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Stereoselective Preparation of Dienol Phosphates from α,β-Ethylenic Aldehydes

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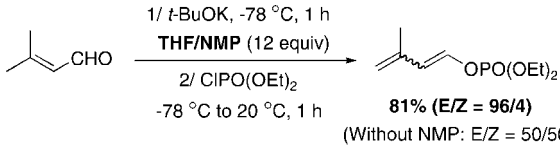


The first stereoselective method of preparation of (*E*)-dienol phosphates from α,β-ethylenic aldehydes is described. The key point is the stereoselective enolization of conjugated alkenals by potassium *tert*-butoxide in the presence of *N*-methylpyrrolidinone (NMP).

Coupling reactions between organometallics and dienyl halides are not frequent since the later are very prone to polymerize and cannot be used successfully. Dienol phosphates are much more stable, thus, they can be stored at ambient temperature without any special precaution and they are easily purified by distillation or by chromatography on a silica gel column. Recently, we have shown that Grignard reagents readily couple with dienol phosphates in the presence of iron salts.[1] This reaction is the first general method to prepare terminal dienes or trienes stereoselectively. Of course, to prepare biologically active terminal dienes like insect sex pheromones, it is necessary to start from geometrically pure dienol phosphates. Unfortunately, when we developed our iron-catalyzed coupling reaction there was no synthetic method to obtain such compounds stereoselectively. Duhamel has reported that butadienyl phosphate is formed by reacting crotonaldehyde with diphenylchlorophosphate in the presence of zinc chloride and triethylamine under reflux for 24 h.[2] The yield is satisfactory (89%) but the stereoselectivity is poor (*E*/*Z* = 80/20). Thus, we turned our attention to the stereoelective synthesis of dienol carbonates reported by Olofson.[3] Good yield and excellent stereoselectivity are obtained by using potassium *tert*-butylate to deprotonate crotonaldehyde then by trapping the resulting dienolate with ethyl chloroformate. We thought that it would be possible to replace ethyl chloroformate by diethyl chlorophosphate. Our first attempt was successful since the *E*-butadienyl phosphate was thus prepared in 86% yield with a stereochemical purity of ≥99% (Scheme 1).

SCHEME 1. Preparation of (*E*)-Buta-1,3-dienyl Diethyl Phosphate from Crotonaldehyde

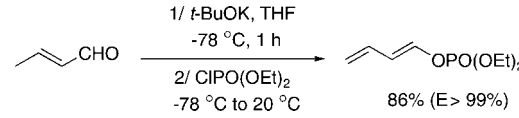
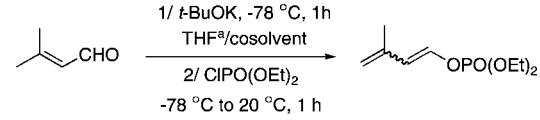


TABLE 1. Effect of a Cosolvent on the Stereoselectivity of the Reaction



entry	cosolvent	*E*/*Z*[b]
1		50/50
2	NMP (2 equiv/4.8 mL)	75/25
3	NMP (6 equiv/14.4 mL)	94/6
4	NMP (12 equiv/28.9 mL)	96/4
5	DMPU (12 equiv/36.1 mL)	96/4
6	DMF (12 equiv/23.2 mL)	96/4
7	NMP (12 equiv/28.9 mL)	96/4[c]
8	NMP (12 equiv/28.9 mL)	51/49[d]

[a] 40 mL of THF were used for 25 mmol of enal. [b] All starting enal is consumed. [c] *t*-BuONa was used instead of *t*-BuOK. [d] NMP was introduced after the enolization step.

Disappointingly, when we tried to apply this method to other α,β-ethylenic aldehydes the stereoselectivity was very poor. Thus, in the case of 3-methyl-2- butenal, we obtained the corresponding dienol phosphate as a 50/50 *E*/*Z* mixture (Table 1, entry 1).

We then studied the influence of various parameters on the stereoselectivity of the reaction. The most interesting results were obtained when the deprotonation was performed in the presence of NMP as a cosolvent (entries 2 to 4). Thus, we showed that the selectivity jumps from 50/50 to 96/4 in favor of the *E* isomer when 12 equiv of NMP was added prior to aldehyde (entry 4).

