Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Highly Cis-Selective Horner-Wadsworth-Emmons (HWE) Reaction of Methyl Bis(2,4-Difluorophenyl) Phosphonoacetate

Keisuke Kokin [a] , Jiro Motoyoshiya [a] , Sadao Hayashi [a] & Hiromu Aoyama [a]

[a] Department of Chemistry, Faculty of Textile Science & Technology , Shinshu University , Ueda, Nagano, 386, Japan

To cite this article: Keisuke Kokin , Jiro Motoyoshiya , Sadao Hayashi & Hiromu Aoyama (1997) Highly Cis-Selective Horner-Wadsworth-Emmons (HWE) Reaction of Methyl Bis(2,4-Difluorophenyl) Phosphonoacetate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:14, 2387-2392, DOI: 10.1080/00397919708004100

To link to this article: http://dx.doi.org/10.1080/00397919708004100

SYNTHETIC COMMUNICATIONS, 27(14), 2387-2392 (1997)

HIGHLY *CIS*-SELECTIVE HORNER-WADSWORTH-EMMONS (HWE) REACTION OF METHYL BIS(2,4-DIFLUOROPHENYL) PHOSPHONOACETATE

Keisuke Kokin, Jiro Motoyoshiya*, Sadao Hayashi, and Hiromu Aoyama

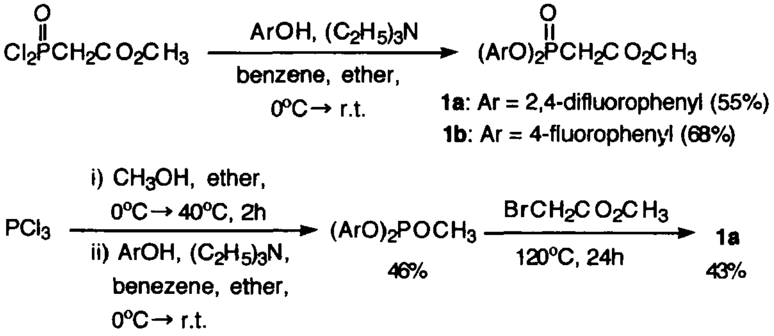
Department of Chemistry, Faculty of Textile Science & Technology, Shinshu University, Ueda, Nagano 386, Japan

ABSTRACT : Of the previously reported Horner-Wadsworth-Emmons (HWE) reaction, the olefination of methyl bis(2,4-difluorophenyl)phosphonoacetate (1a) with various aldehydes gave unsaturated esters in the highest *cis*-selectivity.

The Horner-Wadsworth-Emmons (HWE) reaction, a complement and an improvement of the Wittig reaction, is a powerful method for olefin synthesis. A characteristic feature of the general HWE reaction is the formation of thermodynamically favored *E*-olefins, whereas a few *Z*-selective HWE reagents such as methyl bis(trifluoroethyl)phosphonoacetate[1] and ethyl diphenylphosphonoacetate[2] have been developed. The former has been often used in the natural product syntheses.[3] In the HWE reaction with above modified phosphonates, it is proposed that the *Z*-selectivity increases due to acceleration of elimination rate of phosphoryl group by the effects of electron negative groups such as trifluoroethoxy or phenoxy group.[4,5] However, *cis*-selectivities are sometimes insufficient in the reactions of these phosphonates with aliphatic aldehydes. In order to achieve higher *cis*-selectivity under a convenient condition, we prepared new phosphonates, methyl bis(2,4-difluorophenyl)phosphonoacetate (1a) and methyl bis(4-fluorophenyl)phosphono-acetate (1b) and studied the selectivities in the reactions with various aldehydes.

The phosphonates **1a** and **1b** were prepared by the reaction of the corresponding phenols with dichlorophosphorylacetate in 55% and 68% yields, respectively (Scheme 1). While this synthesis of these phosphonates is based on the previous reported method,[1,2] **1a** could be also prepared by the Arubzov reaction with methyl bromoacetate and methyl bis(2,4-difluorophenyl)phosphite which was obtained from methyl dichlorophosphite[6] and difluorophenol in 43% yield (Scheme 1). This method will be applicable to the synthesis of this type of phosphonates.

Scheme 1



The reactions of **1a** and **1b** with various aromatic or aliphatic aldehydes were carried out in the presence of potassium [bis(trimethyl)silly]amide [KN(TMS)$_2$]/18-crown-6 (Condition A) or sodium hydride (NaH) in tetrahydrofuran (THF) (Condition B and C). The results are summarized in Table 1. The isomeric components of **2a-c,e** and **f** were determined by gas chromatography; the retention times of all *cis*-isomers were shorter than those of *trans*-isomers, which were readily available from methyl diethylphosphonoacetate and corresponding aldehydes. Because of non-volatility, the isomeric ratios of **2d,g,h** were determined by the integrations of vinyl protons in ^{1}H-NMR.

