



## An Improved and General Method for the Synthesis of $\alpha,\beta$ -Unsaturated Oximes from Phosphine Oxide Allenes.

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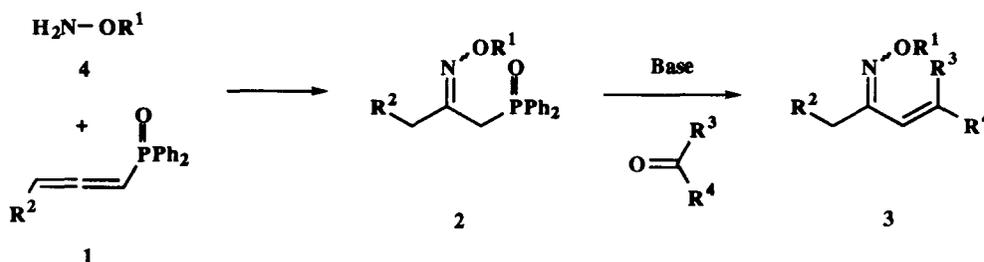
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**Abstract:** A simple and very efficient route to  $\alpha,\beta$ -unsaturated oximes **1** has been developed. These compounds are obtained through olefination reaction of  $\beta$ -oximo phosphine oxide derivatives **2**, easily obtained by addition of hydroxylamine compounds to allenes **3**.

Oxime derivatives are of significant interest not only for their synthetic value as intermediates in organic synthesis<sup>1</sup> and in the preparation of natural products such as Perhydrohistrionicotoxin<sup>2a</sup> and Aflatoxins<sup>2b</sup>, but also for their industrial applications in the areas of agrochemicals,<sup>3</sup> medicinal chemistry<sup>4</sup> (as antihistamine,<sup>4a</sup> cardiotropic,<sup>4b</sup> anticholinergic,<sup>4c</sup>  $\beta$ -blocker agents<sup>4d</sup>) and in the preparation of second and third-generation cephalosporin derivatives, such as Cefuroxime, Cefotaxime and Ceftizoxime, with potent antibacterial activity.<sup>5</sup> Furthermore, the usefulness of the  $\alpha,\beta$ -unsaturated oximes is particularly significant as a result of their activity as insecticides<sup>6a</sup> and antimicrobial agents<sup>6b</sup>, and starting materials in the synthesis of acyclic compounds, such as carbonyl derivatives,<sup>7a</sup> acetylenes<sup>7b</sup> and heterocycles such as pyridines,<sup>8a</sup> pyrimidines,<sup>8b</sup> oxazoles,<sup>8c</sup> pyrazoles<sup>8d</sup> and quinolines.<sup>8e</sup> In this context, it is noteworthy that recently  $\alpha,\beta$ -unsaturated O-silyloximes have been used, for the first time, as silyloxy-activated 1-azadienes in an elegant and short route to the synthesis of the antitumor antibiotic Lavendamycin.<sup>9</sup> In connection with our interest in the synthesis and reactivity of 2-azadienes<sup>10</sup> and activated 1-azadienes,<sup>11</sup> we have used  $\beta$ -functionalized phosphonium salts and phosphine oxides as homologation reagents of carbonyl derivatives into unsaturated hydrazones,<sup>11a</sup> allylamines<sup>12a</sup> and aminodienes.<sup>12b</sup> Here we wish to report a new route to the synthesis of  $\alpha,\beta$ -unsaturated oximes **3** making use of the easily available  $\beta$ -oximo phosphine oxides **2** through simple addition of hydroxylamines to allenes **1**.

Simple  $\alpha,\beta$ -unsaturated oximes **3** are mostly synthesized by the condensation reaction of carbonyl compounds with hydroxylamines<sup>1</sup> (carbon-nitrogen double bond formation). In our case, however, the key step involves the olefination reaction of  $\beta$ -oximo phosphine oxides **2** with carbonyl compounds (carbon-carbon double bond formation<sup>13</sup>).

