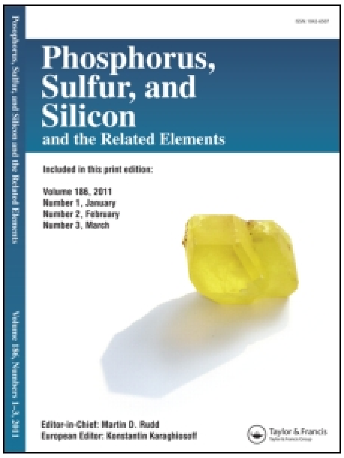

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Regioselective Cycloadditions of β-Substituted Vinylphosphonate with Nitrile Oxides

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Vinylphosphonates have been widely utilized in organic synthesis during the last two decades. In this article, a novel, highly regioselective cycloaddition utilizing nitrile oxides and vinylphosphonate for the synthesis of isoxazoline and fused isoxazoline rings was developed. The method has the advantages in that it tolerates a wide variety of functional groups.

Keywords 1,3-Dipolar cycloadditions; isoxazoline; vinylphosphonates

INTRODUCTION

Vinylphosphonates have been widely utilized in organic synthesis during the last two decades and became very useful for the construction of functionalized organophosphorus compounds.[1–2] In particular, cycloaddition of nitrile oxides to vinylphosphonates is of considerable interest, as the resulting isoxazolines are versatile intermediates in the synthesis of a variety of natural products.[3–4] Furthermore, the phosphonate functional group has been thought to be usually stable under the various transformations of isoxazolines including their reductive N—O bond cleavage.[5]

Recently, we have discovered that 3-diethylphosphonoethylene and vinylphosphonate substituted at the α-position by phosphonyl or carbonyl groups react with nitrile oxides to afford only one regiospecific

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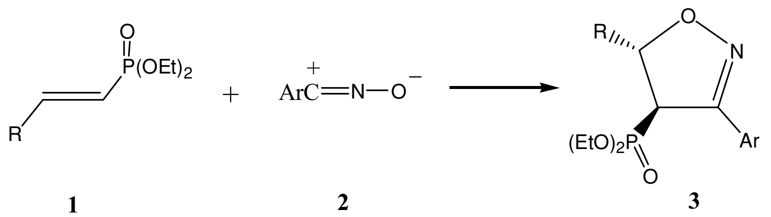
product, which is a valuable intermediate of the synthesis of variously functionalized phosphonates.[6,7] As a continuation of this study, we report here the behavior of β-substituted vinylphosphonate with nitrile oxides. The reaction has been explored with various substituted nitrile oxide to achieve information on the influence of the substituent at the β-position upon the regioselectivity and reactivity of the cycloaddition.

RESULTS AND DISCUSSION

The reaction of β-substituted vinylphosphonate with benzonitrile oxide generated in situ from benzohydroximoyl chloride and triethylamine in THF occurred smoothly at room temperature to afford the products **3** in good yield (shown in Scheme 1). The cycloadducts **3** characterized by elemental analysis and ^1H NMR spectra, in part also by ^{31}P NMR. Their related data are shown in Table I. Using the optimized conditions, cycloaddition of vinylphosphonate with phenyl substituted was faster than that of alkyl substituted. Reaction time was 12–18 h with **3e–g** and 24–48 h with **3a–d**.

β-Substituted vinylphosphonate undergoes a highly regioselective cycloaddition with nitrile oxide. The regioisomer was not detected by TLC and isolated by column chromatography. The structures of the adducts **3** rely upon the data of NMR. The regiochemistry follows from the comparison of the spacings between the isoxazolinic hydrogens. Previous NMR studies proved this technique to be useful for structural assignment of isoxazoline derivatives,[8,9] especially in the case of trans-isomers. A proton in the 5-position absorbs lower field than a 4-proton, owing to the paramagnetic shift caused by the adjacent oxygen atom. In the case of the isoxazoline, $\Delta\delta_{5,4}$ (δ5–δ4) is always notably larger for the 4-isoxazoline (1.4–2 ppm) than for the 5-isomers (1 ppm).[6] Because of the higher deshielding effect of a relative to a phosphonyl substituent,



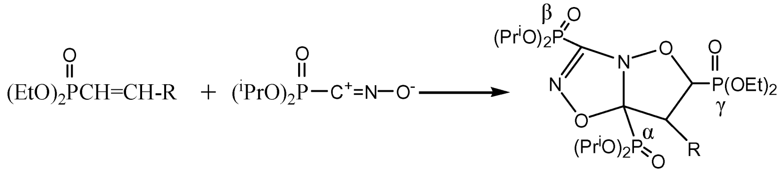
R=C_6H_{13}, Ph,4-NO_2Ph-

SCHEME 1 Cycloaddition of β-substituted vinylphosphonate with aryl nitrile oxides.

