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Reaction of Nitrile Oxides with Vinylphosphonate: A Facile, Regioselective Approach to 5-Phosphonyl-4, 5-dihydroisoxazoles

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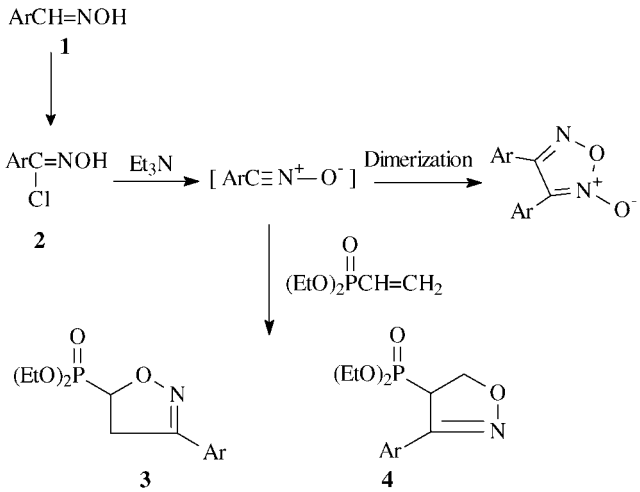
ABSTRACT: *A series of 5-phosphonyl-4,5-dihydroisoxazoles was synthesized from nitrile oxides and diethylvinylphosphonate under very mild conditions in good yields.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:254–257, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10136

INTRODUCTION

Vinylphosphonates have been widely utilized in organic synthesis during the last two decades and have become very useful for the construction of functionalized organophosphorous compounds [1]. Because of their versatility, much attention has recently been given to the development of new types of vinylphosphonates and to their synthetic applications. There are, however, few reports of 5-phosphonyl-4,5-dihydroisoxazoles to our knowledge [2,3].

RESULTS AND DISCUSSION

Reaction of nitrile oxides with vinylphosphonates in dry THF at mild condition regioselectively afforded a variety of 5-phosphonyl-4,5-dihydroisoxazoles **3**. The other possible stereoisomers **4** were not obtained (Scheme 1). The structure of title compounds **3a–i** was determined by ^{1}H NMR and elemental analysis, in part also by ^{31}P NMR. Their data are shown in Tables 1 and 2. We found that the phosphonyl group of dipolarophiles favor the 5-position of the 4,5-dihydroisoxazole ring. This regiospecificity can be explained according to the Perturbation MO treatment of cycloaddition reactivity pioneered by Sustmann [4a,4b]. The compounds **3**



SCHEME 1

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TABLE 1 Physical Data of Compounds **3a–i**

				Anal. Found (Calcd)		
	Ar	*mp (°C)*	*Yield[a] (%)*	*C*	*H*	*N*
3a	Ph	Oil	67.00	54.90 (55.12)	6.37 (6.40)	4.94 (4.95)
3b	*p*-FC_6H_4	Oil	78.54	51.75 (51.83)	5.74 (5.69)	4.78 (4.65)
3c	*p*-ClC_6H_4	72–74	81.89	48.99 (49.15)	5.20 (5.39)	4.28 (4.41)
3d	$OCH_2OC_6H_3$	Oil	72.31	51.19 (51.38)	5.57 (5.54)	4.30 (4.28)
3e	*m*-ClC_6H_4	Oil	70.80	49.01 (49.15)	5.41 (5.39)	4.51 (4.41)
3f	2,4-$Cl_2C_6H_3$	Oil	63.80	44.26 (44.34)	4.41(4.58)	3.81 (3.97)
3g	*p*-$CH_3C_6H_4$	Oil	76.24	56.52 (56.56)	6.89 (6.78)	4.71 (4.71)
3h	*p*-$NO_2C_6H_4$	120–121	76.21	47.46 (47.56)	5.25 (5.22)	8.60 (8.53)
3i	*o*-ClC_6H_4	Oil	75.10	48.92 (49.15)	5.35 (5.39)	4.22 (4.41)

[a]Isolated yield based on vinylphosphonate.

have 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 [4c,4d].

The nitrile N-oxides were prepared from the hydroxamic chlorides obtained by the route given in Scheme 1. The oximes **1** were prepared by known methods [5]. The hydroxamic chlorides **2** were prepared by passing chlorine gas through the solution of the oxime in 8 N hydrochloric acid or in organic solvents at 0°C for 20 min [6,7]. In case of piperonal oxime (**1d**), *t*-butyl hypochlorite instead of chlorine gas was used as chlorinating agent (see Experimental). Originally, compounds **3** were obtained in low yield, that is because nitrile oxides can dimerize to diarylfuroxan. We found that the dimerization reaction could be reduced in dilute solution of nitrile oxides. In order to improve the yield, we made an improvement as follows: Triethylamine is slowly added to the dilute solution of the hydroxamic chlorides in that the nitrile oxide as soon as formed reacted with vinylphosphonate. By this method, compounds **3** could be obtained in good yield.

