-4-Phenyl-3-pyridin-4-yl-but-2-enoic acid ethyl ester (11). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, J = 7.1 Hz, 3H), 4.26 (q, J = 7.1 Hz, 2H), 4.47 (s, 2H), 6.29 (s, 1H), 7.14-7.30 (m, 7H), 8.55 (d, J = 4.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 204.3, 192.7, 188.6, 187.0, 176.1, 167.1, 164.9, 159.5, 158.7, 99.0, 74.4, 69.4, 53.6.

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4. The stereochemistry of the products were confirmed by 2D-NOESY experiment in which only *E*-olefin showed strong correlation between benzylic proton and vinyl proton.
5. Benzyl 2-pyridyl ketone (**2**) was prepared by condensation of benzyl magnesium bromide and 2-pyridinecarboxaldehyde followed by swern oxidation.
6. Because benzyl 2-pyridyl ketones, synthesized by oxidation of the corresponding secondary alcohols, showed instability upon column chromatography on silica gel, the crude benzyl pyridyl ketones were directly used for the Horner-Wadsworth-Emmons reactions. The two-step yields were fair to good (35-80%) but the yields were not optimized.
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