Tetrahedron Letters 52 (2011) 1284-1287

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Z-Selective intramolecular Horner–Wadsworth–Emmons reaction for the synthesis of macrocyclic alkenes

Kaori Ando*, Kaori Sato

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan

ARTICLE INFO	ABSTRACT
Article history: Received 27 November 2010 Revised 23 December 2010 Accepted 11 January 2011 Available online 20 January 2011	The Z-selective intramolecular Horner–Wadsworth–Emmons reaction of the substrates 7–12 (RO) ₂ P(O)CHR'CO ₂ Et (R' = (CH ₂) _n CHO) (R = Ph or <i>o</i> - <i>t</i> BuC ₆ H ₄) gives the 13–18-membered cyclic alkenes selectively (up to $Z:E = 97:3$) in good yields using NaH in THF under high dilution conditions. © 2011 Elsevier Ltd. All rights reserved.

The Horner-Wadsworth-Emmons (HWE) modification of the Wittig reaction is a widely used method for the preparation of α_{β} unsaturated esters.¹ After the first reports by Stork and Nakamura and by Nicolaou et al. in 1979,² the intramolecular HWE reaction has been one of the most reliable macrocyclization procedures. These reactions gave E- α . β -unsaturated lactones or cyclic ketones with high selectivity. Since there are many bioactive macrolides containing the Z- α , β -unsaturated lactone moiety, we started our research on the Z-selective intramolecular HWE reaction. Recently, we reported the Z-selective intramolecular HWE reaction for the synthesis of macrocyclic lactones (Scheme 1).^{3,4} When the ω -formylated HWE substrates 1 were added to a THF suspension containing 3 equiv of NaH at 0 °C or NaI-DBU at room temperature over 1-10 h, the intramolecular HWE reaction occurred to give 12-18-membered ring lactones in 61–99% yields with 95–100% Z selectivity. There is another type of intramolecular HWE reaction as shown in Scheme 2. This type of intramolecular HWE reaction has been used for the synthesis of bioactive compounds^{5,6} such as (+)-Desepoxyasperdiol,^{5a} (–)-Asperdiol,^{5b} and Anisomelic acid.^{6a,b} Only a limited number of the intermolecular HWE reaction with the phosphonate reagents having α -substituents larger than a methyl group have been reported. In these cases, relatively poor stereoselectivity has been observed for both *E*- and *Z*-selective HWE reactions.⁷ The same is true for the intramolecular HWE reaction. During the total synthesis of 6-epi-sarsolilide A. Xu et al. obtained the Z product with only 8:3 selectivity in 30% yield using our Z-selective Ph reagent^{4b-g} (R = Ph in 2).^{6d} On the other hand, almost no product was obtained under a variety of conditions using Still's reagent^{4a} ($R = CF_3CH_2$ in 2). Since stereo-defined synthesis of carbon-carbon double bonds with high selectivity is critically important, we decided to establish satisfactory reaction conditions. Here, we report our results of the intramolecular HWE reaction giving 13-18-membered ring alkenes selectively.

The intramolecular HWE reaction substrates were planned to be prepared by alkylation of the phosphonate reagents **6** with alkyl iodides, which were prepared as follows (Scheme 3). The commercially available diols were mono-protected as the THP ethers and followed by tosylation using Tanabe's procedure⁸ to give **3b** and **3c** in 96–98% yields. On the other hand, tosylation using TsCl and pyridine gave **3a** in a moderate 78% yield. Both **3b** and **3c** were converted into the ethers by the reaction with diols in the presence of NaH in DMSO and the following tosylation gave the tosylates **3d–3g**. Pentadecanolide was subjected to the base-catalyzed transesterification and the resulting hydroxy group was protected as the THP ether **4**. The ethyl ester group was reduced with LiAlH₄ followed by tosylation to give the tosylate **3h**. These tosylates **3a** and **3d–3h** were converted into the corresponding iodides **5a–5f** by nucleophilic substitution with NaI.

HWE reagents **6a**,^{4c} **6b**,⁹ **6c**, and **6d** were alkylated with the above iodides **5a–5f** by using NaH in DMSO, followed by deprotection of the THP ethers and oxidation with PCC to give the intramolecular HWE substrates **7–12** (Scheme 4). Since these substrates were not so stable, the substrates were stored in a freezer and used within 1 week.

