1,3-Dipolar cycloadditions of substituted vinylphosphonate with nitrile oxides or nitrones

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1,3-dipolar cycloaddition reactions are among the most important synthetic manipulations allowing the construction of five-membered ring carbocycles and heterocycles. Vinylphosphonates and its analogues have found wide application in organic chemistry during the last two decades and have become very useful for the construction of functionalised organophosphorous compounds. In this report, we have developed a method for the synthesis of β-Substituted vinylphosphonates and the novel structural heterocyclic compound containing a phosphonyl group.

Keyword: 1,3-dipolar, cycloaddition, vinylphosphonates, nitrile oxides

1,3-dipolar cycloaddition reactions are among the most important synthetic manipulations allowing the construction of five-membered ring carbocycles and heterocycles.[1-2]

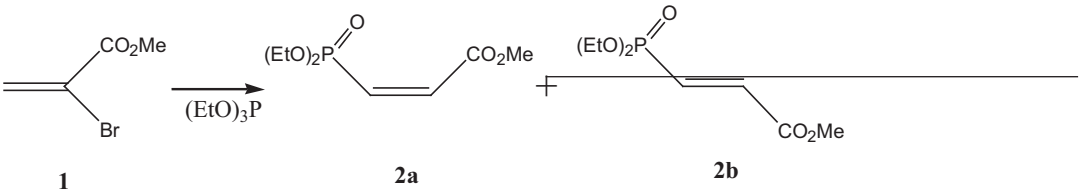
Vinylphosphonates and its analogues have found wide application in organic chemistry during the last two decades and have become very useful for the construction of functionalised organophosphorous compounds.[3-4] Nitrile oxides and nitrones undergo smooth reactions with vinylphosphonate to give isoxazolines and isoxazolidines containing a phosphonyl group, respectively. Both classes of heterocycle are versatile intermediates for the syntheses of natural products and biologically active compounds.[5]

In order to extend the scope of the vinylphosphonate cycloaddition reactions, its reactions as a dipolarophile with nitrile oxides and nitrones are investigated here. For our investigation, the requisite 1,3-dipoles were prepared according to literature reports. Nitrile oxides were prepared efficiently from either the corresponding hydroximoyl chlorides or primary nitro compounds via base induced dehydrochlorination, respectively.

Recently, we have discovered that diethyl vinylphosphonate react with nitrile oxides to afford only one regiospecific products which are valuable intermediates of the synthesis of variously functionalised phosphonates.[4] As a continuation of this study, we report here the behaviour of β-substituted vinylphosphonates toward nitrile oxides.

β-substituted vinylphosphonates was synthesised according to Coover's method.[6] The synthetic route is shown in Scheme 1. Under N_2 atmosphere, triethyl phosphite was dropwised to α-bromide methacrylate at –15°C. After the reaction was completed, evaporation of EtBr afforded a crude product in 60% yield. Detected by TLC, two spots were found. Purified by chromatography on a silica gel column (PE: EA = 4 : 1), pure **2a** (26.5%) and **2b** (73.5%) were obtained. They can also be separated by distillation in vacuum (**6a**: b.p. 148–152°C/3 mm; **6b**: 150–154°C/3 mm). Their structure were distinguished according to ^{1}H NMR (different chemical displacement of hydrogen on C =C) and polarity on a silica gel column(**2b** has low polarity). From ^{1}H NMR, two $^3J_{HH}$ coupling constants 13.95 Hz and 17.55 Hz were observed. According to $^3J_{tran} > {}^3J_{syn}$, we can confirm $^3J_{syn}$ = 13.95 Hz, corresponding to **2a**.

The reaction of β-substituted vinylphosphonate with benzonitrile oxide generated *in situ* from benzohydroximoyl chloride and triethylamine in ether occurred smoothly at room temperature to afford the products **3** and **4** in good yield. The cycloadducts characterised by elemental analysis and ^{1}H NMR spectra. Their related data are shown in Table 1 and 2, respectively.



1 **2a** **2b**

Scheme 1 The synthesis of β-substituted vinylphosphonates.