TABLE I 1,3-Dipolar Cycloaddition Reaction of β-Substituted Vinylphosphonate with Benzonitrile Oxide

Product	R	Ar	Time (h)	Yield*(%)
3a	C_6H_{13}	4-FC_6H_4	24	62.49
3b	C_6H_{13}	4-ClC_6H_4	24	56.16
3c	C_6H_{13}	4-MeC_6H_4	36	58.55
3d	C_6H_{13}	C_6H_5	48	56.42
3e	C_6H_5	C_6H_5	16	56.63
3f	C_6H_5	4-MeC_6H_4	18	47.16
3g	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	12	68.75

*Isolated yield based on substituted vinylphosphonate.



1 **4** **5**

a-c: R= C_6H_{13}, C_6H_5, 4-$O_2NC_6H_4$

SCHEME 2 Cycloaddition of β-substituted vinylphosphonate with phosphonyl nitrile oxides.

the spacing of a 4-phosphonyl substituted isoxazoline is larger than that of the 5-phosphonyl regioisomer. The trend becomes more manifest in the spectra of the isoxazolines carrying phenyl substituents.

Next, we examined the scope of β-substituted vinylphosphonate with nitrile oxides. When β-substitute vinylphosphonate **1** reacted with diisopropanyl phosphonyl nitrile oxides **4**, only regioselectively 2:1 addition product **5** was obtained (shown in Scheme 2). The requisite nitrile oxides **4** were prepared according to the literature routes from the corresponding hydroximoyl bromides via base induced dehydrobromidination.[10] Meanwhile, when excessive β-substitute vinylphosphonate **1** was added, only 2:1 cycloadduct was obtained. A variety of β-substitute vinylphosphonate readily reacted with phosphonyl nitrile oxides to produce the corresponding 2:1 cycloadduct in moderate yields.

CONCLUSION

In conclusion, we have developed a novel 1,3-cyclic addition reaction utilizing nitrile oxides and vinylphosphonate for the synthesis of 4-phosphonyl isoxazoline and fused isoxazoline rings. The method has advantages in that it tolerates a wide variety of functional groups, is straightforward, and provides good yields of products from readily accessible starting materials. Further study is underway to expand the scope of this methodology, as well as to ascertain mechanistic details of the cycloaddition process.

EXPERIMENTAL

General

All 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 300 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 **1** were synthesized according to Kiddle and Babler[11] and Monique et al.[12] Benzonitrile oxides were prepared efficiently from the corresponding hydroximoyl chlorides via base induced dehydrochlorination.[13]

General Procedure for the Synthesis of 3a–g

To a stirred solution of compounds 1 (2.0 mmol) and hydroxamic chlorides (2.2 mmol) in dry THF (15 mL) under N_2, a solution of Et_3N (0.22 g, 2.2 mmol) in dry THF (15 mL) was added dropwise at −10°. The mixture was stirred at room temperature until the consumption of vinylphosphonates, 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 **3a–g** as a solid or oil.

3a: ^{1}H NMR: δ 0.85 (t, 3H); 1.14–1.80 (m, 16H); **3.60** (dd, 1H, $J = 4.16$, 19.8 Hz); 3.87–4.17 (m, 4H); **5.04** (m, 1H); 7.15 (m, 2H); 7.81(m, 2H); ^{31}P NMR: 19.81; anal. calcd. for $C_{19}H_{29}FNO_4P$: C, 59.21; H, 7.58; N, 3.63. Found C, 58.91; H, 7.68, N, 3.73.

3b: ^{1}H NMR: δ 0.84 (t, 3H); 1.13–1.79 (m, 16H); **3.70** (dd, 1H, $J = 4.06$, 19.6 Hz); 3.9–4.2 (m, 4H); **5.1** (m, 1H); 7.33 (d, 2H, $J = 8.84$ Hz); 7.75 (d, 2H, $J = 8.84$ Hz); anal. calcd. for $C_{19}H_{29}ClNO_4P$: C, 56.79; H, 7.27; N, 3.49. Found C, 56.75; H, 7.17, N, 3.52.

3c: ^{1}H NMR: δ 0.86 (t, 3H); 1.12–1.82 (m, 16H); 2.33 (s, 3H); **3.61** (dd, 1H, $J = 4.12$, 19.7 Hz); 3.86–4.16 (m, 4H); **5.06** (m, 1H); 7.20 (d, 2H, $J = 8.12$ Hz); 7.68 (d, 2H, $J = 8.12$ Hz); anal. calcd. for $C_{20}H_{32}NO_4P$: C, 62.98; H, 8.45; N, 3.67. Found C, 63.02; H, 8.20, N, 3.76.