The intramolecular HWE reaction of **10** is summarized in Table 1.¹⁰ The HWE reaction of **10a** (R = Ph) was performed using a procedure similar to that of the intramolecular HWE reaction of **1.**³ That is, a THF solution of **10a** was added to a THF suspension containing 3 equiv of NaH over 4 h at room temperature (entry 1). The 15-membered compound **13** was obtained in 88% yield with 78:22 *Z* selectivity¹¹ (the yield of *Z*-**13** is 69%). Since oligomeric (dimeric and/or trimeric) cyclic compounds were also obtained in 2% yield, the reaction was performed at 60 °C. A lower yield and lower selectivity were observed (entry 2). Although NaI-DBU was the most favorable base for the intramolecular HWE reaction of **1.**³ lower 69:31 selectivity was observed for **10a** (entry 3). Also, the use of *t*-BuONa, *t*-BuOK, and LiCI-DBU as a base did not improve the selectivity and/or the yield (entries 4–6). In the presence of the stronger base *t*-BuOK, decomposition of **10a** cocurred. In our





^{*} Corresponding author. Tel./fax: +81 58 293 2674. *E-mail address:* ando@gifu-u.ac.jp (K. Ando).





 Table 1

 Intramolecular HWE reaction of 10



previous study, we found ortho-substituted phenyl reagents (R = o-MeC₆H₄ and o-*i*PrC₆H₄ in **6**) showed higher Z selectivity than the Ph reagent **6a**.^{4c} After that, Touchard et al. reported the improvement of selectivity at 0 °C using the *o*-*t*BuC₆H₄ reagent **6b**.^{9,12,3} In the presence of 3 equiv of NaH, the o- $tBuC_6H_4$ reagent **10b** reacted to give **13** in 47% yield with 95:5 selectivity at room temperature (entry 7). Generally, the reactivity of the $o-tBuC_6H_4$ reagents is lower than that of the Ph reagents because of steric effects.^{3,9} When the reaction of **10b** was performed at 60 °C, an improved yield of 63% was obtained with 97:3 Z selectivity (entry 8). The reaction using NaI-DBU again gave much lower selectivity than that using NaH (entries 10 and 11). Thus, Z-13 was prepared by the reaction of **10a** in a high yield with moderate 78:22 selectivity or by the reaction of **10b** with higher 97:3 selectivity in a moderate yield using 3 equiv of NaH in THF. On the other hand, the reaction of the Et reagent **10c** gave only low yields and low E selectivity using LiCl-DBU in MeCN13 or LDA in toluene (entries 12 and 13). The crude mixture contained 13% of 10c in entry 12, while there was no 10c left in entry 13. The use of NaH in THF gave low Z selectivity (entry 14). Although the use of the smaller trimethyl phosphonoacetate reagent 10d gave improved yields, the selectivity was low in the presence of LiCl-DBU in MeCN or NaH in THF (entries 15 and 16).

(RO) ₂ P(O)CHCO ₂ Et	2^{C} Et	D ₂ C
(CH ₂) ₄ O(CH ₂) ₈ CHO	~	-0
10a R = Ph, 10b R = <i>o</i> - <i>t</i> BuC ₆ H ₄ 10c R = Et. 10d R = Me (Me ester)	<i>Z</i> -13	<i>E</i> -13

Entry	10	Solvent	Base	Condition ^a	Yield 13 (%)	Oligomer (%)	Z:E
1	10a	THF	NaH	rt, 4 h	88	2	78:22
2	10a	THF	NaH	60 °C, 4 h	79	-	75:25
3	10a	THF	NaI-DBU	rt, 4 h	83	-	69:31
4	10a	THF	t-BuONa	rt, 4 h	81	-	70:30
5	10a	THF	t-BuOK	rt, 4 h	23	-	80:20
6	10a	THF	LiBr-DBU	rt, 4 h	75	-	72:28
7	10b	THF	NaH	rt, 4 h	47	-	95:5
8	10b	THF	NaH	60 °C, 4 h	63	-	97:3
9	10b	THF	NaH	Reflux, 4 h	41	-	92:8
10	10b	THF	NaI-DBU	rt, 4 h	66	3	86:14
11	10b	THF	NaI-DBU	60 °C, 4 h	64	-	85:15
12	10c	MeCN	LiCl-DBU	60 °C, 4 h	40	6	42:58
13	10c	Toluene	LDA	rt, 2 h	8	20	38:62
14	10c	THF	NaH	60 °C, 4 h	47	11	62:38
15	10d	MeCN	LiCl-DBU	60 °C, 4 h	58 ^b	2	48:52
16	10d	THF	NaH	60 °C, 4 h	65 ^b	-	72:28

^a The addition was carried out over the specified time. The final concentration was 0.01 mol L⁻¹.

^b The corresponding Me ester was obtained.