The required  $\beta$ -oximo phosphine oxides **2** were very easily prepared in high yields through nucleophilic addition of hydroxylamine (**4**,  $R^1 = H$ ) and *O*-*tert*-butyldimethylsilyl hydroxylamine (**4**,  $R^1 = t\text{BuMe}_2\text{Si}$ ) to substituted allenes **1** in chloroform (see scheme 1). The structures of **2** were ascertained on the basis of their spectroscopic data,<sup>15</sup> which indicate that they are isolated as a mixture of the *syn* and the *anti* oximes.



Scheme 1

Table 1. Compounds **2** and **3** obtained.

Compound	$R^1$	$R^2$	$R^3$	$R^4$	Yield (%)	<i>syn/anti</i> ratio	m. p. (°C)
<b>2a</b>	H	H			80 <sup>a</sup>	50 / 50	190-191
<b>2b</b>	H	CH <sub>3</sub>			74 <sup>a</sup>	0 / 100	150-151
<b>2c</b>	SiMe <sub>2</sub> tBu	H			84 <sup>a</sup>	36 / 64 <sup>c</sup>	oil <sup>e</sup>
<b>2d</b>	SiMe <sub>2</sub> tBu	CH <sub>3</sub>			86 <sup>a</sup>	26 / 74 <sup>c</sup>	oil <sup>e</sup>
<b>3aa</b>	H	H	H	CH <sub>3</sub> CH(CH <sub>3</sub> )CH <sub>2</sub>	81 <sup>b</sup>	33 / 67 <sup>d</sup>	oil <sup>e</sup>
<b>3ab</b>	H	H	H	2-C <sub>5</sub> H <sub>4</sub> N	72 <sup>b</sup>	0 / 100 <sup>d</sup>	124-125
<b>3ac</b>	H	H	H	<i>p</i> -CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	79 <sup>b</sup>	0 / 100 <sup>d</sup>	139-140 <sup>f</sup>
<b>3ad</b>	H	H	Ph	Ph	80 <sup>b</sup>	56 / 44 <sup>d</sup>	oil <sup>e</sup>
<b>3ae</b>	H	H	-(CH <sub>2</sub> ) <sub>5</sub> -		74 <sup>b</sup>	0 / 100	oil <sup>e</sup>
<b>3ba</b>	H	CH <sub>3</sub>	H	<i>p</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	88 <sup>b</sup>	100 / 0 <sup>d</sup>	148-149
<b>3bb</b>	H	CH <sub>3</sub>	H	CH <sub>3</sub> CH(CH <sub>3</sub> )CH <sub>2</sub>	77 <sup>b</sup>	74 / 26 <sup>d</sup>	oil <sup>e</sup>
<b>3ca</b>	SiMe <sub>2</sub> tBu	H	H	<i>p</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	80 <sup>b</sup>	26 / 74 <sup>d</sup>	oil <sup>e</sup>
<b>3da</b>	SiMe <sub>2</sub> tBu	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	71 <sup>b</sup>	0 / 100 <sup>d</sup>	oil <sup>e</sup>

<sup>a</sup> Yield of isolated product **2** based on **1**. <sup>b</sup> Yield of isolated product **3** based on **2**. <sup>c</sup> *Syn/anti* ratio determined by <sup>31</sup>P-NMR. <sup>d</sup> *Syn/anti* ratio determined by <sup>1</sup>H-NMR. <sup>e</sup> Purified by flash chromatography. <sup>f</sup> (E): 140-1°C.<sup>18</sup>

Thus, the <sup>31</sup>P-NMR spectrum of the crude reaction mixture of **2a** showed absorptions at  $\delta_P$  28.4 and 28.7 ppm in an approximate isomer ratio of 50 : 50 indicated by the relative peak areas for the *syn* and *anti*

compounds, while the  $^{13}\text{C-NMR}$  spectrum of **2a** shows absorptions at  $\delta_{\text{C}}$  13.6 and 19.5 ppm assignable to the *anti* and the *syn* methyl group of the oxime. This steric compression shift of about 5.9 ppm, in which the signal of the methyl group is shifted to higher field for the *anti* isomer, is similar to that previously reported in other oximes.<sup>16,17</sup>

