Diethyl [3-Cyano-2-Oxo-3-(Triphenylphosphoranylidene)propyl]phosphonate: A Useful Horner-Wadsworth-Emmons Reagent for α-Keto (Cyanomethylene)triphenylphosphoranes from Carbonyl Compounds

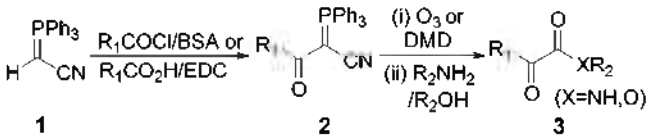
Kieseung Lee

Department of Chemistry, Woosuk University, Chonbuk 565-701, Korea. E-mail: kslee@woosuk.ac.kr
Received August 2, 2007

Key Words : α-Keto (cyanomethylene)triphenylphosphorane, Acyl cyanophosphorane, α-Keto amide, α-Keto ester

Recently α-keto amide/ester units[1] have attracted much attention in organic and medicinal chemistry due to the presence of these highly electrophilic units in many bioactive natural products and synthetic peptides.[1,2] Among a number of synthetic routes reported recently,[3] Wasserman's approach[3c] in which α-keto (cyanomethylene)triphenylphosphoranes **2** are used as the key intermediates according to Scheme 1, stands out for its mild conditions and the outstanding convergence. Although this approach has been widely employed in the synthesis of bioactive compounds[2c,d,5] including tricarbonyls[6a] and human lipase inhibitors[6b,c] by us, there is a shortcoming that the key intermediates **2** can be derived only from carboxylic acids/acid chlorides. In light of that there are abundant carbonyl compounds (aldehydes/ketones) as natural/synthesized form, it would be highly desirable to use carbonyl compounds for the synthesis of phosphoranes **2**. Herein we wish to report the first direct synthesis of phosphoranes **2** from carbonyl compounds utilizing a new Horner-Wadsworth-Emmons (HWE)[7] reagent **4** according to the procedures described in Scheme 2.

The requisite HWE reagent **4** was successfully prepared *via* two-step route: coupling of chloroacetyl chloride with phosphorane **1**/BSA (*N,O*-Bis(trimethylsilyl)acetamide) gave 4-chloro-3-oxo-2-(triphenyl-phosphoranylidene)butanenitrile,[8] which was heated in $P(OEt)_3$ (110 °C, 24 h, Ar) to afford a new HWE reagent **4**, diethyl [3-cyano-2-oxo-3-(triphenylphosphoranylidene)-propyl]phosphonate, in excellent overall yield.[9] A variety of carbonyl compounds were condensed with **4**, and the resulting β,γ-unsaturated α-keto cyanophosphoranes **5** were hydrogenated over Pd-C/H_2 (1 atm) to α-keto cyanophosphoranes **2** (Table 1).[10]



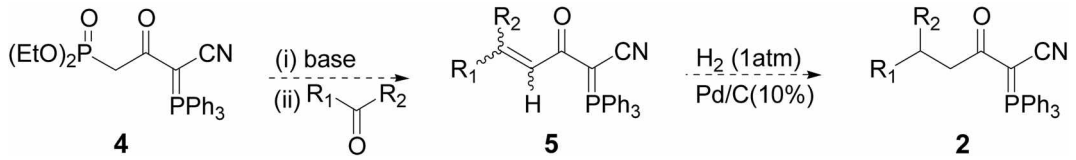
1 2 3

Scheme 1. Wasserman's approach to α-keto amide/ester units.

Condensation of simple aryl/aliphatic aldehydes with **4** gave exclusively (*E*)-olefins in excellent yields (run 1, 2, 4, 5). 2,6-Dimethylbenzaldehyde, however, required longer reaction time obviously owing to the steric hindrance (run 3). The reaction of *N*-BOC-2-aminoacetaldehyde with **4** is of special interest since it ultimately could afford γ-aminobutyric acid (GABA)-derived α-keto amide/ester units, which have been incorporated into bioactive compounds.[11] Under the standard conditions, *N*-BOC-2-aminoacetaldehyde furnished **5f** in 89% yield (run 6). The condensation of ketones with **4**, however, has been found very sluggish and incomplete. In the case of acephenone, **5g** was obtained in 69% yield with a ratio (*E*/*Z*, 4/6) (run 7).

The hydrogenation went straightforward simply by stirring the slurry of **5** and Pd-C (10%, 10-30 wt%) in solvent (THF/MeOH, 1/1) under H_2 (1 atm). Simple aryl/aliphatic/α-aminoacetaldehyde-derived phosphoranes **5** were hydrogenated perfectly in 3 h with Pd-C (10 wt%) (run 1',2',4'-6'). However, sterically hindered aryl aldehyde/ketone-derived phosphoranes **5** required higher loading of Pd-C (30 wt%) and longer reaction time (run 3',7',8'). No detectable byproducts were formed during this step (confirmed by TLC and ^{1}H NMR), signifying the stability of cyanophosphorane subunit under hydrogenation conditions. Thus, usual work-up without chromatography afforded pure phosphoranes **2** in quasi-quantitative yields.