Table 2Intramolecular HWE reaction of 8

(RO) ₂ P(O)CHCO ₂ Et (RO) ₂ P(O)CHCO ₂ Et (CH ₂) ₁₄ CHO	D ₂ C EtC	
8a R = Ph, 8b R = <i>o</i> - <i>t</i> BuC ₆ H ₄ 8c R = Et. 8d R = Me (Me ester)	<i>Z</i> -14	<i>E</i> -14

Entry	8	Solvent	Base	Condition ^a	Yield 14 (%)	Oligomer (%)	Z:E
1	8a	THF	NaH	rt, 4 h	66	11	91:9
2	8a	THF	NaH	Reflux, 6 h	72	_	78:22
3	8a	THF	NaI-DBU	Reflux, 4 h	71	_	80:20
4	8b	THF	NaH	60 °C, 4 h	79	6	87:13
5	8c	MeCN	LiCl-DBU	rt, 4 h	23	2	39:61
6	8d	MeCN	LiCl-DBU	60 °C, 4 h	53 ^b	2	37:63
7	8d	THF	NaH	60 °C, 4 h	67 ^b	1	64:36

^a The addition was carried out over the specified time. The final concentration was 0.01 mol L⁻¹.

^b The corresponding Me ester was obtained.

The results of the intramolecular HWE reaction of **8** are summarized in Table 2. Using both high dilution conditions and NaH as a base at room temperature, the 16-membered compound **14** was obtained in 66% yield with 91:9 *Z*-selectivity using the Ph reagent **8a** (entry 1). Oligomeric cyclic compounds were also obtained in



11% yield. The formation of oligomers was suppressed when the reaction was performed in refluxing THF and 72% yield of **14** was obtained however with disappointing 78:22 selectivity (entry 2). In this reaction, NaI-DBU gave a similar result (entry 3). The *o*-tBuC₆H₄ reagent **8b** reacted in the presence of 3 equiv of NaH at 60 °C to give **14** in 79% yield with 87:13 selectivity (entry 4). Thus, the 16-membered **Z-14** was obtained in a good yield with good selectivity from either the Ph reagent **8a** or the *o*-tBuC₆H₄ reagent **8b**. On the other hand, *E***-14** was obtained from the Et reagent **8c** in a low yield and with low selectivity using LiCl-DBU in MeCN (entry 5). The yield was improved using the smaller Me reagent **8d** but the selectivity was still low (entry 6). The use of NaH in THF also brought about low *Z* selectivity for **8d** (entry 7).

The reactions of 7, 9, 11, and 12 were similarly performed and the results are summarized in Figure 1. While the reaction of the Ph reagent 7a at room temperature gave mainly oligomeric by-products in 78% vield, the reaction in refluxing THF gave the 13-membered compound 15 in 70% vield with 76:24 Z-selectivity along with oligomers (11%). The use of the $o-tBuC_6H_4$ reagent **7b** brought some improvement of the selectivity, but the yield was miserable. It seems that the intramolecular HWE reaction is unfavorable for 7 bearing a shorter alkyl chain aldehyde because of ring strain. The 14-membered cyclic compound Z-16 was more selectively available using the Ph reagent **9a** or the $o-tBuC_6H_4$ reagent **9b** with 84:16 and 87:13 *Z* selectivity in 69 and 57% yield, respectively. The reaction of the o-tBuC₆H₄ reagent **11b** in the presence of 3 equiv of NaH at 60 °C occurred smoothly to give the 17membered compound 17 with 92:8 Z selectivity in 75% yield. The reaction of the Et reagent 11c using LiCl-DBU in MeCN gave E-17 in 37:63 E selectivity in 56% yield. The 18-membered cyclic compound **18** was also prepared from the *o*-*t*BuC₆H₄ reagent **12b** using NaH in THF at 60 °C in 69% yield with 88:12 selectivity. A similar 89:11 selectivity was obtained from the reaction at room temperature in 65% yield.

In summary, the intramolecular HWE reaction of the substrates **7–12** (R = Ph or *o-t*BuC₆H₄) gives the corresponding 13–18membered cyclic alkenes **Z-13–Z-18** selectively in good to high yields using NaH in THF at room to refluxing temperature. The substrates should be added to a THF suspension containing NaH over a few hour-period. On the other hand, both the Et or Me reagents gave mainly cyclic *E* compounds by using LiCl-DBU in MeCN and mainly *Z* compounds by using NaH in THF with low selectivity. We believe the *Z*:*E* selectivity is kinetically controlled.¹⁴ Compared with the diarylphosphonate reagents, the diethylphosphonate reagents are less reactive and gave very low yields. Although the *E*-selective formation of the macrocyclic compounds are not satisfactory, we succeeded in showing that the *Z*-selective intramolecular HWE reaction is useful for the synthesis of macrocyclic alkenes.

