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Excess sodium ions improve Z selectivity in Horner–Wadsworth–Emmons olefinations with the Ando phosphonate

Petri M. Pihko* and Taina M. Salo

Laboratory of Organic Chemistry, Department of Chemical Technology, Helsinki University of Technology, POB 6100, FIN-02015 HUT, Finland

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Abstract—New, improved conditions for Z selective Horner–Wadsworth–Emmons olefinations with Ando's bis(o-methylphenyl)phosphonates are reported. A combination of NaH and NaI affords Z olefins in up to >99:1 selectivity and good yields. © 2003 Elsevier Science Ltd. All rights reserved.

Di- and trisubstituted (Z)-olefins bearing an allylic stereocentre are highly useful intermediates in stereoselective synthesis. The Z double bond imposes a considerable conformational bias on the molecule dictated by allylic 1,3-strain.¹ This bias is reflected in the reactions of these olefins, which are often highly diastereoselective.² Synthesis of (Z)-olefins with high selectivities, vields, and optical purities, is therefore an important objective. For the Horner-Wadsworth-Emmons (HWE) olefination³ using (phosphono)acetates and their derivatives, two Z selective methods have attained widespread use: the Still-Gennari method⁴ employing [bis(trifluoroethyl)phosphono]acetates and the Ando method⁵ using (diarylphosphono)acetates such as 1. While the Ando method has been reported to be more selective in many cases,6 it has not yet attained the popularity of the Still-Gennari method.

In this paper, we present new, simple conditions that improve the Z selectivities with the Ando reagent 1 and afford useful *methyl* esters in high Z selectivity.⁷

We began by examining the role of the countercation in the Ando olefination. With benzaldehyde, Ando^{5a,b} has conducted a full comparison between lithium, sodium and potassium bases. The potassium bases (KHMDS or KHMDS/18-crown-6) were reported to give the best Z selectivities, in accord with the results obtained by

Still and Gennari. Somewhat surprisingly, with aliphatic and especially α -branched aldehydes, the use of NaH was recommended (no selectivity data was reported for lithium or potassium bases).^{5b} Furthermore, the conditions employed by Ando require as much as 140 mol% of NaH relative to the phosphonate. Since using an excess of base might rapidly erode the enantiopurities of valuable α -chiral aldehydes, we decided to examine the selectivities using substoichiometric amounts of base relative to phosphonate 1 (Table 1). With aliphatic aldehydes (n-octanal 2 and cyclohexanecarboxaldehyde 3), NaH was clearly the most Z selective among the bases examined. The potassium and lithium bases (KHMDS and n-BuLi) were both inferior to NaH. Addition of 18-crown-6 to KHMDS improved the Z selectivity with cyclohexanecarboxaldehyde to 85:15, but in comparison, NaH afforded 93:7 selectivity (entry 6). The same trend held both at -78°C and at 23°C (entries 5, 7 and 9). Raising the temperature from -78 to 23°C eroded the Z selectivities in all cases, mostly so with the lithium cation.⁸

The next variable to be studied was the base/phosphonate stoichiometry. With **3**, increasing the amount of NaH from 90 to 140 mol% improved the Z:E selectivity from 90:10 to 94:6, equalling the results reported by Ando^{5b} for the corresponding ethyl ester (Table 1, footnote d). Increasing the amount of base did not bring about any further improvement in selectivity.

At this point, we reasoned that an excess of the countercation appears to be beneficial for selectivity. As

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^{*} Corresponding author. Tel.: +358 9 451 2536; fax: +358 9 451 2538; e-mail: petri.pihko@hut.fi

Table 1. Effect of countercation on Z selectivity of HWE olefination with 1 and aliphatic aldehydes



Entry	Aldehyde	Base ^a	Temp. (°C)	Z:E ratio ^b	Note
1	<i>n</i> -Octanal (2)	<i>n</i> -BuLi	-78	75:25	
2	<i>n</i> -Octanal	NaH	-78	86:14	
3	<i>n</i> -Octanal	KHMDS	-78	78:22	
4	CyCHO (3)°	n-BuLi	-78	83:17	
5	CyCHO	n-BuLi	23	45:55	
6	CyCHO	NaH	-78	93 :7 ^d	
7	CyCHO	NaH	23	82:18	
8	CyCHO	KHMDS	-78	76:24 ^e	32% conversion
9	CyCHO	KHMDS	23	70:30	40% conversion

^a Reactions were conducted in THF (5 mL/mmol aldehyde) using 110 mol% of base and 120 mol% phosphonate 1. Unless otherwise stated, all reactions proceeded to >90% conversion (determined by ¹H NMR and TLC) within 2 h.