Of the previously reported HWE reaction, **1a** showed the highest *cis*-selectivity independently of the structure and electronic nature of aldehydes under Condition A. It is worthy to note that the olefination with **1a** gave the synthetically sufficient selectivity in a more convenient condition (Condition C). The lower yields in the reactions of aliphatic aldehydes are mainly due to the volatility of the products, but this will be improved by careful treatment after the reaction. The obtention of *E,Z*-conjugated dienes is synthetically interesting, because such structures are often presented in insect pheromones, whose syntheses have been achieved by salt-free phosphonium ylides.[7] On the other hand, the olefination of **1b** also showed high *cis*-selectivity, but in some reactions the selectivity was lower than **1a**. The lower reaction temperature affected increment of *cis*-selectivity. The HWE reaction with mono-fluorinated phosphonate **1b** and aliphatic aldehydes gave higher *cis*-selectivity than previously reported ethyl diphenylphosphonoacetate[2] in the same reaction condition. It is obvious, from these results, that introduction of the electron negative fluorine atoms on phenyl groups contributes to increment of *cis*-selectivity.

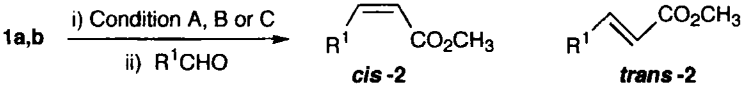
Thus, we showed that difluorophenoxy groups on phosphorus atom were very effective to increase *cis*-selectivity in the HWE reaction and its application to other phosphonates bearing alternative carbanion stabilizing groups is undergoing in our laboratory.

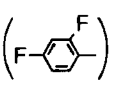
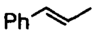
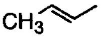
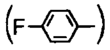
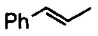
Experimental Section

All solvents were dried by standard method. ^{1}H-NMR spectra were obtained on JEOL PMX60 using TMS as an internal standard in $CDCl_3$. HRMS spectra were determined on HITACHI M-80B mass spectrometer.

Methyl bis(2,4-difluorophenyl)phosphonoacetate (1a) ; Typical Procedure : A solution of methyl dichlorophosphorylacetate (4.00g, 20.9mmol) in benzene (30ml) was added to 2,4-difluorophenol (5.45g, 41.9mmol) and triethylamine (6.71ml, 48.2mmol) dissolved in benzene (60ml) and ethyl ether (20ml) at 0°C. After the reaction mixture was stirred for 4h at room temperature, precipitated ammonium chloride was filtered off and the filtrate was washed with

Table 1. Reaction Condition and *cis/trans* Ratio in the Horner-Wadsworth-Emmons Reaction of Phosphonate **1a** and **1b** with Various Aldehydes



Phosphonate(Ar)	R^1	Product	Condition[a]	Yield(%)[b]	*cis/trans* Ratio[c]
1a 	Ph	2a	A	80	98 : 2
			B	93	96 : 4
	n-C_7H_{15}	2b	A	54	98 : 2
			B	82	95 : 5
	n-C_5H_{11}	2c	A	45	>99 : 1
			B	45	94 : 6
		2d	A	80	>99 : 1[d]
		2e	B	54	93 : 7
	$(CH_3)_2CH$	2f	B	54	92 : 8
	p-$NO_2C_6H_4$	2g	A	100	>99 : 1[d]
	p-$CH_3OC_6H_4$	2h	A	78	>99 : 1[d]
1b 	Ph	2a	A	86	98 : 2
			B	100	78 : 22
			C	99	90 : 10
	n-C_7H_{15}	2b	A	65	94 : 6
			B	82	87 : 13
			C	82	93 : 7
	n-C_5H_{11}	2c	A	45	87 : 13
			B	38	86 : 14
			C	80	91 : 9
		2d	A	48	>99 : 1[d]
			C	90	86 : 14[d]

a. Condition A: $KN(TMS)_2$, 18-crown-6, -78°C, THF. Condition B: NaH, 0°C, THF. Condition C: NaH, 0°C→ -78°C, THF. b. Isolated yield by column chromatography. c. The ratios were determined by gas chromatography. d. The ratios were determined by ^{1}H-NMR.

saturated $NaHCO_3$ (3 x 60ml), saturated NH_4Cl and brine and dried over Na_2SO_4. Removal of the solvent followed by purification by column chromatography [silica gel/hexane-AcOEt (4/1)] provided **1a** (4.34g, 55%) as a colorless oil.

