Pergamon

Tetrahedron Letters, Vol. 35, No. 10, pp. 1581-1584, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0123-F

Z-selective Formation of Trisubstituted α,β-Unsaturated Nitrile by the Horner-Emmons Reaction

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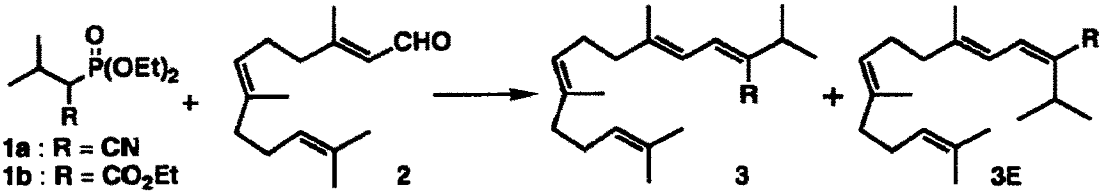
Abstract: Conditions which allow the Horner-Emmons reaction of phosphononitrile to proceed Z-selectively were clarified. The generality and usefulness of the procedure were demonstrated by an application to a stereoselective synthesis of plaunotol (9).

The stereochemistry of the double bonds in naturally occuring terpenoids has been clearly defined and is critically important in exhibiting the biological activities. Synthesis of double bonds of defined stereochemistry with high selectivity has been one of the important objectives of organic chemistry in recent years. The Wittig and its related reactions have served as the most powerful method for the construction of double bonds,[1] and even the highly Z-selective versions at levels synthetically useful for preparing trisubstituted double bonds have been developed. These require special devices, namely bis(trifluoroethyl) phosphonoester,[2] or a designated substrate, α-alkoxy ketone.[3] The bis(trifluoroethyl) phosphonoester method has frequently been applied to natural product synthesis.[4] However, it gives ester as a product, and more than two steps are required if a nitrile or an aldehyde is the desired product, since direct transformation of an aliphatic α,β-unsaturated ester into aldehyde is unreliable in practice.[5]



In the process of our synthetic study of a marine cembranoid, we found that the Horner-Emmons reaction of a phosphononitrile **1a**, which had a bulky isopropyl group on the α-carbon, with E,E-farnesal (**2**) proceeded smoothly at a low temperature and gave the desired conjugated nitrile **3** with high Z-selectivity in high yield.[6] The Z-selective reaction needed no special reagents or substrates. If the present reaction similarly provides an excellent Z-selectivity from a phosphononitrile having no bulky group other than **1a** and a non-conjugated aldehyde, it would be one of the most convenient procedures for trisubstituted Z-olefin synthesis.

Table 1: Z:E ratios for the Horner-Emmons Reaction of **1a** and **1b** with E,E-Farnesal(**2**)

Entry	Phosphonate	Base	Solvent	Temp	Z : E[a]
1	**1a**	n-BuLi	THF[b]	-78°C	2.1 : 1
2	**1a**	n-BuLi	Et_2O[b]	-78°C	19.7 : 1
3	**1a**	n-BuLi	Tol.[b]	-78°C	24.2 : 1
4	**1a**	n-BuLi	n-Hex.[b]	-78°C	9.3 : 1
5	**1a**	$LiN(SiMe_3)_2$	THF[b]	-78°C	2.2 : 1
6	**1a**	$LiN(SiMe_3)_2$	Et_2O[b]	-78°C	21.2 : 1
7	**1a**	$LiN(SiMe_3)_2$	Tol.	-78°C	35.1 : 1
8	**1a**	$NaN(SiMe_3)_2$	Tol.	-78°C	8.8 : 1
9	**1a**	$KN(SiMe_3)_2$	THF/HMPA[c]	-78°C	1 : 1.5
10	**1a**	$KN(SiMe_3)_2$	THF	-78°C	2.9 : 1
11	**1a**	$KN(SiMe_3)_2$	Tol.	-78°C	25.6 : 1
12	**1a**	$KN(SiMe_3)_2$	Tol./n-Hex.[d]	-78°C	15.7 : 1
13	**1a**	$KN(SiMe_3)_2$	Tol.	-42°C	15.0 : 1
14	**1a**	$KN(SiMe_3)_2$	Tol.	0°C	10.3 : 1
15	**1a**	NaH	DMF	-42°C	1 : 1.3
16	**1a**	NaH	Tol.	-78°C	8.4 : 1
17	**1a**	KH	Tol.	-78°C	11.4 : 1
18	**1a**	t-BuOK	Tol.	-42°C	11.3 : 1
19	**1b**	n-BuLi	THF[b]	-20°C	2.3 : 1
20	**1b**	n-BuLi	Tol.[b]	-20°C	1 : 1