The structure of compound **3c** was confirmed by X-ray crystallography. The molecular structure is shown in Fig. 1. Crystallographic data for **3c**: $C_{26}H_{34}Cl_2N_2O_8P_2$, $M_r = 635.39$. Cell parameters from a least-squares fit of the setting angles of 25 reflections with θ range 1.84° to 25.02° at $T = 293(2)$ K, Triclinic, space group $P\bar{1}$, $a = 11.198(4)$ Å,

TABLE 2 ^{1}H NMR Data of Compounds **3a–i**: δ (ppm), J (Hz)

3a[a]	7.46–7.49 (m, 2H), 7.21–7.23 (m, 3H), 4.69 (dd, 1H, $^3J_{HH} = 10.54$, $^2J_{PH} = 11.46$), 4.02–4.09 (m, 4H), 3.48 (dd, 2H, $^3J_{HH} = 10.60$, $^3J_{PH} = 23.29$), 1.11–1.21 (m, 6H)
3b	7.54–7.61 (m, 2H), 7.03 (d, 2H, $J = 8.42$), 4.80 (dd, 1H, $^2J_{PH} = 11.46$, $^3J_{HH} = 10.42$), 4.12–4.19 (m, 4H), 3.57 (dd, 2H, $^3J_{HH} = 10.43$, $^3J_{PH} = 23.16$), 1.21–1.31 (m, 6H)
3c	7.58 (d, 2H, $J = 8.42$), 7.37 (d, 2H, $J = 8.41$), 4.85 (dd, 1H, $^3J_{HH} = 11.36$, $^2J_{PH} = 10.44$), 4.14–4.25 (m, 4H), 3.58 (dd, 2H, $^3J_{HH} = 11.36$, $^3J_{PH} = 23.02$), 1.28–1.37 (m, 6H)
3d	7.23 (s, 1H), 6.97 (d, 1H, $J = 8.43$), 6.77 (d, 1H, $J = 8.43$), 5.97 (s, 2H), 4.81 (dd, 1H, $^3J_{HH} = 10.72$, $^2J_{PH} = 11.88$), 4.16–4.23 (m, 4H), 3.57 (dd, 2H, $^3J_{HH} = 10.74$, $^3J_{PH} = 23.05$), 1.25–1.36 (m, 6H)
3e	7.23–7.63 (m, 4H), 4.85 (dd, 1H, $^3J_{HH} = 11.16$, $^2J_{PH} = 10.86$), 4.18–4.25 (m, 4H), 3.58 (dd, 2H, $^3J_{HH} = 11.16$, $^3J_{PH} = 23.11$), 1.28–1.37 (m, 6H)
3f	7.52 (d, 1H), 7.41 (s, 1H), 7.26 (d, 1H), 4.85 (dd, 1H, $^2J_{PH} = 11.48$, $^3J_{HH} = 10.44$), 4.16–4.24 (m, 4H), 3.74 (dd, 2H, $^3J_{HH} = 10.44$, $^3J_{PH} = 23.05$), 1.28–1.36 (m, 6H)
3g	7.47 (d, 2H, $J = 8.15$), 7.13 (d, 2H, $J = 8.15$), 4.78 (dd, 1H, $^3J_{HH} = 11.18$, $^2J_{PH} = 10.42$), 4.12–4.19 (m, 4H), 3.57 (dd, 2H, $^3J_{HH} = 11.08$, $^3J_{PH} = 23.28$), 2.30 (s, 3H), 1.21–1.31 (m, 6H)
3h	8.25 (d, 2H, $J = 8.6$), 7.82 (d, 2H, $J = 8.6$), 4.95 (dd, 1H, $^2J_{PH} = 11.23$, $^3J_{HH} = 10.97$), 4.19–4.26 (m, 4H), 3.64 (dd, 2H, $^3J_{PH} = 23.28$, $^3J_{HH} = 10.97$), 1.29–1.38 (m, 6H)
3i	7.18–7.47 (m, 4H), 4.79 (dd, 1H, $^2J_{PH} = 11.2$, $^3J_{HH} = 10.94$), 4.07–4.17 (m, 4H), 3.69 (dd, 2H, $^3J_{HH} = 10.94$, $^3J_{PH} = 23.5$), 1.21–1.29 (m, 6H)

[a]δ ^{31}P of **3a** is 18.71 ppm.

