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An Improved and General Method for the Synthesis of α,β-Unsaturated Oximes from Phosphine Oxide Allenes.

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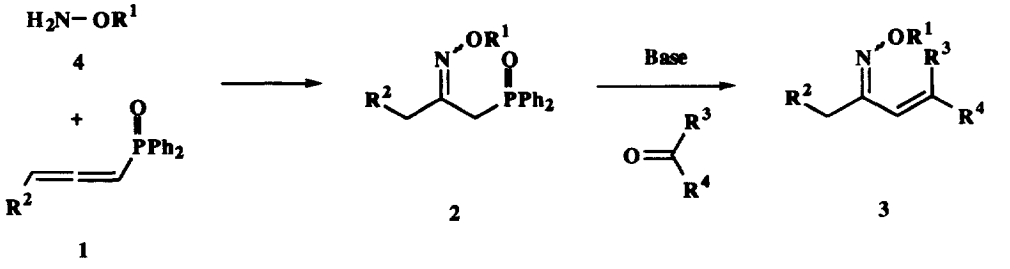
Abstract: A simple and very efficient route to α,β-unsaturated oximes **1** has been developed. These compounds are obtained through olefination reaction of β-oximo phosphine oxide derivatives **2**, easily obtained by addition of hydroxylamine compounds to allenes **3**.

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

Simple α,β-unsaturated oximes **3** are mostly synthesized by the condensation reaction of carbonyl compounds with hydroxylamines[1] (carbon-nitrogen double bond formation). In our case, however, the key step involves the olefination reaction of β-oximo phosphine oxides **2** with carbonyl compounds (carbon-carbon double bond formation[13]).

The required β-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}BuMe$_2$Si) to substituted allenes **1** in chloroform (see scheme 1). The structures of **2** were ascertained on the basis of their spectroscopic data,[15] 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 (%)	*syn/anti* ratio	m.p. (°C)
2a	H	H			80[a]	50 / 50	190-191
2b	H	CH_3			74[a]	0 / 100	150-151
2c	$SiMe_2{}^tBu$	H			84[a]	36 / 64[c]	oil[e]
2d	$SiMe_2{}^tBu$	CH_3			86[a]	26 / 74[c]	oil[e]
3aa	H	H	H	$CH_3CH(CH_3)CH_2$	81[b]	33 / 67[d]	oil[e]
3ab	H	H	H	2-C_5H_4N	72[b]	0 / 100[d]	124-125
3ac	H	H	H	*p*CH_3O-C_6H_4	79[b]	0 / 100[d]	139-140[f]
3ad	H	H	Ph	Ph	80[b]	56 / 44[d]	oil[e]
3ae	H	H		-$(CH_2)_5$-	74[b]	0 / 100	oil[e]
3ba	H	CH_3	H	*p*CH_3-C_6H_4	88[b]	100 / 0[d]	148-149
3bb	H	CH_3	H	$CH_3CH(CH_3)CH_2$	77[b]	74 / 26[d]	oil[e]
3ca	$SiMe_2{}^tBu$	H	H	*p*CH_3-C_6H_4	80[b]	26 / 74[d]	oil[e]
3da	$SiMe_2{}^tBu$	CH_3	H	$C_6H_5CH_2CH_2$	71[b]	0 / 100[d]	oil[e]

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

Thus, the ^{31}*P-NMR* spectrum of the crude reaction mixture of **2a** showed absorptions at δ_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}C-NMR* spectrum of **2a** shows absorptions at δ_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.[16,17]

β-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[19] 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, [20] which indicate that they are isolated as the *syn* and *anti* isomers. Thus, *^{13}C-NMR* spectrum of **3aa** shows absorptions at δ_C 9.7 and 16.7 ppm for the methyl group of the *anti* and the *syn* isomer in accordance with previous reported data.[17] Vicinal $^3J_{HH}$ coupling constants in the range of 16-17 Hz between the vinylic protons of **3** (R^3 = 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 α,β-unsaturated oximes **3** are useful intermediates in the synthesis of acyclic,[7] cyclic[8] and biologically active[6,9] compounds. Further studies of compounds **3** are now in progress in our laboratories.

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REFERENCES AND NOTES

1. For an excellent review see: Unterhalt, B. *Houben-Weyl. Methoden der Organischen Chemie*, Band E 14b; Klamann, D; Hagamann, H., Eds.; G. Thieme Verlag: Stuttgart, 1990, p. 287.
2. a) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. b) Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3775.
3. Roman, S. A. *US Patent* 4219565 (1980); C.A. **1981**, *94*, 15280.
4. a) Astoin, J. N.; Lepagne, F.; Fromant, J. P. M. J. *E. Patent* 82059 (1983); C.A. **1983**, *99*, 175381w. b) Thuillier, G.; Laforest, J.; Bessin, P. *US Patent*, 4207319 (1980); C.A. **1980**, *93*, 220574a. c) Haney, W. G.; Brown, R. G., Isaacson, E. I.; Delgado, J. N. *J. Pharm. Sci.* **1977**, *66*, 1602. d) Leclerc, G.; Mann, A.; Wermuth, C. G.; Bieth, N.; Schwartz, J. *J. Med. Chem.* **1977**, *20*, 1657.
5. Reuben, B. G., Wittcoff, H. A. in *Pharmaceutical Chemicals in Perspective*. J. Willey: New York, 1989, p.142. Bateson, J. H.; Burton, G.; Fell, C. M.; Smulders, C. H. *J. Antibiot.* **1994**, *47*, 253.
6. a) Nakayama, A.; Iwamura, H.; Niwa, A.; Nakagawa, Y.; Fujita, T.; *J. Agric. Food. Chem.* **1985**, *33*, 1034. Bird, J. G.; Conway, R. J.; Farquharson, G. J.; Watson, K. G.; Tucker, P. G. *E. Patent* 104876 (1984); C.A. **1984**, *101*, 110737g.b) Attia, A.; Michael, M. *Pharmazie*. **1982**, *37*, 551.

