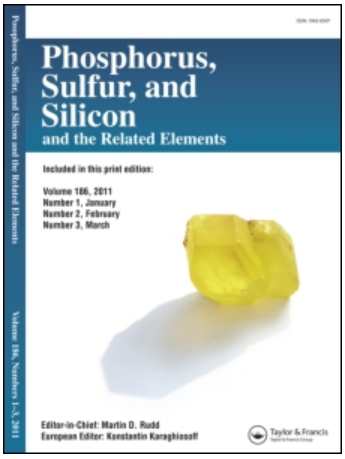

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STUDIES ON CYCLOADDITION REACTIONS OF VINYLPHOSPHONATES WITH NITRONES

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Cycloaddition reactions of vinylphosphonates with nitrones were studied. A series of 4-phosphonyl-3-aryl-N-arylisoxazolidines were synthesized by the reaction of vinylphosphonates with nitrones. The structure of ***3a*** *was confirmed by X-ray single-crystal diffraction.*

Keywords: Cycloaddition reactions; isoxazolindines; nitrones; vinylphosphonates

INTRODUCTION

Vinylphosphonates and its analogues that bear electron-withdrawing substituents at the α position have found wide application in organic chemistry 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 been given recently to the development of new types of vinylphosphonates and to their synthetic applications.[2,3]

Previous studies showed that vinylphosphonates can behave as dipolarophiles and react with nitrile oxide to form heterocyclic compounds containing a phosphonyl group through [2 + 3] cycloaddition.[4,5] In this article, we report the behavior of vinylphosphonates toward nitrones.

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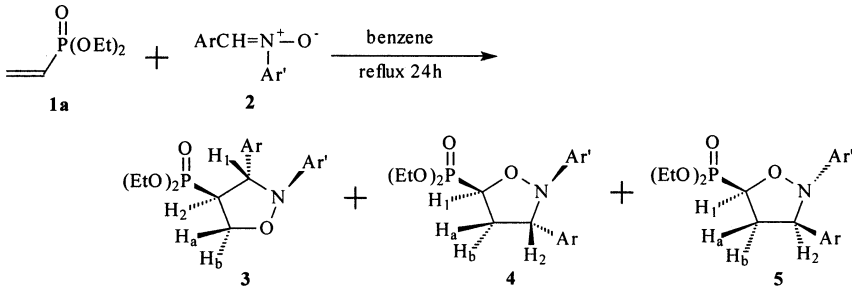
RESULTS AND DISCUSSION

The reactions of vinylphosphonate **1a** with **2a–h** are very simple and convenient. After refluxing vinylphosphonate **1** in benzene with an excess of nitrone **2**, for about 24 h, a mixture of isoxazolindines (Scheme 1) was produced. The crude mixture was analyzed by HPLC to determine the ratio of isomers (shown in Table I), and the corresponding adducts **3** were separated by column chromatography. The adducts **4** and **5** could not be separated by column chromatography. In order to study this reaction, **4f** and **5f** were separated by preparative HPLC. As illustrated in Scheme 1, all reactions gave three cycloadducts. The isoxazolidine **3** was the major product; its structure was confirmed by X-ray crystallography (Figure 1). The structure and stereochemistry of isoxazolidines **4** and **5** were ascertained by careful examination of the ^{1}H NMR spectra using NOE experiments and MS spectra.



SCHEME 1

The ^{1}H NMR spectra of compounds **4** and **5** are very similar, but they are not similar to the ^{1}H NMR spectra of compounds **3**. The irradiation

TABLE I Physical Data of Compounds **3a–h**

				Ratio of isomers		
Entry	Ar	Ar′	Yield* (%)	3	4	5
a	4-ClC_6H_4	C_6H_5	54.89	72.09	10.80	17.11
b	3-$NO_2C_6H_4$	C_6H_5	55.67	51.16	30.40	18.44
c	C_6H_5	C_6H_5	54.42	70.52	8.87	20.61
d	3,4-$OCH_2OC_6H_4$	C_6H_5	68.04	76.22	8.34	15.44
e	4-FC_6H_4	C_6H_5	66.37	70.24	10.45	19.31
f	4-$NO_2C_6H_4$	C_6H_5	69.41	65.65	17.85	16.50
g	4-ClC_6H_4	4-ClC_6H_4	71.43	82.28	4.64	13.08
h	4-FC_6H_4	4-ClC_6H_4	70.86	74.98	10.22	14.80

*Isolated total yield based on vinylphosphonate.

