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ALLENES THROUGH HORNER-WADSWORTH-EMMONS OLEFINATION OF ALKENYLPHOSPHONATES

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Mono- and di-substituted allenes 5 were synthesized by successive Horner-Wadsworth-Emmons olefination starting from methylenebisphosphonate 1 and two carbonyl compounds. The key to success is KH or KH-18-crown-6 as a base for the second HWE olefination of hydroxyalkenylphosphonates 4.

Keywords: Allene; 18-crown-6; double olefination; Horner-Wadsworth-Emmons reaction; phosphonate

We have been engaged in the chemistry of lithium phosphonates¹ in which Baylis-Hillmann type products 4 were obtained upon LDA treatment of alkenylphosphonates 3 with aldehydes and subjected to Horner-Wadsworth-Emmons (HWE) olefination using NaH as a base, giving the corresponding allenes 5 in up to 72% yields.² Allenes are recent focus of versatile class of intermediates in a variety of organic synthetic processes.³ The major allene synthesis relies on a S_N2' replacement of propargylic leaving groups⁴ and others involve dehydrohalogenation of vinylic halides,⁵ reductive elimination of halogenated cyclopropanes,⁶ and so on.⁷⁻¹⁰ Our synthesis is conceptually different from these and is advantageous in the retrosynthetic simplicity. Two sp^2 and one sp carbon atoms of allene functionality are constructed by sequential double HWE olefinations of the three components, methylenebisphosphonate 1 with two carbonyl compounds as shown in Scheme 1.¹¹ Realization of this scenario is critically dependent on the efficacy of the second HWE olefination of hydroxyalkenylphosphonate 4, because the

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first olefination of methylenebisphosphonate 1 to 3 through 2 is a wellestablished high yield process.¹² We describe herein the high yield HWE olefination of alkenylphosphonate 3 with a wide range of carbonyl compounds. The accurate selection of a base for HWE olefination of 4 was the key for success.

It readily comes to an answer that olefination of **4** requires formation of an unfavorable phosphooxetane that involves one sp^2 carbon in the four-membered ring. Furthermore, the 120 degree bond angle by the sp^2 carbon is a significantly unfavorable factor in intramolecular nucleophilic attack of an alcoholic oxygen nucleophile to P=O phosphorous electrophile to form the four-membered ring. The analysis leads to suggestion that olefination of **4** requires efficient activation of a nucleophilic alcoholic oxygen. However, strong base is likely to deprotonate allene protons to result in isomerization into alkyne and diene. We began our studies to find an appropriate base for olefination of **4**.

We set 4a ($R^1 = Ph$, $R^2 = t$ -Bu, R = Et or *i*-Pr) as an olefination testing hydroxyphosphonate to allene **5a** ($R^1 = Ph$, $R^2 = t$ -Bu), because **4a** and 5a are the most simple alcohol and allene with regard to abstractable protons (Table I). The lithium alkoxide, generated by treating 4a (R = Et) with 1 equiv of BuLi in THF, was the least reactive alkoxide to afford **5a** in 30% yield along with concomitant formation of inseparable complex mixture after 5 h under reflux (Entry 1 in Table I). The excellent conversion was achieved by treating the potassium alkoxide, formed with KH, in THF at 60°C for 5 min to give 5a in 92% yield (Entry 3 in Table I). The reaction of 4a (R = Et, *i*-Pr) can be performed at much lower temperature $(0^{\circ}C)$ for 0.5 h by further addition of 0.1 equiv of 18-crown-6 to give 5a in the same 92% yield (Entry 6 in Table I). At the higher reaction temperature (60°C) for 5 min and in the presence of 1 equiv of 18-crown-6, the major product was the isomerized alkyne in 75% yield (Entry 4 in Table I). Isomerization of **5a** could be prevented by lowering reaction temperature to 0° C affording **5a** in 89% yield (Entry 5

Entry	R	Base	18-crown-6 (equiv)	Temp (°C)	Time (min)	Yield (%) 5
1	Et	BuLi		Reflux	300	30
2	\mathbf{Et}	NaH		50	30	72
3	\mathbf{Et}	KH		60	5	92
4	i-Pr	KH	1.0	60	5	25
5	i-Pr	KH	1.0	0	15	89
6	i-Pr	KH	0.1	0	30	92
7	\mathbf{Et}	KDA		60	60	41
8	\mathbf{Et}	KHMDS		25	15	88
9	\mathbf{Et}	KOH^a		150	80	55
10	\mathbf{Et}	$t ext{-BuOK}^b$		40	15	62
11	Et	$t ext{-BuOCs}$		60	10	70

TABLE I Base Dependency of Olefination Efficacy of 4a

^{*a*}DMSO was used as a solvent. ^{*b*}1.5 equiv.

in Table I). The effects of 18-crown-6 are apparent and favorable for the olefination through nucleophilic activation of the potassium alkoxide. Other potassium bases were less effective than KH (Entries 7–10 in Table I). The softer base, *t*-BuOCs was less effective than KH (Entry 11 in Table I). Thus we could find KH and KH-18-crown-6 as suitable olefination bases for **4a**.

The conditions found above were successfully applicable to olefination of other hydroxyphosphonates **4** as summarized in Table II.

TABLE II Effects of Substituents R^1 and R^2 on the Reaction of 4

R ² OH	KH 1.0 eq		_н
R ¹ PO(O <i>i</i> -Pr) ₂	THF	н	$\overline{R^2}$
4		5	;

Entry	4	\mathbb{R}^1	\mathbb{R}^2	18-crown-6 (equiv)	$\begin{array}{c} Temp \\ (^{\circ}C) \end{array}$	Time (min)	Yield (%) 5
1	а	Ph	t-Bu	0.1	0	30	92
2	b	Ph	c-Hex		60	10	61
3	с	Ph	$Ph(CH_2)_2$		60	20	71
4	d	Ph	Me		60	20	40
5	d	Ph	Me	0.1	0	60	73
6	е	Ph	Ph		60	40	17
7	f	t-Bu	$Ph(CH_2)_2$		60	20	79
8	g	c-Hex	$Ph(CH_2)_2$	0.1	60	60	77
9	ĥ	Н	$Ph(CH_2)_2$	1.0	60	10	42
10	i	<i>t</i> -Bu	Ph		60	60	55

The olefination proceeded smoothly to give the corresponding allenes **5b–d** in good yields even when methine, methylene, and methyl groups (\mathbb{R}^2) are adjacent to the allene function (Entries 2–5 in Table II). Especially, KH-crown base improved the reaction yield to 73% from 40% even when \mathbb{R}^2 is a methyl group that is readily deprotonated (Entry 5 in Table II). When methylene is at one end of the allene such as **5f–h** ($\mathbb{R}^2 = Ph(CH_2)_2$), the reaction proceeded smoothly to afford the allenes in relatively high yields (Entries 7–9 in Table II).

In conclusion, mono- and di-substituted allenes were efficiently synthesized by successive Horner-Wadsworth-Emmons olefinations starting from methylenebisphosphonate **1** and two carbonyl compounds.

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