a) Determined by GC analysis (SE30, 3%, 2m). b) n-Hexane which came from an organometallic stock solution was present in the reaction mixture (ca. 10%v/v). c) THF/HMPA = 9/1 (v/v). d) Tol./n-Hex. = 1/1 (v/v).

In this communication, we describe the examination of reaction conditions for providing high Z-selectivity using nitrile **1a** and aldehyde **2**,[7] and evidence for the generality and efficiency of the present reaction by applying it to a stereoselective total synthesis of plaunotol (**9**), a diterpenoid having remarkable antipeptic ulcer activities.[8,3b]

The reaction of nitrile **1a** and aldehyde **2** was examined under various reaction conditions and the results are shown in Table 1. To the anion generated from **1a** (1.3 equiv.) and a base (1.2 equiv.) in the solvent and at the temperature[9] indicated in Table 1 was added **2** at the same temperature under argon atmosphere. The mixture was gradually warmed to room temperature overnight with cotinuous stirring, and the yields[10] and Z:E ratios were determined by GC analysis after usual workup. The influence of the solvents on Z:E ratio was remarkable. The lower the polarity of solvent, the higher was the Z-selectivity, except in the case of n-hexane (Entries 1-4, 5-7, and 9-12). Reverse stereoselectivity was observed when HMPA or DMF was used (Entries 9 and 15). It is of interest that the reaction mixtures were in a wet gel state in the cases preferentially providing Z-isomer.[11] The lower the reaction temperature, the higher was the Z-selectivity, as shown in a set of the same base and solvent (Entries 11, 13, and 14). Use of Na^+ as a counter of the anion of **1a** did not provide as high Z-selectivity as those in the case of

Li^+ or K^+ in toluene at -78°C (Entries 7, 8, and 11). Considerably high Z-selectivities (Z:E = 24-35:1) could be realized using n-BuLi, $LiN(SiMe_3)_2$, or $KN(SiMe_3)_2$ as a base in toluene at -78°C (Entries 3, 7, and 11). Use of metal hydrides or potassium t-butoxide as a base was also effective for the predominant formation of Z-isomer, although the selectivities were not high (Entries 15-18).[5] It is noteworthy that the corresponding phosphonate ester **1b**[12] did not provide as a high Z-selectivity as observed in **1a** in toluene (Entries 19 and 20). The ester **1b** did not react with **2** at a temperature below -20 °C.[13,14]

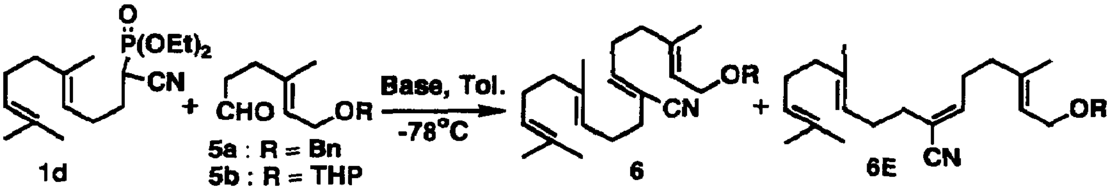
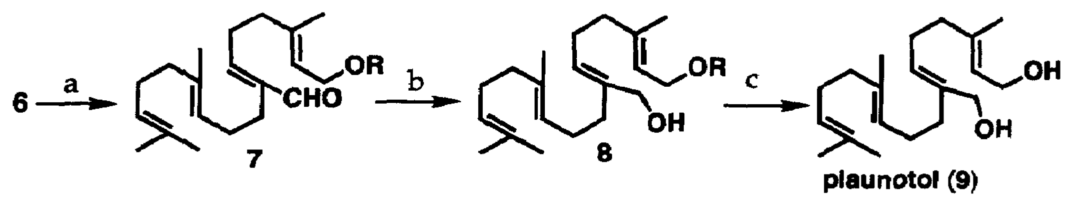


Table 2: Z-selective Horner-Emmons reaction of 1d with 5

Base	R	Z : E[a]	Yield[b]
$LiN(SiMe_3)_2$	Bn	4.3 : 1	78%
$KN(SiMe_3)_2$	Bn	7.0 : 1	88%
$KN(SiMe_3)_2$	THP	7.7 : 1	95%

a) Determined by capillary GC. b) Isolated yield.