^b The Z:E ratios were determined from crude reaction mixtures by ¹H NMR by integration of the vinyl proton signals.

^c Cy = cyclohexyl.

^d With 90 mol% NaH, Z:E selectivity drops to 90:10. With 140 mol% NaH, selectivity increases slightly (to 94:6).

^e With added 18-crown-6 (500 mol%) the selectivity improved to 85:15.

discussed above, we wanted to keep the amount of base to a minimum to allow α -chiral aldehydes to be used as substrates. As such, we reasoned that we could simply use one equivalent of base and supply the excess cation in the form of NaI or LiBr to increase the Z selectivity. This hypothesis was evaluated using two α -branched aldehydes, cyclohexanecarboxaldehyde **3** and TBS-protected lactaldehyde **4**⁹ (Table 2). With *n*-butyllithium as a base, addition of LiBr or NaI did not appreciably increase the Z:E ratio. However, with an all-sodium combination (NaH as a base and NaI as an additive), very high selectivities were obtained (up to >99:1 Z:E, entries 4–6 and 10, Table 2). These conditions turned out to be more selective than Still's KHMDS/18-crown-6 base system (85:15 Z:E with 3, footnote e in Table 1) or the more recent DBU/NaI reagent combination reported by Ando (entries 3 and 9). Addition of 50–100 mol% of NaI appears to be sufficient for good Z selectivities; with 300 mol% NaI (entry 6) the Z selectivity drops slightly.

A range of aldehydes was screened (Table 3) to probe the scope of these NaH/NaI conditions. Aliphatic aldehydes gave excellent Z:E selectivities ranging from 93:7

Table 2. Effect of added cation source on Z selectivity in HWE olefinations with 1^{a}

Entry	Aldehyde	Base (110 mol%)	Additive (mol%)	Temperature (°C)	Z:E ratio ^b	Note
1	СуСНО (3)	n-BuLi	LiBr (200)	-20	60:40	60% conversion; very slow at -78°C
2	3	n-BuLi	NaI (200)	-78	78:22	
3	3	DBU	NaI (100)	-78	88:12	95:5 selectivity with the <i>ethyl</i> ester ^{5e}
4	3	NaH	NaI (50)	-78	95:5°	
5	3	NaH	NaI (100)	-78	95:5	
6	3	NaH	NaI (300)	-78	94:6	
7		n-BuLi	LiBr (200)	-78	88:12	
8	4	n-BuLi	NaI (200)	-78	92:8	
9	4	DBU	NaI (100)	-78	95:5	
10	4	NaH	NaI (100)	-78	>99:1	

^a Reactions were conducted in THF (5 mL/mmol with LiBr, 10 mL/mmol with NaI as an additive), using 110 mol% of base and 120 mol% of phosphonate. Unless otherwise stated, all reactions proceeded to >90% conversion (as judged by ¹H NMR and TLC) within 2 h.

^b The Z:E ratios were determined from crude products by ¹H NMR.

^c A control experiment with **3** using NaH (110 mol%) and NaBr (100 mol%) in THF (15 mL/mmol) afforded 94:6 Z:E selectivity. However, even at this concentration, a small portion of NaBr remained undissolved. NaI is preferred to NaBr due to its far higher solubility in THF.

Table 3. Z selective HWE olefinations with phosphonate 1 using the NaH/NaI combination¹⁰



^aReaction conditions: 130 mol% phosphonate 1, 100 mol% NaI, 130 mol
% NaH, THF (10 mL/mmol aldehyde), -78 °C, 2 h (except in entry 5, where the reaction took 5 h at -78 °C).

- ^bThe Z:E ratios were determined from crude reaction mixtures by ¹H NMR.
- ^cYield represents the combined isolated yield of Z and E isomers.
- ^dDetermined by HPLC using Chiralcel OD column.¹¹
- ^eWith **8**, the *Z*:*E* selectivity was ~50:50 if NaH (110 mol%) was used as a base.

^fPure **Z-8** could be isolated in 75% yield.

to 99:1 and very high yields (88–100%). As expected, α -branched aldehydes (entries 2, 3 and 6) turned out to give slightly better selectivities than unbranched aldehydes (entries 1 and 5). The only exception was aldehyde 8 (entry 7), which gave only 84:16 Z selectivity. In agreement with the results obtained by Ando,^{5a,b} benzaldehyde (entry 4) gave inferior selectivity under these conditions (70:30). To demonstrate the mildness of the reaction conditions, the enantiomeric purities of Zenoates Z-7 and Z-8 derived from sensitive α -chiral amino aldehydes 7 and 8 (entries 6 and 7) were determined by chiral HPLC. In both cases the products were obtained in excellent enantiomeric purity.