This improvement of the stereoselectivity is due to the presence of NMP during the deprotonation step. Thus, when this polar cosolvent is only added just before trapping the dienolate by diethyl chlorophosphate, there is no effect on the selectivity (entry 8). It is not possible to improve the *E*/*Z* ratio by adding more than 12 equiv of NMP. On the other hand, the selectivity is clearly less satisfactory with use of only 2 equiv of this cosolvent (entry 2). Similar results were obtained by using other polar cosolvents like DMF or DMPU in place of NMP (entries 5 and 6). In addition, sodium or potassium *tert*-butylate can be used indifferently (entry 7). The influence of polar cosolvents on the stereoselectivity of the deprotonation of alkylketones[4] or esters[5] is well established. However, it is,

(1) Cahiez, G.; Habiak, V.; Gager, O. *Org. Lett.* **2008**, *10*, 2389.
(2) Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045.
(3) De Cusati, P. F.; Olofson, R. A. *Tetrahedron. Lett.* **1990**, *31*, 1405.
(4) See for instance: (a) Fataftah, Z A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

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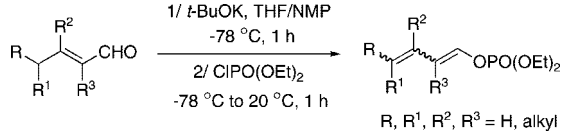
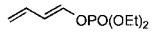
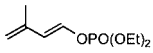
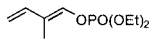
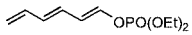
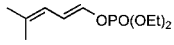
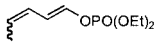
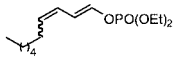
TABLE 2. Preparation of Dienol Phosphates from α,β-Ethylenic Aldehydes



entry	dienol phosphate	yield (%)	stereoselectivity
1		86[a]	*E* > 99%
2		81	*E*/*Z*= 96/4
3		84	*E* > 99%
4		58	*E*.*E* > 99%
5		78	*E* > 99%
6		78	$E/Z_{C1\text{-}C2} \geq 99\%$ $Z/E_{C3\text{-}C4} = 97/3$
7		97	$E/Z_{C1\text{-}C2} \geq 99\%$ $Z/E_{C3\text{-}C4} = 76/24$

[a] See the Supporting Information of ref 1.

to the best of our knowledge, the first time that such an influence is reported in the case of conjugated ethylenic and dienic aldehydes.

Several terminal dienol phosphates were prepared according to this procedure. Yields and stereoselectivities are excellent (Table 2, entries 1 to 3). It is very interesting to note that these conditions can also be successfully applied to conjugated dienic aldehydes. Thus 2,4-hexadienal stereoselectively led to hexatrienylphosphate in satisfactory yield (Table 2, entry 4). The reaction has also been extended to the preparation of nonterminal dienol phosphates (Table 2, entries 5 to 7). In this case, the first double bond C1−C2 is always formed stereoselectively (≥99%) whereas the selectivity is sometimes lesser for the second one (C3−C4): 97/3 from 2,4-pentadienal but 76/24 from 2,4-decadienal (entries 6 and 7).

In conclusion, we described herein the first stereoselective preparation of dienol and trienol phosphates. The key step is the stereoselective deprotonation of conjugated ethylenic or dienic aldehydes by potassium *tert*-butylate. We showed that the presence of NMP is essential to control the stereoselectivity of the reaction. The synthetic interest of this new method of preparation is well illustrated by our recent report on the coupling of Grignard reagents with terminal dienol phosphates under iron catalysis.[1] We especially showed that dienol and trienol phosphates are a valuable alternative to the corresponding dienyl and trienyl halides to prepare various compounds of biological interest having a terminal dienic system such as insect pheromones.

Experimental Section

Preparation of Dienol Phosphates: General Procedure. An oven-dried and nitrogen-flushed 100-mL four-necked flask, equipped with a mechanical stirrer and a thermometer, was charged with potassium *tert*-butylate (3.36 g, 30 mmol) and THF (40 mL). At −78 °C, NMP (28.9 mL, 300 mmol) was added dropwise, and after 5 min aldehyde (25 mmol) was added dropwise under stirring. After 1 h, diethyl chlorophosphate (4.74 g, 27.5 mmol) was added dropwise, then the reaction was allowed to warm to ambient temperature. Stirring was continued for 2 h, then the reaction mixture was quenched with a 1 M aqueous HCl solution (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The product was purified by distillation under reduced pressure or by column chromatography.

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Supporting Information Available: Complete compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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