7. For recent contributions in this field see: a) Shinada, T.; Yoshihara, K. *Tetrahedron Lett.* **1995**, *36*, 6701. b) Boivin, J.; Pillot, E.; Williams. A.; Roger, W.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 3333.

8. a) Vijn, R. J.; Arts, H. J.; Green, R.; Castelijns, A. M. *Synthesis.* **1994**, 573. Hosukawa, T.; Shimo, N.; Maeda, K.; Sonoda, A; Murahashi, *Tetrahedron Lett.* **1976**, *17*, 383. b) Zielinski, W.; Mazik, M. *Heterocycles.* **1993**, *36*, 1521. c) Talapatra, S. K.; Chaudhuri, P.; Talapatra, B. *Heterocycles.* **1980**, *14*, 1279. d) Unterhalt, B.; Pindur, U. *Arch. Pharm. (Weinhein).* **1985**, *318*, 956. e) Forrester, A. R., Gil, M.; Thomson, R. H. *J. Chem. Soc. Chem. Commun.* **1976**, 677.

9. Behforouz, M.; Gu, Z,; Cai, W.; Horn, M. A.; Ahmadian, M. *J. Org. Chem.* **1993**, *58*, 7089.

10. a) Palacios, F.; Pérez de Heredia, I.; Rubiales, G. *J. Org. Chem.* **1995**, *60*, 2384. b) Palacios, F.; Alonso, C.; Rubiales, G. *Tetrahedron.* **1995**, *51*, 3683. c) Palacios, F.; Pérez de Heredia, I.; Rubiales, G.; *Tetrahedron Lett.* **1993**, *34*, 4377. d) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1988**, *29*, 4863. e) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 3497.

11. a) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron.* **1994**, *50*, 12727. b) Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett.* **1989**, *30*, 5493.

12. a) Palacios, F.; Aparicio, D.; García, J. *Synlett.* **1994**, 260. b) Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 6713.

13. While we were developing the experimental work there appeared a very specific example of Wittig olefination of phenanthren-9-one derivatives with stabilized phosphorus ylides for the synthesis of methoxyimino phenanthren-ylidenes[14]. However, in this reaction the carbon-carbon double bond formation involves the use of functionalized carbonyl compounds containing the oxime group.

14. Nicolaides, D. N.; Awad, R. W.; Papageorgian, G. K.; Stephanidou, J. *J. Org. Chem.* **1994**, *59*, 1083.

15. All new compounds reported here gave satisfactory elemental analysis. Spectral data for **2a**. *^{1}H-NMR* ($CDCl_3$, TMS, 300 MHz) δ 1.94 and 1.96 (s, 3H, *anti*- and *syn*-CH_3), 3.29 (d, 2H, $^2J_{PH}$ = 14.0 Hz, *syn*-CH_2), 3.59 (d, 2H, $^2J_{PH}$ = 15.1 Hz, *anti*-CH_2), 7.26-7.85 (m, 10H, arom), 9.09 and 9.34 (s, 1H, *anti*- and *syn*-OH) ppm. *^{13}C-NMR* ($CDCl_3$, TMS, 75 MHz) δ 13.6 and 19.5 (*anti*- and *syn*-CH_3), 28.8 (d, $^1J_{PC}$ = 65.3 Hz, *anti*-CH_2), 35.3 (d, $^1J_{PC}$ = 66.7 Hz, *syn*-CH_2), 126.8-132.8 (C-arom), 145.6 and 147.3 (*syn*- and *anti*-C=N) ppm. *^{31}P-NMR* ($CDCl_3$, H_3PO_4, 120 MHz) δ 28.4 and 28.7 (*syn*- and *anti*-isomers) ppm.

16. Levy, G. C.; Nelson G. L. *J.Am. Chem. Soc.* **1972**, *94*, 4897. Hawkes,G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017. Geneste, P.; Durand, R.; Kamenda, J. M.; Beirbeok, H.; Martino, R.; Saunders, J. R. *Can. J. Chem.* **1978**, *56*, 1940. Allen, M.; Roberts, J. D. *Can. J. Chem.* **1981**, *59*, 451. Gordon, M. S.; Scriba, S. A.; Kramer, J. G. *J. Org. Chem.* **1984**, *49*, 97.

17. Unterhalt, B. *Arch. Pharm. (Weinhein).* **1978**, *311*, 366.

18. Unterhalt, B. *Arch. Pharm. (Weinhein).* **1966**, *299*, 626.

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**: *^{1}H-NMR* ($CDCl_3$, TMS, 300 MHz) δ 0.89-0.93 (m, 6H, CH_3), 1.67-1.73 (m, 1H, CH), 1.98 and 2.00 (s, 3H, *anti*- and *syn*-CH_3), 2.03-2.13 (m, 2H, CH_2), 6.04-6.09 (m, 3H, *anti*-CH=CH, and *syn*-CH=), 6.83 (d, 1H, $^3J_{HH}$ = 16.0 Hz, *syn*-=CH) ppm.*^{13}C-NMR* ($CDCl_3$, TMS, 75 MHz) δ 9.7 and 16.7 (*anti*- and *syn*-CH_3), 22.3 (CH_3), 28.2 (CH), 42.1 and 42.4 (*anti*- and *syn*-CH_2), 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.

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