In summary, we present new, highly Z selective conditions for Horner–Wadsworth–Emmons olefinations employing Ando's bis(*o*-cresyl)phosphonoacetate **1**. With aliphatic aldehydes, our new NaH/NaI procedure gave better selectivities than any of the published procedures (including Ando's new NaI/DBU conditions^{5e} or Still's KHMDS/18-crown-6 conditions⁴). The conditions are sufficiently mild to preserve the stereochemical integrity of α -chiral aldehyde substrates and employ only inexpensive reagents. The fact that an *excess* of sodium ions is required for highest selectivities strongly suggests that these HWE reactions take place via cation-chelated intermediates and transition states.¹⁵ In preliminary studies, we have found that adding an excess of cation gives excellent results with the Still–Gennari phosphonates, too, when aliphatic aldehydes are employed. A full account of these studies is forthcoming.

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- 10. Typical experimental procedure: To a solution of phosphonate 1 (435 mg, 1.30 mmol) in THF (12 mL) at 0°C was added NaI (150 mg, 1.00 mmol). After 5 min, NaH (60% dispersion, 52 mg, 130 mol%) was added (CAU-TION: evolution of hydrogen!), and the resulting solution was cooled to -78° C. The aldehyde (1.00 mmol) was then added dropwise (either neat or as a solution in 1 mL of THF). After 2 h at -78° C, half-saturated NH₄Cl (10 mL) was added and the reaction mixture was extracted with Et₂O (2×20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure (100 mmHg). The crude product was purified by flash chromatography.
- 11. Characterization data for new compounds Z-7 and Z-8: Z-7 (data for pure Z isomer, obtained by recrystallization from hexanes): white needles; $R_{\rm f}$ (50% EtOAc/hexanes) = 0.55; $[\alpha]_{D} = -124$ (c 0.99, MeOH); mp 78–79°C; IR (CDCl₃) 3444, 2981, 1717, 1498, 1438, 1368, 1205, 1163, 1047 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.12 (m, 1H), 5.75 (dd, 1H, J=1.3, 11.5 Hz), 5.17 (m, 1H), 4.75 (m, 1H), 3.71 (s, 3H), 1.42 (s, 9H), 1.26 (d, 3H, J=6.7 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 166.1, 155.2, 152.1, 118.6, 79.5, 51.3, 45.4, 28.3, 20.2. Anal. calcd for C₁₁H₁₉NO₄: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.48; H, 8.37; N, 6.07. The enantiomeric purity was determined before recrystallization by HPLC (Chiralcel OD column, 5:95 *i*-PrOH/hexanes, 0.9 mL/min) $t_r = 19.5$ min; *E*-7: $t_r = 21.6 \text{ min}, ent-Z-7: t_r = 30.2 \text{ min}.$ Authentic ent-Z-7 was prepared from Boc-L-alaninal.

Z-8 colourless oil; R_f (30% EtOAc/hexanes, UV/PMA) = 0.49; [α]_D = -56.0 (*c* 0.72, CHCl₃); IR (thin film) 3050, 2930, 1715, 1420, 1220, 1085 cm⁻¹; ¹H NMR ((CDCl₂)₂, 400 MHz, 360 K) δ 7.33 (m, 5H), 6.27 (dd, 1H, *J*=7.6, 11.7 Hz), 5.84 (d, 1H, *J*=11.7 Hz), 5.51 (m, 1H), 5.15 (d, 1H, *J*=12.9 Hz), 5.13 (d, 1H, *J*=12.9 Hz), 4.30 (dd, 1H, *J*=7.0, 8.9 Hz), 3.81 (dd, 1H, *J*=3.2, 9.1 Hz), 3.69 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H); ¹³C NMR ((CDCl₂)₂, 100 MHz, 360 K) δ 165.7, 152.3, 149.8, 136.4, 128.1 (2C), 127.6, 127.4 (2C), 119.6, 94.5, 68.8, 66.6, 55.7, 51.0, 26.5, 24.1; HRMS (CI, NH₃) calcd for MH⁺ (C₁₇H₂₂NO₅) 320.1498, found: 320.1487, Δ =3.4 ppm; HPLC (Chiralcel OD column, 5:95 *i*-PrOH/hexanes, 0.9 mL/min) *t*_r=16.8 min; *ent-Z*-8: *t*_r=12.5 min. Authentic *ent-Z*-8 was prepared starting from D-serine.

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