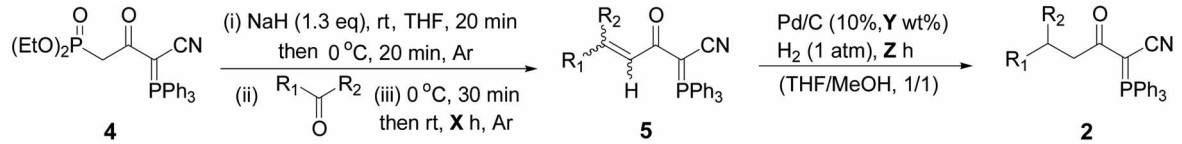
In conclusion, we have developed a new synthetic route for β,γ-unsaturated α-keto cyanophosphoranes/α-keto cyanophosphoranes from carbonyl compounds utilizing a new HWE reagent **4**. We are currently applying this new synthetic route for heterocyclic/heteroaromatic/chiral α-amino aldehydes, and extending the same approach to the synthesis of α-keto alkoxycarbonylphosphoranes[12] from carbonyl compounds utilizing a new HWE reagent having alkoxycarbonylphosphorane subunit.



4 5 2

Scheme 2. A new synthetic approach to α-keto cyanophosphoranes **2** from carbonyl compounds utilizing a new HWE reagent **4**.

Table 1. Condensation of **4** with carbonyl compounds and subsequent hydrogenation of **5** to **2** over Pd-C (10%)/H_2 (1 atm)



4 **5** **2**

Run	R_1	R_2	**X** (h)	**5** (Yield, %)[a]	Run	**Y** (wt%)	**Z** (h)	**2** (Yield, %)[f]
1	Ph-	H	1	**5a** (93)[b]	1'	10	3	**2a** (98)
2	2-MePh-	H	3	**5b** (91)[c]	2'	10	10	**2b** (97)
3	2,6-$(Me)_2$Ph-	H	22	**5c** (87)[c]	3'	30	24	**2c** (95)
4	$Ph(CH_2)_2$-	H	1	**5d** (89)[c]	4'	10	3	**2d** (98)
5	$CH_3(CH_2)_6$-	H	1	**5e** (88)[c]	5'	10	3	**2e** (97)
6	$BOCNHCH_2$-	H	1	**5f** (89)[c]	6'	10	3	**2f** (91)
7	Ph-	CH_3-	24	**5g** (69)[d,e]	7'	30	10	**2g** (99)
8	Ph-	Ph-	22	**5h** (58)[e]	8'	30	6	**2h** (99)

[a]Isolated yield after flash column chromatography on SiO_2. [b](*E*)-Stereochemistry is unambiguously confirmed by comparing mp, IR, ^1H, ^{13}C NMR of **5a** with those of product prepared from *trans*-cinnamic acid according to the known procedure.[15] [c](*E*)-Stereochemistry is confirmed by coupling constant (*ca* 15 Hz) between two *vinylic* protons. [d]The stereochemistry is confirmed by nOe experiment, and the ratio of ((*E*)-/(*Z*)-olefin) is determined to be *ca* 4/6 by ^1H NMR. [e]Starting acetophenone and benzophenone are recovered in 26% & 37% yield, respectively. [f]Isolated yield after filtering, washing the filtered-cake (THF & MeOH), concentration in *vacuo*.

Acknowledgements. The author thank Prof. Yong Hae Kim at KAIST for valuable discussions and encouragement for this project