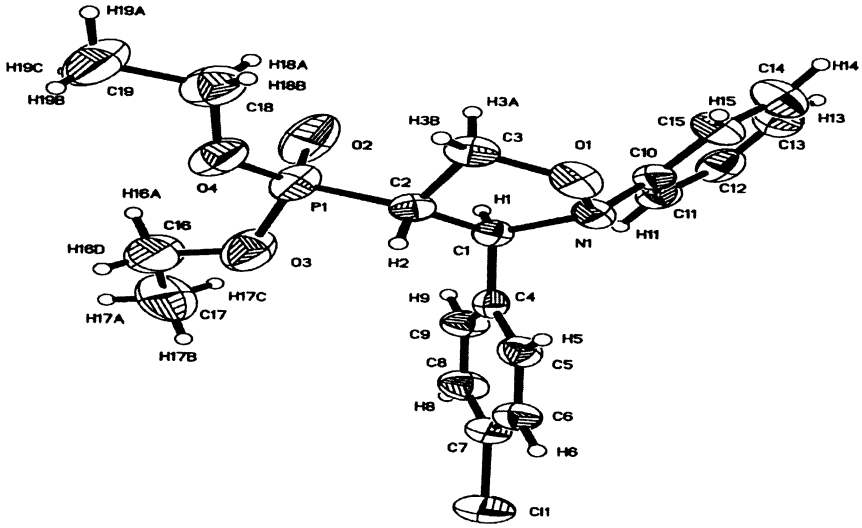


FIGURE 1 The molecular structure of **3a**.

of H_1 in **4f** resulted in enhancement (about 10%) of the signals for H_b but no effect was detected at H_a. The same experiment performed on H_2 in **4f** produced signal enhancements for Ha (about 43%) and 19% for H_b. All these effects are in agree with a cis configuration for H_1 with H_b and a cis configuration for H_2 with H_a.

The MS spectra of compounds **4f** and **5f** are not the same. As we know, compound **4f** is more stable than compound **5f**. So, the molecular ion of compound **4f** (its relative abundance is 100%) is greater than that of compound **5f** (relative abundance is 10%). The molecular ion of **4f** produced fragment ions at M/Z 379, corresponding to a loss of $CH_2{=}CH_2$ from M^+, and M/Z 299, corresponding to $[M\text{-}PhNO]^+$. However, compound **5f** does not give these fragment ions.

In summary, we have developed a good method for the synthesis of the novel structural heterocyclic compound containing a phosphonyl group. The reactions are very simple, convenient, and efficient. Applications of these heterocyclic compounds are currently being examined.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were carried on a Yanaco CHN Corder MT-3 apparatus. ^1H NMR spectra were measured with a Bruker AC-P200 spectrometer with tetramethylene silane (TMS) as the internal and with $CDCl_3$ as the solvent. The HPLC system used

was Beckman System Gold™ HPLC, consisting of 110B Solvent Delivery Module, Analog Interface Module 406, and Diode Array Detector Module 168. Column utilized was SILICA (25 cm × 4.6 mm I.D.; 5 μm particle size). Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Solvents were purified and dried by standard procedures. Compound **1** was synthesized according to Rambaud et al.,[6] Degenhardt and Burdsall,[7] Mcintosh and Sieler.[8] Compound **2** was synthesized according to Nunno and Scilimati.[9]

General Procedure Cycloaddition of Nitrones 2 with Vinylphosphonates 1

To a solution of the corresponding nitrone (1.2 mmol) in benzene was added the vinylphosphonates **1** (1 mmol), and the resulting solution was heated under an N_2 atmosphere at reflux for 24 h. Then, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The diastereomeric ratio of the residue was determined by HPLC analysis. The cycloadduction products **3a–h** were separated by column chromatography (eluenting with petroleum ether/ethyl acetate 7:1). The adducts **4f** and **5f** were separated by preparative HPLC (eluenting with petroleum ether/isopropanol 9:1).