To investigate the generality of the present reaction, a total synthesis of the natural product plaunotol **9** was performed. First of all, the Horner-Emmons reaction of nitrile **1d**, which was prepared by alkylation of diethyl phosphonoacetonitrile with homogeranyl iodide[15] in 65% yield, with aldehydes **5**[16] was carried out under the same reaction conditions as those which allowed the reaction of **1a** to proceed highly Z-selectively. The desired products with preferential Z-isomers **6**[17] were obtained in high yield as shown in Table 2, and the isomers were easy to separate by SiO_2 column chromatography. The Z-selectivities observed are comparable to those reported in the natural product syntheses employing the bis(trifluoroethyl) phosphonoester methodology.[4]



Scheme: a) DIBAL, Tol, -78°C; H_2O then SiO_2 (R =Bn, 73%; R = THP, 63%); b) $NaBH_4$, MeOH (R = Bn, 95%; R = THP, 90%); c) Li, $EtNH_2$, -78°C (R = Bn, 74%) or cat. pTsOH, MeOH (R = THP, 81%)

The synthesis of plaunotol **9** from **6** is illustrated in the Scheme, and involves a reduction of nitrile to alcohol and a deprotection. Thus, after DIBAL reduction of nitrile group in **6**, even mild hydrolysis[18] of the resulting imines resulted in isomerization of the enal moiety to afford ca. a 1:1 mixture of geometrical isomers of 7 which indicated the unexpected lability of enal. However, we found that direct flash SiO_2 column chromatography of the imines gave 7 as a single isomer in good yields along with a small amount of the E-isomers (R = Bn, Z:E = 8.4:1; R = THP, Z:E = 19.5:1). Finally, $NaBH_4$ reduction of 7 followed by removal of the protecting groups afforded a diol, of which spectral data (^1H NMR and IR) were identical with those in the literature,[8a] in fairly good overall yield.

In summary, it was shown that the Horner-Emmons reaction of phosphonate nitrile proceeds Z-selectively under selected reaction conditions without special reagent or substrate. This method was applied successfully to the stereoselective synthesis of 9, and its Z-selectivity was comparable to that by the bis(trifluoroethyl) phosphonoester procedure.

Acknowledgement: The author is grateful to Dr. Y.Morinaka for helpful discussion.

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7. E,E-Farnesal 2 of 96.6% purity (capillary GC) obtained by $BaMnO_4$ oxidation of E,E-farnesol was used. The corresponding MnO_2 oxidation in n-hexane resulted in isomerization of enal moiety (3-4%).
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9. In the case of metal hydrides and potassium t-butoxide, the anion was formed at 0°C.
10. Yields were typically 90-100% based on the unreacted 2 (0-10%).
11. This fact may be correlated with the mechanism which provides Z-isomer.
12. The predominant formation of Z-isomer (Z:E = 2.7:1) from **1b** and **2** in THF was reported in the literature. See: J. E. McMurry, J. G. Rico, and Y. Shih, Tetrahedron Lett., **30**, 1173 (1989).
13. Instead of the desired **3**, an unknown compound was formed at a long reaction time.
14. The highly Z-selective reaction (Z:E = 9-19:1) using phosphonoacetates at low temperature was reported. See: H. Nagaoka and Y. Kishi, Tetrahedron, **37**, 3873 (1981).
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16. Prepared from the corresponding geranyl ethers in two steps: 1) epoxidation of the terminal double bond, and 2) oxidative cleavage of the epoxide.
17. Structural assignments for all the new compounds were made by ^1H NMR (250 MHz), IR, MS and/or combustion analysis.
18. Aueous $AcOH^6$ and NaF/H_2O^{19} methods were attempted.
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(*Received in Japan* 12 *November* 1993)