Acknowledgment

This work was partially supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

- 1. For a review: Maryanoff, B. E.; Reitz, A. B. Chem. Rev. 1989, 89, 863-927.
- (a) Stork, G.; Nakamura, E. J. Org. Chem. 1979, 44, 4010–4011; (b) Nicolaou, K.
 C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. J. Org. Chem. 1979, 44, 4011–4013.
- Ando, K.; Narumiya, K.; Takada, H.; Teruya, T. Org. Lett. 2010, 12, 1460–1463.
 For Z-selective HWE reactions: (a) Still, W. C.; Gennari, C. Tetrahedron Lett. 1983, 24, 4405–4408; (b) Ando, K. Tetrahedron Lett. 1995, 36, 4105–4108; (c) Ando, K. J. Org. Chem. 1997, 62, 1934–1939; (d) Ando, K. J. Org. Chem. 1998, 63, 8411–8416; (e) Ando, K. J. Org. Chem. 1999, 64, 8406–8408; (f) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. J. Org. Chem. 2000, 65, 4745–4749; (g) Ando, K. J. Synth. Org. Chem. Jpn. 2000, 58, 869–876.
- (a) Tius, M. A.; Fauq, A. H. J. Am. Chem. Soc. **1986**, 108, 1035–1039; (b) Tius, M. A.; Fauq, A. H. J. Am. Chem. Soc. **1986**, 108, 6389–6391; (c) Stocksdale, M. G.; Ramurthy, S.; Miller, M. J. J. Org. Chem. **1998**, 63, 1221–1225; (d) Yao, H.; Gao, Y.; Liu, P.; Sun, B.; Xu, X. Synlett **2007**, 571–574.
- (a) Marshall, J. A.; DeHoff, B. S. *Tetrahedron Lett.* **1986**, *27*, 4873–4876; (b) Marshall, J. A.; DeHoff, B. S. *Tetrahedron* **1987**, *43*, 4849–4860; (c) Kodama, M.; Shiobara, Y.; Sumitomo, H.; Fukuzumi, K.; Minami, H.; Miyamoto, Y.

Tetrahedron Lett. **1986**, 27, 2157–2160; (d) Zhang, J.; Xu, X. Tetrahedron Lett. **2000**, 41, 941–943.

- (a) Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. J. Org. Chem. **1986**, 51, 1735– 1741; (b) Medina, J. C.; Guajardo, R.; Kyler, K. S. J. Am. Chem. Soc. **1989**, 111, 2310–2311; (c) Hammond, G. B.; Cox, M. B.; Wiemer, D. F. J. Org. Chem. **1990**, 55, 128–132; (d) Noguchi, H.; Aoyama, T.; Shioiri, T. Tetrahedron **1995**, 51, 10545–10560.
- Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. Tetrahedron 1999, 55, 2183.
- 9. Touchard, F. P.; Capelle, N.; Mercier, M. Adv. Synth. Catal. 2005, 347, 707-711.
- 10. A typical procedure for the *Z*-selective intramolecular HWE reaction (entry 8 in Table 1): To a stirred suspension of NaH (55%) (0.026 g, 0.60 mmol) in THF (12 mL) was added a solution of **10b** (0.130 g, 0.20 mmol) in THF (8 mL) at 60 °C over 4 h under Ar atmosphere by a motor-driven syringe and the resulting mixture was stirred for 0.5 h at the same temperature. The reaction was quenched with water (15 mL) and extracted with AcOEt (20 mL). The extract was washed with brine, dried (MgSO₄), and concentrated. After the *Z*:*E* ratio (97:3) of the crude mixture was determined by 400 MHz ¹H NMR, **13** was isolated by flash chromatography (hexane/AcOEt = 30:1) as a colorless oil (0.036 g, 63% yield) (*Z*:*E* = 97:3).
- 11. The E:Z ratios were determined by integration of the vinyl proton signals in 400 MHz ¹H NMR spectra of the crude reaction mixture. All the HWE products described in this paper were characterized by 400 MHz ¹H NMR spectra and mass spectroscopy.
- For the amide reagents, (o-tBuC₆H₄O)₂P(O)CH₂CONR¹R², see: (a) Ando, K.; Nagaya, S.; Tarumi, Y. *Tetrahedron Lett.* **2009**, *50*, 5689–5691; For the polymersupported reagents, see: (b) Ando, K.; Suzuki, Y. *Tetrahedron Lett.* **2010**, *51*, 2323–2325.
- Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
- For a computational investigation of the reaction mechanism, see: Ando, K. J. Org. Chem. 1999, 64, 6815–6821.