3a: ^{1}H NMR (ppm): 1.01–1.08 (m, 6H), 2.85–3.11 (m, 1H, PCH), 3.85–3.89 (m, 4H), 4.88 (dd, 1H, NCH, J = 17.2, 5.7 Hz), 4.37 (ddd, 1H, J = 8.34 Hz), 4.18 (ddd, 1H, J = 12.56, 8.34 Hz), 6.85–7.45 (m, 9H). m.p. 114–116°C. Anal. calcd. for $C_{19}H_{23}NO_4PCl$:C, 57.65; H, 5.86; N, 3.54. Found: C, 57.42; H, 5.98; N, 3.38.

3b: ^{1}H NMR (ppm): 1.06–1.25 (m, 6H), 2.85–3.11 (m, 1H, PCH), 3.90–4.08 (m, 4H), 4.16 (ddd, 1H, J = 8.34, 14.6 Hz), 4.38 (ddd, 1H, J = 8.34 Hz), 5.06 (dd, 1H, NCH, J = 16.68, 5.22 Hz), 6.92–6.96 (m, 2H, Ph), 7.19–7.23 (m, 3H, Ph), 7.48–7.56 (m, 1H, ArH), 7.94 (d, 1H, J = 7.3 Hz, ArH), 8.13 (d, 1H, J = 7.3 Hz, ArH), 8.44 (s, 1H, ArH). m.p. 120–122°C. Anal. calcd. for $C_{19}H_{23}N_2O_6P$: C, 56.16; H, 5.70; N, 6.70. Found: C, 56.17; H, 5.60; N, 6.77.

3c: ^{1}H NMR (ppm): 1.06–1.15 (m, 6H), 2.96–3.18 (m, 1H, PCH), 3.91–3.98 (m, 4H), 4.19 (ddd, 1H, J = 9.06, 14.0 Hz), 4.41 (ddd, 1H, J = 9.06 Hz), 4.89 (dd, 1H, NCH, J = 6.26, 16.68 Hz), 6.92–7.21 (m, 4H, Ph), 7.27–7.58 (m, 6H, Ph). Oil, anal. calcd. for $C_{19}H_{24}NO_4P$: C, 63.15; H, 6.69; N, 3.88. Found: C, 62.90; H, 6.40; N, 3.88.

3d: ^{1}H NMR (ppm): 1.08–1.17 (m, 6H), 2.85–3.16 (m, 1H, PCH), 3.92–4.03 (m, 4H), 4.11–4.16 (m, 1H), 4.36–4.41 (m, 1H), 4.78 (dd, 1H, NCH, J = 6.26, 15.64 Hz), 5.94 (s, 2H), 6.76 (d, 1H, J = 8.34 Hz, ArH), 6.95–7.23 (m, 7H, ArH). Oil. anal. calcd. for $C_{20}H_{24}NO_6P$: C, 59.26; H, 5.97; N, 3.46. Found: C, 59.36; H, 5.92; N, 3.43.

3e: ^{1}H NMR (ppm): 1.07–1.15 (m, 6H), 2.91–3.09 (m, 1H, PCH), 3.92–3.99 (m, 4H), 4.16 (ddd, 1H, J = 9.38, 12.5 Hz), 4.37 (ddd, 1H, J = 9.38 Hz), 4.87 (dd, 1H, NCH, J = 6.26, 16.68 Hz), 6.92–7.25 (m, 7H, ArH), 7.49–7.56 (m, 2H, ArH). m.p. 118–120°C. anal. calcd. for $C_{19}H_{23}NO_4PF$:C, 60.15; H, 6.11; N, 3.69. Found: C, 60.08; H, 6.15; N, 3.78.

