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Cycloaddition of Nitrile Oxides to Substituted Vinylphosphonates

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ABSTRACT: *Cycloaddition of nitrile oxides to substituted vinylphosphonates was performed. A series of 4,5-dihydroisoxazoles containing phosphonyl group were synthesized under very mild condition in excellent regiospecificity.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:309–311, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10149

INTRODUCTION

Vinylphosphonates have been widely utilized in organic synthesis during the last two decades and have been developed as a very useful template for the construction of functionalized organophosphorus compounds [1]. Much attention has recently been given to the development of new types of vinylphosphonates and their synthetic applications [2, 3].

Recently, we discovered that 3-diethylphosphonoethylene reacts with nitrile oxides to afford regiospecific products which are valuable intermediates of the synthesis of variously functionalized phosphonates [4].

As a continuation of this study, we report here the behavior of vinylphosphonates substituted at the 1-position by a phosphonyl or carbonyl group (**1a,b**), toward nitrile oxides. The reaction has been explored with various *p*-substituted benzonitrile oxides to achieve information on the influence of the substituent upon the regioselectivity and reactivity.

RESULTS AND DISCUSSION

The reaction of **1a,b** with benzonitrile oxides generated in situ from benzohydroximoyl chlorides and triethylamine in ether occurred smoothly at room temperature to afford the regiospecific products **2a–h** in good yield (see Scheme 1). The cycloadducts **2** were characterized by elemental analysis and ^{1}H NMR spectra, and in part also by ^{31}P NMR. Their data are shown in Tables 1 and 2. No regioisomer could be detected. The direction of cycloaddition is as expected according to the Perturbation MO treatment of cycloaddition reactivity pioneered by Sustmann [5a,b]. The compounds **2** represent the most favorable orientation because the 1,3-dipolar cycloaddition reaction is controlled by the interaction between the LUMO of the dipole and the HOMO of the dipolarophile. The dipole LUMO has its largest coefficient on carbon, and this becomes united with the unsubstituted dipolarophile carbon, the site of highest HOMO coefficient for a variety of substituents [5c,d].

Compared to the reaction of 3-diethyl-phosphonoethylene with nitrile oxides could be completed in 36 h [4], whereas the reactions of **1a** and **1b** with nitrile oxides take place rapidly in 12 h. The more electron-deficient dipolarophiles react faster.

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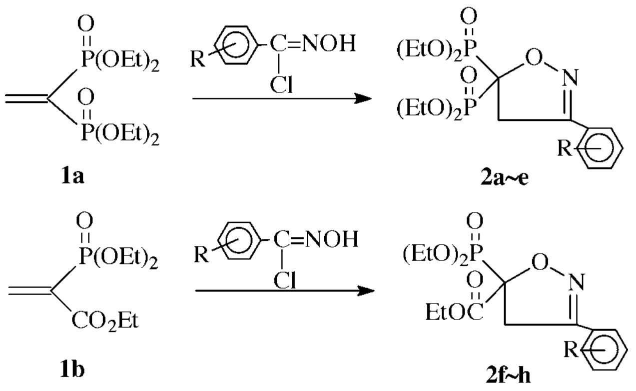

SCHEME 1

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were carried on a Yanaco CHN Corder MT-3 apparatus. ^{1}H and ^{31}P NMR spectra were measured by using a Bruker AC-P200 spectrometer with TMS and 85% H_3PO_4 as the internal and external reference respectively and with $CDCl_3$ as the solvent. Solvents used were purified and dried by standard procedures. Compounds **1a** and **1b** were synthesized according to Ref. [6,7]. The hydroxamic chlorides were synthesized according to Ref. [8,9].

General Procedure for the Synthesis of **2a–h**

To a stirred solution of **1a** or **1b** (2.0 mmol) and hydroxamic chlorides (2.2 mmol) in dry ether (30 ml) under N_2, a solution of Et_3N (0.22 g, 2.2 mmol) in dry ether (10 ml) was added dropwise at −10°C. The mixture was stirred at room temperature until the consumption of **1**, monitored by TLC. Then, the reaction mixture was filtered to remove triethylamine hydrochloride and the solvent was evaporated in vacuum. The residue was chromatographed on a silica gel column with petroleum ether/ethyl acetate [3:1(v/v)] to give pure **2a–h** as a white solid or oil.