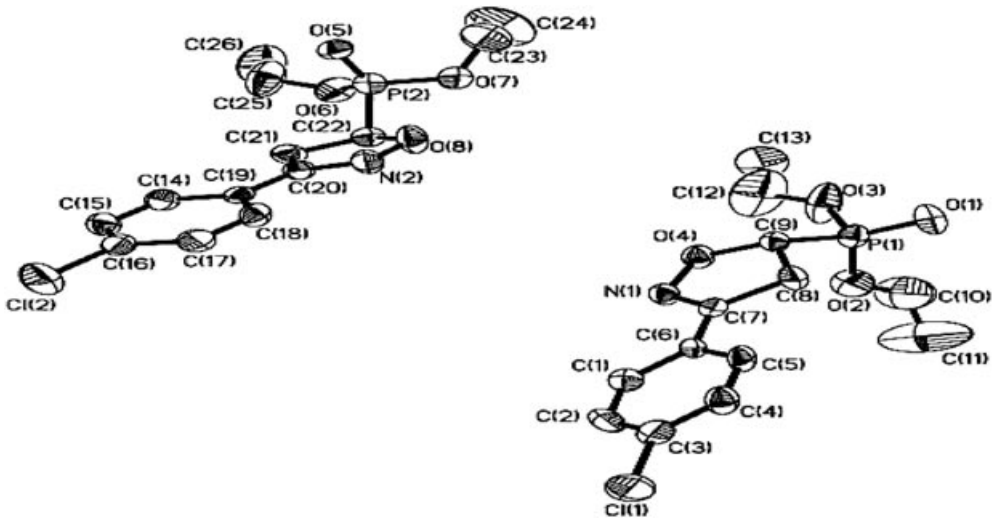

FIGURE 1 The molecular structure of 3c. The hydrogen atoms are omitted for clarity. Selected distances (Å) and angles (degrees): P1–C9 = 1.791(6) [1.768(7)], C8–C9 = 1.520(8) [1.525(8)], C9–O4 = 1.460(6) [1.440(8)], N1–O4 = 1.402(6) [1.418(7)], C7–C8–C9 = 100.6(5) [102.0(6)], N1–O4–C9 = 109.1(4) [109.9(5)], C8–C9–P1 = 114.4(5) [115.1(5)], O4–C9–P1 = 111.7(5) [110.0(5)].

$b = 12.539(5)$ Å, $c = 13.036(6)$ Å, $V = 1575.7(11)$ Å^3, $\alpha = 65.900(7)^\circ$ $\beta = 77.793(9)^\circ$ $\gamma = 71.281(8)^\circ$, $Z = 2$, $\mu = 0.355$ mm^{-1}, colorless plate, $D_x = 1.339$ Mg/m^3, $F(000) = 664$. Direct method is used for solution and full-matrix least-squares for refinement. The crystallographic data was deposited at CCDC [8]. X-ray analysis has shown that there are two types of independent molecules in the unit cell. The dihedral angles between benzene and isoxazole ring are 8.7° and 11.7° respectively.

In summary, we have provided a facile, regioselective approach to 5-phosphonyl-4,5-dihydroisoxazoles which can be a precursor to variously functionalized phosphonates. The further studies on the application of title products are in progress.

EXPERIMENTAL

Melting points were 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.

3-Diethylphosphonoethylene was synthesized according to [9].

*α-Chloropiperonal Oxime (***2d***)*

To a solution of piperonal oxime (5.16 g, 30 mmol) in dichloroethane (30 ml) and isopropanol (15 ml), *t*-butyl hypochlorite (4.0 g, 36 mmol) was added dropwise at −15°C. After being stirred for 30 min, the solution was concentrated in vacuum and petroleum ether (10 ml) was added. It was then filtered and a white solid was obtained in 80% yield, mp 126–127°C.

General Procedure for the Synthesis of **3a–i**

To a stirred solution of diethylvinylphosphonate (0.32 g, 2.0 mmol) and hydroxamic chlorides (2.2 mmol) in dry THF (30 ml) under N_2, a solution of Et_3N (0.22 g, 2.2 mmol) in dry THF (10 ml) was added dropwise at −10°C. After being stirred at room temperature for 36 h, 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 **3a–i** as a white solid or oil.

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