$\beta$ -Oximo phosphine oxides **2** could be suitable to efficiently achieve the homologation of oximes into their vinylogous compounds. Phosphine oxides **2** were treated with a base<sup>19</sup> followed by addition of aromatic, heteroaromatic and aliphatic aldehydes and ketones (see Table 1) leading to 1-azadienes **3** with high *E* stereoselectivity of the carbon-carbon double bond in excellent yield, after aqueous work up and flash-chromatography. The structure of **3** were assigned on the basis of their spectroscopic data,<sup>20</sup> which indicate that they are isolated as the *syn* and *anti* isomers. Thus,  $^{13}\text{C-NMR}$  spectrum of **3aa** shows absorptions at  $\delta_{\text{C}}$  9.7 and 16.7 ppm for the methyl group of the *anti* and the *syn* isomer in accordance with previous reported data.<sup>17</sup> Vicinal  $^3J_{\text{HH}}$  coupling constants in the range of 16-17 Hz between the vinylic protons of **3** ( $\text{R}^3 = \text{H}$ ) are consistent with the *E* configuration of the carbon-carbon double bond. Therefore, this procedure is highly stereoselective affording the *E* stereoisomer exclusively.

In conclusion, we describe a new strategy for an improved, general and simple method of synthesis of activated 1-azadienes **3** from phosphine oxide allenes **1** and under mild reaction conditions. These  $\alpha,\beta$ -unsaturated oximes **3** are useful intermediates in the synthesis of acyclic,<sup>7</sup> cyclic<sup>8</sup> and biologically active<sup>6,9</sup> compounds. Further studies of compounds **3** are now in progress in our laboratories.

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15. All new compounds reported here gave satisfactory elemental analysis. Spectral data for **2a**. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, TMS, 300 MHz) δ 1.94 and 1.96 (s, 3H, *anti*- and *syn*-CH<sub>3</sub>), 3.29 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 14.0 Hz, *syn*-CH<sub>2</sub>), 3.59 (d, 2H, <sup>2</sup>J<sub>PH</sub> = 15.1 Hz, *anti*-CH<sub>2</sub>), 7.26-7.85 (m, 10H, arom), 9.09 and 9.34 (s, 1H, *anti*- and *syn*-OH) ppm. <sup>13</sup>C-NMR (CDCl<sub>3</sub>, TMS, 75 MHz) δ 13.6 and 19.5 (*anti*- and *syn*-CH<sub>3</sub>), 28.8 (d, <sup>1</sup>J<sub>PC</sub> = 65.3 Hz, *anti*-CH<sub>2</sub>), 35.3 (d, <sup>1</sup>J<sub>PC</sub> = 66.7 Hz, *syn*-CH<sub>2</sub>), 126.8-132.8 (C-arom), 145.6 and 147.3 (*syn*- and *anti*-C=N) ppm. <sup>31</sup>P-NMR (CDCl<sub>3</sub>, H<sub>3</sub>PO<sub>4</sub>, 120 MHz) δ 28.4 and 28.7 (*syn*- and *anti*-isomers) ppm.
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19. In the case of **2a** and **2b** two equivalents of methyl lithium as base were used, while in the case of the silyl oximes **2e** and **2d** only one equivalent of methyl lithium was used.
20. Spectral data for **3aa**: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, TMS, 300 MHz) δ 0.89-0.93 (m, 6H, CH<sub>3</sub>), 1.67-1.73 (m, 1H, CH), 1.98 and 2.00 (s, 3H, *anti*- and *syn*-CH<sub>3</sub>), 2.03-2.13 (m, 2H, CH<sub>2</sub>), 6.04-6.09 (m, 3H, *anti*-CH=CH, and *syn*-CH=), 6.83 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 16.0 Hz, *syn*-=CH) ppm. <sup>13</sup>C-NMR (CDCl<sub>3</sub>, TMS, 75 MHz) δ 9.7 and 16.7 (*anti*- and *syn*-CH<sub>3</sub>), 22.3 (CH<sub>3</sub>), 28.2 (CH), 42.1 and 42.4 (*anti*- and *syn*-CH<sub>2</sub>), 120.7 and 128.3 (*syn*- and *anti*-HC=), 135.2 and 139.3 (*anti*- and *syn*-=CH), 153.1 and 156.3 (*syn*- and *anti*-C=N) ppm.