Table 1 Physical data of compounds **3** and **4**

Entry	Ar	Time/h	Yield[a]/%	Anal.found(calcd.)		
				C	H	N
3a	4-$O_2NC_6H_4$	8	58.85	46.58(46.63)	4.95(4.92)	7.21(7.25)
4a	4-$O_2NC_6H_4$	8	17.15	46.61(46.63)	4.88(4.92)	7.31(7.25)
3b	3,4-$OCH_2OC_6H_3$	5	40.76	50.03(49.88)	5.19(5.23)	3.76(3.64)
4b	3,4-$OCH_2OC_6H_3$	5	34.24	50.05(49.88)	5.25(5.23)	3.51(3.64)
3c	4-$O_2NC_6H_4$	5	41.08	46.68(46.63)	4.98(4.92)	7.17(7.25)
4c	4-$O_2NC_6H_4$	5	39.92	46.57(46.63)	4.86(4.92)	7.19(7.25)

[a]Isolated yield based on substituted vinylphosphonate.

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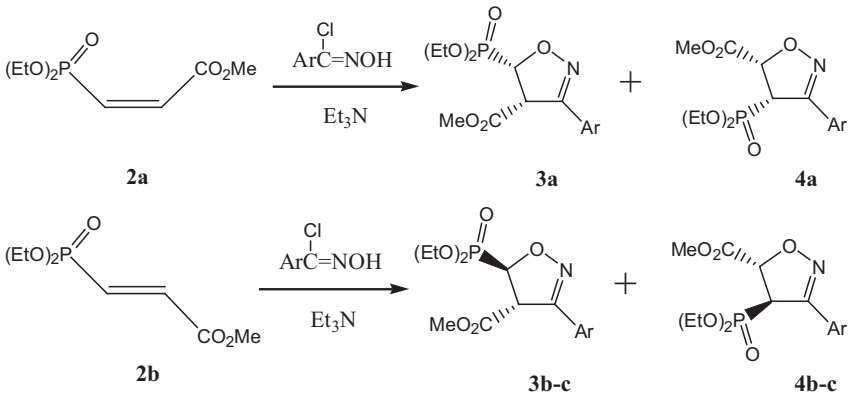
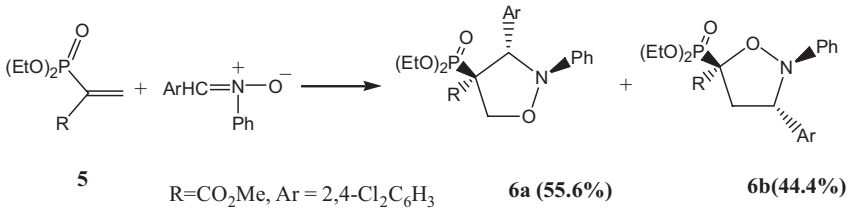


Scheme 2 Cycloaddition of nitrile oxides to α-substituted vinylphosphonates.

Table 2 The ^{1}H NMR data of compound **3** and **4**

	^{1}H NMR(ppm)
3a	1.23–1.37 (m, 6H); 3.76 (s, 3H); 4.19–4.26 (m, 4H); 4.82 (dd, 1H, *J* = 7.3, 21.88 Hz); 5.27 (d, 1H, *J* = 7.3 Hz); 7.90 (d, 2H, *J* = 8.98 Hz); 8.25 (d, 2H, *J* = 8.98 Hz)
4a	1.18–1.34 (m, 6H); 3.83 (s, 3H); 3.96–4.34 (m, 4H); 4.44 (dd, 1H, *J* = 4.18, 19.82 Hz); 5.49 (dd, 1H, *J* = 4.18, 21.9 Hz); 8.04 (d, 2H, *J* = 8.62 Hz); 8.25 (d, 2H, *J* = 8.62 Hz)
3b	1.16–1.30 (m, 6H); 3.66 (s, 3H); 4.10–4.17 (m, 4H); 4.73 (dd, 1H, *J* = 6.24, 22.41 Hz); 5.15 (d, 1H, *J* = 6.24 Hz); 5.93 (s, 2H); 6.73 (d, 1H, *J* = 8.20 Hz); 7.05 (d, 1H, *J* = 8.20 Hz); 7.18 (s, 1H)
4b	1.19–1.36 (m, 6H); 3.79 (s, 3H); 3.99–4.14 (m, 4H); 4.34 (dd, 1H, *J* = 3.14, 19.8 Hz); 5.42 (dd, 1H, *J* = 3.14, 21.3 Hz); 5.98 (s, 2H); 7.36 (s, 1H); 6.81 (dd, 1H, *J* = 8.28 Hz); 7.30 (dd, 1H, *J* = 8.28 Hz)
3c	1.23–1.37 (m, 6H); 3.73 (s, 3H); 4.19–4.29 (m, 4H); 4.81 (dd, 1H, *J* = 6.86, 21.88 Hz); 5.28 (d, 1H, *J* = 6.86 Hz); 7.90 (d, 2H, *J* = 8.45 Hz); 8.25 (d, 2H, *J* = 8.45 Hz)
4c	1.18–1.31 (m, 6H); 3.82 (s, 3H); 3.99–4.20 (m, 4H); 4.45 (dd, 1H, *J* = 3.14, 19.82 Hz); 5.55 (dd, 1H, *J* = 3.14, 20.86 Hz); 8.03 (d, 2H, *J* = 8.63 Hz); 8.25 (d, 2H, *J* = 8.63 Hz)