References and Notes

1. (a) Otto, H. H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133. (b) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.
2. (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Koto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (b) Schmodt, H.; Weinbrenner, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1003. (c) Han, W.; Hu, Z.; Jiang, X.; Wasserman, Z. R.; Decicco, C. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1111. (d) Tavares, F. X.; Deaton, D. A.; Miller, A. B.; Miller, L. R.; Wright, L. L.; Zhou, H.-Q. *J. Med. Chem.* **2004**, *47*, 5049.
3. (a) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913. (b) Ocain, T. D.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451. (c) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364. (d) Kim, S.-K.; Nuss, J. M. *Tetrahedron Lett.* **1999**, *40*, 1827. (e) Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, *7*, 10245. (f) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873. (g) Ma, M.; Li, C.; Peng, L.; Xie, F.; Zhang, X.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 3927.
4. Wong, M. K.; Yu, C.-W.; Yue, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606.
5. (a) Wasserman, H. H.; Chen, J.-H.; Xia, M. *J. Am. Chem. Soc.* **1999**, *121*, 1401. (b) Wasserman, H. H.; Zhang, R. *Tetrahedron* **2002**, *58*, 6277. (c) Haberhauer, G. *Synlett* **2004**, 1003. (d) Price, W. S.; Fletcher, S.; Jorgensen, M. R.; Miller, A. D. *Synlett* **2006**, 1933.
6. (a) Wasserman, H. H.; Lee, K.; Xia, M. *Tetrahedron Lett.* **2000**, *41*, 2511. (b) Lee, K. *Bull. Korean Chem. Soc.* **2002**, *23*, 351. (b) Lee, K.; Kim, D.-K. *J. Kor. Chem. Soc.* **2004**, *48*, 161.
7. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.
8. Listvan, V. N.; Dombrovskii, A. V. *Z. Obs. Khim.* **1968**, *38*, 610.
9. *Analytical data for* **4**: a white solid; mp 180.0-182.0 °C; IR (KBr) 2173, 1586, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, 6H, J = 7.1 Hz), 3.37 (d, 2H, $J_{H\text{-}P}$ = 22.0 Hz), 4.16 (m, 4H), 7.49-7.71 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, $J_{C\text{-}P}$ = 5.8 Hz), 38.4 (dd, $J_{1,C\text{-}P}$ = 129.9 Hz, $J_{2,C\text{-}P}$ = 7.4 Hz), 51.0 (dd, $J_{1,C\text{-}P}$ = 126.7 Hz, $J_{2,C\text{-}P}$ = 5.0 Hz), 62.2 (d, $J_{C\text{-}P}$ = 5.8 Hz), 121.9 (d, $J_{C\text{-}P}$ = 15.7 Hz), 122.8 (d, $J_{C\text{-}P}$ = 93.5 Hz), 129.1 (d, $J_{C\text{-}P}$ = 13.2 Hz), 133.1 (d, $J_{C\text{-}P}$ = 3.3 Hz), 133.6 (d, $J_{C\text{-}P}$ = 10.8 Hz), 186.9 (dd, $J_{1,C\text{-}P}$ = 6.6 Hz, $J_{2,C\text{-}P}$ = 5.0 Hz); HRMS calcd for $C_{26}H_{27}NO_4P_2$ 479.1415, found 479.1412; Anal. calcd for $C_{26}H_{27}NO_4P_2$: C, 65.13; H, 5.68; N, 2.92. found: C, 65.36; H, 5.67; N, 2.96.
10. *General procedure for* **5**: To a solution of **4** (0.50 mmol, 240.0 mg) in THF (15 mL) was added NaH (1.3 eq, 26.1 mg, 60% in oil), and the resulting slurry was stirred for 20 min at rt, then for 20 min at 0 °C under Ar. To this was added benzaldehyde (1.0 eq, 50.8 mL) by syringe, and the mixture was stirred for 30 min at 0 °C, then for 1 h at rt. The reaction was quenched by H_2O (15 mL), and extracted with Et_2O (20 mL × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/Hexane, 15/1) to afford **5a** (201.0 mg, 93%) as a pale-yellow solid; mp 232.0-234.0 °C; IR (KBr) 2172, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.70 (m, 22H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.9 (d, $J_{C\text{-}P}$ = 128.3 Hz), 122.1 (d, $J_{C\text{-}P}$ = 15.7 Hz), 123.2 (d, $J_{C\text{-}P}$ = 93.5 Hz), 123.7 (d, $J_{C\text{-}P}$ = 9.1 Hz), 128.1, 128.6, 129.2 (d, $J_{C\text{-}P}$ = 12.4 Hz), 129.3, 133.1 (d, $J_{C\text{-}P}$ = 3.3 Hz), 133.6 (d, $J_{C\text{-}P}$ = 9.9 Hz), 135.4, 138.9 (d, $J_{C\text{-}P}$ = 1.7 Hz), 185.8 (d, $J_{C\text{-}P}$ = 3.3 Hz); HRMS calcd for $C_{29}H_{22}NOP$ 431.1439, found 431.1430.
General procedure for **2**: A slurry of **5a** (216.0 mg, 0.50 mmol) and Pd-C (10%, 21.6 mg) in solvent (5 mL, THF/MeOH, 1/1) was stirred for 3 h under H_2 (1 atm) using balloon. The mixture was filtered, and the filtered-cake was washed with THF (15 mL) and MeOH (15 mL). Concentration in *vacuo* and drying under high vacuum provided **2a** (212.6 mg, 98%) as a white solid; mp 172.0-174.0 °C; IR (KBr) 2172, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.70 (m, 15H), 7.18-7.32 (m, 5H), 3.16 (t, 2H, J = 7.1 Hz), 3.06 (t, 2H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 40.4 (d, $J_{C\text{-}P}$ = 7.4 Hz), 48.7 (d, $J_{C\text{-}P}$ = 126.6 Hz), 122.6 (d, $J_{C\text{-}P}$ = 16.6 Hz), 123.2 (d, $J_{C\text{-}P}$ = 93.5 Hz), 125.8, 128.2, 128.7, 129.1 (d, $J_{C\text{-}P}$ = 13.2 Hz), 133.0 (d, $J_{C\text{-}P}$ = 3.3 Hz), 133.5 (d, $J_{C\text{-}P}$ = 9.9 Hz), 141.5, 195.9 (d, $J_{C\text{-}P}$ = 3.3 Hz); HRMS calcd for $C_{29}H_{24}NOP$ 433.1596, found 433.1596.
11. (a) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 6758. (b) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2269.
12. Lee, K.; Im, J.-M. *Tetrahedron Lett.* **2001**, *42*, 1539.