3d: ^{1}H NMR: δ 0.85 (t, 3H); 1.12–1.79 (m, 16H); **3.71** (dd, 1H, $J = 4.14$, 19.82 Hz); 3.89–4.2 (m, 4H); **5.1** (m, 1H); 7.37 (m, 3H); 7.79 (m, 2H); anal. calcd. for $C_{19}H_{30}NO_4P$: C, 62.11; H, 8.23; N, 3.81. Found C, 62.03; H, 8.17, N, 3.92.

3e: ^{1}H NMR: δ 1.17–1.31 (m, 6H); 3.92–4.15 (m, 5H); **6.09** (dd, 1H, $J = 5.22$, 20.84 Hz); 7.23–7.38 (m, 6H); 7.77–7.80 (m, 4H); anal. calcd. for $C_{19}H_{22}NO_4P$: C, 63.50; H, 6.17; N, 3.90. Found C, 63.31; H, 6.04, N, 3.94.

3f: ^{1}H NMR: δ 1.13–1.24 (m, 6H); 2.25 (s, 3H); 3.91–4.14 (m, 5H); **5.98** (dd, 1H, $J = 4.18$, 20.86 Hz); 7.08 (d, 2H, $J = 8.34$ Hz); 7.60 (d, 2H, $J = 8.34$ Hz); anal. calcd. for $C_{20}H_{24}NO_4P$: C, 64.33; H, 6.48; N, 3.75. Found C, 64.36; H, 6.25, N, 3.53.

3g: yellow solid, mp 144–146°. ^{1}H NMR: δ 1.21–1.37 (m, 6H); **3.93** (dd, 1H, $J = 5.22$, 19.82 Hz); 4.03–4.18 (m, 4H); **6.23** (dd, 1H, $J = 5.22$, 21.9 Hz); 7.53 (d, 2H, $J = 8.83$ Hz); 7.98 (d, 2H, $J = 9.04$ Hz); 8.23 (d, 4H, $J = 8.8$ Hz); anal. calcd. for $C_{19}H_{20}N_3O_8P$: C, 50.79; H, 4.49; N, 9.35. Found C, 50.94; H, 4.30, N, 9.24. HRMS (ESI): m/z calcd. for $C_{19}H_{20}N_3O_8P$: 449.0988; found: 449.0995.

General Procedure for the Synthesis of 5

To A stirred solution of phosphonyl hydroximoyl bromides (0.432 g, 1.5 mmol) and β-substituted vinylphosphonate (15 mmol) in dry ether (10 mL), a solution of Et_3N (0.2 g, 2 mmol) in dry ether (10 mL) was added dropwise at −10°. After half an hour, the solution ascends to ambient temperature. The reaction mixture was stirred continue for three days. After filtered, the solvent was evaporated in vacuum. The residue was chromatographed on a silica gel column with petroleum ether/ethyl acetate 1:3 to give pure **5a–c** as an oil.

5a: yield 19.6%, ^{1}H NMR: δ 7.32 (m, 5H), 5.89–6.03 (dd, 1H), 4.69(m,4H), 4.12–4.22 (m, 5H), 1.20–1.39 (m, 30H), ^{31}P NMR: δ 0.89 ($^{\alpha}$P), –3.25($^{\beta}$P), 18.53 ($^{\gamma}$P); anal. calcd. for it, found(calcd): C47.72 (47.71), H6.79 (6.93), N 4.29(4.28).

5b: yield 31.4%, ^{1}H NMR: δ 4.65–4.75 (m, 5H), 3.99–4.10 (m, 5H), 1.08–1.41 (m, 40H), 0.73–0.76 (m, 3H), ^{31}P NMR: δ 1.08 ($^{\alpha}$P), –3.14 ($^{\beta}$P), 19.2 ($^{\gamma}$P).; anal. calcd. for it, found(calcd): C46.98 (47.13) 8.13(8.06) 4.28(4.23).

5c: yield 56.1%, ^{1}H NMR: δ 8.19–8.23 (d, 2H), 7.51–7.55 (d, 2H), 6.06 (dd, 1H), 4.83 (m, 4H), 4.21 (m, 5H), 1.23–1.37 (m, 30H), ^{31}P NMR: δ 0.53

($^{\alpha}$P), –3.32 ($^{\beta}$P), 17.68 ($^{\gamma}$P); anal. calcd. for it, found (calcd): 44.59(44.64) 6.35(6.34) 5.98(6.01).

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