3f: ^{1}H NMR (ppm): 1.07–1.17 (m, 6H), 2.89–3.07 (m, 1H, PCH), 3.95–4.10 (m, 4H), 4.12–4.20 (m, 1H), 4.38 (ddd, 1H, J = 8.34 Hz), 5.06 (dd, 1H, NCH, J = 6.26, 17.72 Hz), 6.92–6.96 (m, 2H, Ph), 7.21–7.25 (m, 3H, Ph), 7.78 (d, 2H, J = 8.91 Hz, ArH), 8.21 (d, 2H, J = 8.91 Hz, ArH). m.p. 134–136°C. anal. calcd. for $C_{19}H_{23}N_2O_6P$:C, 56.16; H, 5.70; N, 6.70. Found: C, 56.12; H, 5.63; N, 6.95. MS (m/z): 406 (0.22), 376 (0.06), 269 (0.36), 251 (0.44), 226 (1.00), 179 (0.63), 77 (0.94).

3g: ^{1}H NMR (ppm): 1.15–1.24 (m, 6H), 2.90–3.07 (m, 1H, PCH), 3.98–4.39 (m, 6H), 4.79 (dd, 1H, NCH, J = 7.3, 17.74 Hz), 6.89–7.37 (m, 8H, ArH). Oil. anal. calcd. for $C_{19}H_{22}NO_4PCl_2$:C, 53.04; H, 5.15; N, 3.26. Found: C, 53.11; H, 5.17; N, 3.34.

3h: ^{1}H NMR (ppm): 1.10–1.17 (m, 6H), 2.88–3.11 (m, 1H, PCH), 3.94–4.02 (m, 4H), 4.04–4.19 (m, 1H), 4.37 (ddd, 1H, J = 8.34 Hz), 4.79 (dd, 1H, NCH, J = 6.24, 16.68 Hz), 6.86 (d, 2H, J = 9.16 Hz, ArH), 6.99–7.18 (m, 4H, ArH), 7.45–7.52 (m, 2H, ArH). Oil. anal. calcd. for $C_{19}H_{22}NO_4PFCl$:C, 55.15; H, 5.36; N, 3.39. Found: C, 54.98; H, 5.36; N, 3.29.

4f: ^{1}H NMR (ppm): 1.23–1.33 (m, 6H), 2.71–2.43 (m, 1H, Ha), 3.28–2.90 (m, 1H, H_b), 4.11–4.12 (m, 4H), 4.4 (dd, 1H, H_2), 4.8 (dd, 1H, H_1), 6.94–6.99 (m, 2H, Ph), 7.23–7.26 (m, 3H, Ph), 7.69 (d, 2H, J = 8.37 Hz, ArH), 8.22 (d, 2H, J = 8.37 Hz, ArH). m.p. 108–110°C. MS (m/z): 406 (1.00), 378 (0.02), 299 (0.05), 269 (0.09), 239 (0.27), 227 (0.28), 176 (0.35), 109 (0.23), 91 (0.59), 77 (0.44).

5f: ^{1}H NMR (ppm): 1.23–1.34 (m, 6H), 2.72–2.44 (m, 1H, H_b), 3.29–2.91 (m, 1H, H_a), 4.12–4.23 (m, 4H), 4.41 (dd, 1H, H_2), 4.79 (dd, 1H, H_1); 6.97–7.02 (m, 2H, Ph), 7.17–7.24 (m, 3H, Ph), 7.64 (d, 2H, J = 8.71 Hz, ArH), 8.22 (d, 2H, J = 8.71 Hz, ArH). m.p. 112–114°C. MS (m/z): 406 (0.10), 389 (0.01), 285 (0.04), 269 (0.69), 239 (1.00), 225 (0.39), 176 (0.45), 109 (0.31), 91 (0.49), 77 (0.65).

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