TABLE 1 Mp, Reaction Time (h), Yield (%), and Analysis **2a–h**

					Anal. Found (Calcd)		
	R	*mp*	*Time*	*Yield*[a]	*C*	*H*	*N*
2a	H	Oil	12	69.33	48.50 (48.69)	6.47 (6.49)	3.19 (3.34)
2b	4-F	75–77	12	82.80	46.71 (46.69)	5.94 (5.99)	3.28 (3.20)
2c	4-Cl	108–110	12	93.40	44.77 (44.99)	5.77 (5.78)	3.08 (3.09)
2d	4-MeO	73–75	10	65.79	47.98 (48.11)	6.43 (6.50)	3.06 (3.12)
2e	3,4-OCH_2O	Oil	10	74.70	46.60 (46.66)	5.92 (5.87)	3.03 (3.02)
2f	4-MeO	Oil	18	66.72	52.74 (52.99)	6.45 (6.28)	3.56 (3.64)
2g	4-Cl	Oil	24	90.50	49.18 (49.30)	5.42 (5.43)	3.32 (3.59)
2h	3,4-OCH_2O	Oil	18	76.80	50.94 (51.13)	5.59 (5.55)	3.55 (3.51)

[a] Isolated yield based on **1a,b**.

TABLE 2 ^{1}H NMR Data of **2a–h**

	^{1}H NMR (ppm)
2a[a]	7.62–7.59 (m, 2H); 7.37–7.34 (m, 3H); 4.22–4.27 (m, 8H); 3.93 (t, 2H, $J = 22.24$ Hz); 1.24–1.32 (m, 12H)
2b	7.60–7.67 (m, 2H); 7.04–7.23 (m, 2H); 4.22–4.33 (m, 8H); 3.93 (t, 2H, $J = 23.67$ Hz); 1.27–1.35 (m, 12H)
2c	7.55 (d, 2H, $J = 8.42$ Hz); 7.39 (d, 2H, $J = 8.41$ Hz); 4.24–4.30 (m, 8H); 3.93 (t, 2H, $J = 23.71$ Hz); 1.28–1.36 (m, 12H)
2d	7.57 (d, 2H, $J = 8.68$ Hz); 6.89 (d, 2H, $J = 8.67$ Hz); 4.21–4.30 (m, 8H); 3.93 (t, 2H, $J = 23.59$ Hz); 3.81 (s, 3H); 1.22–1.33 (m, 12H)
2e	7.23 (s, 1H); 7.02 (d, 1H, $J = 8.64$ Hz); 6.8 (d, 1H, $J = 8.62$ Hz); 5.98 (s, 2H); 4.21–4.31 (m, 8H); 3.91 (t, 2H, $J = 23.76$ Hz); 1.27–1.35 (m, 12H)
2f	7.57 (d, 2H, $J = 8.41$ Hz); 6.88 (d, 2H, $J = 8.42$ Hz); 4.24–4.31 (m, 6H); 3.96 (dd, 1H, $J = 5.4, 20.5$ Hz); 3.92 (dd, 1H, $J = 5.4, 22.6$ Hz); 3.80 (s, 3H); 1.27–1.36 (m, 9H)
2g	7.58 (d, 2H, $J = 8.41$ Hz); 7.36 (d, 2H, $J = 8.41$ Hz); 4.25–4.33 (m, 6H); 3.98 (dd, 1H, $J = 6.48, 20.6$ Hz); 3.93 (dd, 1H, $J = 6.48, 22.7$ Hz); 1.29–1.37 (m, 9H)
2h	7.23 (s, 1H); 7.02 (d, 1H, $J = 9.72$ Hz); 6.79 (d, 1H, $J = 9.72$ Hz); 5.98 (s, 2H); 4.27–4.30 (m, 6H); 3.95 (dd, 1H, $J = 3.24, 20.6$ Hz); 3.92 (dd, 1H, $J = 3.24, 22.6$ Hz); 1.26–1.37 (m, 9H)

[a] ^{31}P of **2a** is 18.71 ppm.

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