Scheme 3 Cycloaddition of nitrones to α-substituted vinylphosphonates.

We next examined the scope of electron-deficient alkene with a nitrone. When reacted with a nitrone, substituted vinylphosphonate showed analogous behaviour. *N*-benzylideneaniline *N*-oxide generated *in situ* from the corresponding nitro compounds reacted with vinylphosphonate **5** to give a mixture product **6a** and **6b** (shown in Scheme 3).

The reactions of vinylphosphonate **5** with *N*-benzylideneaniline *N*-oxide are very simple and convenient. After refluxing vinylphosphonate **5** in benzene with an excess of nitrone about 12 h, a mixture of isoxazolindines was produced. The adducts **6a** and **6b** can be separated by column chromatography. The ratio of isoxazolidine **6a** and **6b** is 55: 44. The differentiation between stereoisomers **6a** and **6b** was obvious and was based on observed chemical shifts.

We have developed a simple, convenient and efficient method for the synthesis of β-substituted vinylphosphonates and the novel structural heterocyclic compound containing a phosphonyl group. Applications of these heterocyclic compound are being examined.

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. Solvents used were purified and dried by standard procedures.

General procedure for cycloaddition of nitrile oxides to β-substituted vinylphosphonates

To a stirred solution of compounds 2 (2.0 mmol) and hydroxamic chlorides (2.2 mmol) in dry THF (20 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. 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 to give pure **3** and **4**.

Procedure for cycloaddition of nitrones to α-substituted vinylphosphonates

To a solution of the 2,4-dichlorophenyl nitrone (2.2 mmol) in benzene (15 ml) was added the vinylphosphonates 5 (2 mmol) and the resulting solution was heated under an N_2 atmosphere at reflux for 12 h. Then, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The cycloadduction products **6** were separated by column chromatography (eluenting with petroleum ether/ethyl acetate 7: 1).

6a: M.p. 128–130°C yield 41.28% Anal. Calcd. for $C_{22}H_{26}Cl_2NO_6P$: C 52.60, H 5.22, N 2.79, Found: C 52.80, H 5.29, N 2.80, ^{1}H NMR(ppm): 0.87–1.00 (m, 6H); 1.20–1.27 (m, 3H); 3.81–3.91 (m, 6H); 4.59 (dd, 1H, *J* = 18.76, 13.56 Hz); 4.99 (dd, 1H, *J* = 13.56, 9.38 Hz); 5.84 (d, 1H, NCH *J* = 18.35 Hz); 6.90 (m, 3H); 7.20 (m, 3H); 7.36 (s, 1H); 7.59 (d, 1H, *J* = 8.45 Hz).

6b: M.p. 110–112°C yield 33.02% Anal. Calcd. for $C_{22}H_{26}Cl_2NO_6P$: C52.6, H 5.22, N 2.79, Found: C 52.51, H 5.17, N 2.76, ^{1}H NMR(ppm): 1.20–1.38 (m, 9H); 2.88–3.01 (m, 1H); 3.25–3.45 (m, 1H); 4.17–4.30 (m, 6H); 4.85 (dd, 1H, NCH, *J* = 5.6,

9.82 Hz); 6.96–7.24(m, 6H, ArH); 7.39 (s, 1H, ArH); 7.48 (d, 1H, J = 8.44 Hz, ArH).

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