^{1}H NMR δ: 3.40 (d, 2H, J_{PH} = 22Hz), 3.77 (s, 3H), 6.60-7.60 (m, 6H); MS (70ev) 378 (M^+); HRMS *m/z* calcd for $C_{14}H_8O_4F_4P$ (M^+ - ·OCH_3): 347.0096. Found: 347.0096.

Methyl bis(4-fluorophenyl)phosphonoacetate (1b)

^{1}H NMR δ: 3.25 (d, 2H, J_{PH} = 22Hz), 3.75 (s, 3H), 6.80-7.43 (m, 8H); MS (70ev) 342 (M^+); HRMS *m/z* calcd for $C_{14}H_{10}O_4F_2P$ (M^+ - ·OCH_3): 311.0261. Found: 311.0283.

Methyl bis(2,4-difluorophenyl)phosphite ; A solution of methanol (0.26g, 8.02mmol) in ethyl ether (1ml) was added to a previously ice-cooled solution of phosphorous trichloride (0.7ml, 8.02mmol) in ethyl ether (0.5ml) and the mixture was heated at 40°C for 2h. Then, the reaction mixture was added dropwise to 2,4-difluorophenol (2.14g, 16.5mmol) and triethylamine (2.7ml, 16.5mmol) dissolved in benzene (15ml) and ethyl ether (5ml) at 0°C. After stirring for 3h at room temperature, the usual work-up and purification by kugelrohr distillation afforded pure phosphite (1.17g, 46%, oven-temp. 170°C/4mm).

^{1}H NMR δ: 3.82 (d, 3H, J_{PH} = 10Hz), 6.53-7.33 (m, 6H); HRMS *m/z* calcd for $C_{13}H_9O_3F_4P$ 320.0202. Found: 320.0224.

Methyl bis(2,4-difluorophenyl)phosphonoacetate (1a) by the Arubzov reaction : A mixture of methyl bis(2,4-difluorophenyl)phosphite (1.17g, 3.66mmol) and methyl bromoacetate (0.51g, 3.32mmol) was heated at 120°C for 24h. Purification of column chromatography [silica gel/hexane-AcOEt (4/1)] gave **1a** (0.54g, 43%) as a colorless oil.

***cis*-Methyl cinnamate (2a)** ; Typical Procedure - *Condition A* : A solution of $KN(TMS)_2$ (0.5mol/l toluene solution, 2.0ml, 1.00mmol) was added dropwise to a solution of **1a** (0.38g, 1.00mmol) and 18-crown-6 (1.32g 5.00mmol) in THF (20ml) at -78°C and the mixture was stirred at this temperature for 1h under N_2. A solution of benzaldehyde (0.11g, 1.00mmol) in THF (2ml) was then added and the mixture was stirred for 12h; the reaction was quenched with saturated NH_4Cl at room temperature. The THF layer was separated and the product was further extracted with Et_2O (2 x 20ml) from aqueous layer. The combined extract was washed with brine and dried on Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using benzene as an eluant to give **2a** in 80% yield.

Condition B : A solution of **1a** (0.38g, 1.00mmol) in THF (5ml) was added dropwise to a suspension of NaH (50% in oil, 0.05g, 1.00mmol) in THF (10ml) at 0°C and the mixture was stirred at the same temperature for 1h under N_2. After addition of benzaldehyde (0.11g, 1.00mmol) in THF (5ml) at 0°C, the mixture was stirred at same temperature for 8h. The usual work-up and column chromatography gave **2a** in 93% yield.

Condition C : After the carboanion of **1b** was prepared similarly to Condition B, the aldehyde was added dropwise at -78°C and the mixture was stirred at same temperature for 8h. The following treatment was done as described above.

Acknowledgment. We thank Mrs. Eiko Tsuchida (Faculty of Engineering, Shinshu University) for the mesurement of the mass spectra.

REFERENCES

1. Still, W. C. and Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
2. Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105.
3. Recent application of Still's reagent, see ; Minami, T., Utsunomiya, T., Nakamura, S., Okubo, M., Kitamura, N., Okada, Y., and Ichikawa, J. *J. Org. Chem.* **1994**, *59*, 6717.
4. Ando, K. *The 22nd Symposium in Okayama on Progress of Reaction and Synthesis*, **1996**, 1.
5. Maryanoff, B. E. and Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863 and references cited therein.
6. Cook, H. G., Ilett, J. D., Saunders, B. C., Stacey, G. J., Watson, H. G., Wilding, I. G. E., and Woodcock, S. J. *J. Chem. Soc.* **1949**, 2921.
7. Bestmann, H. J., Vostrowsky, O., Paulus, H., Billmann, W., and Stransky, W. *Tetrahedron Lett.* **1977**, 121.

(Received in Japan 28 December 1996)