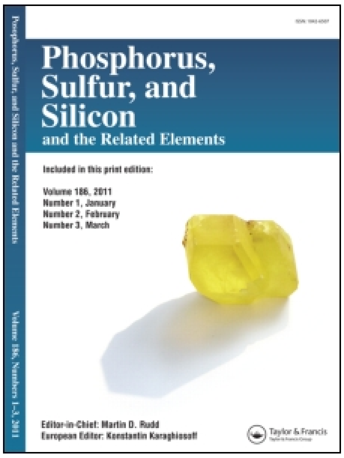

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Studies on Organophosphorus Compounds 103 Reaction of Dialkyl 1-Alkyl(Aryl)-2-Nitroeth-1-Enyl Phosphonates with Non-Carbon Nucleophiles

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 103 REACTION OF DIALKYL 1-ALKYL(ARYL)-2-NITROETH-1-ENYL PHOSPHONATES WITH NON-CARBON NUCLEOPHILES

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Dialkyl 1-alkyl-2-nitroeth-1-enyl phosphonates gave normal Michael addition products with alkoxide anions. Reaction of dialkyl 1-aryl-2-nitro-1-enyl phosphonate with oxygen and nitrogen nucleophiles afforded unexpected phosphoryl enolate or phosphoryl enamine respectively via NO_2/alkoxy or NO_2/amine substitution. A tentative mechanism was discussed.

Keywords: Michael addition; nucleophilic substitution; phosphonyl enolate and -enamine

INTRODUCTION

As polyfunctionalized phosphonic acid derivative, 1-alkyl(aryl)-2nitro eth-1-enylphosphonates (1-alkyl(aryl)-2-nitrovinylphosphonate for short) are of particular interest as a building block in organic synthesis. The Michael addition of active methylene anions as carbon nucleophiles to 2-nitrovinylphosphonate has been described.[1] The investigation of chemical performance of 1-alkyl or 1-aryl-2-nitrovinylphosphonates during nucleophilic reaction aroused our interest. Meanwhile, our trials on the nucleophilic addition of carbanion derived from acetylacetone toward 1-aryl-2-nitrovinylphosphonate was unsuccessful.[2]

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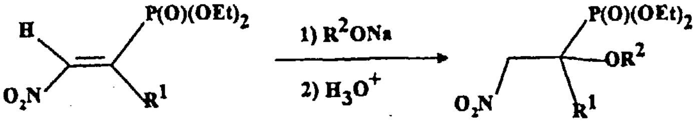
* Dedicated to Professor William E. McEwen on the occasion of his 75th birthday.

Direct addition of alkoxide anion to nitroalkene constitute a general method for the preparation of nitroalkylether[3, 4]. The yield of such a reaction is usually poor due to partial polymerization of the nitroalkenes. As found by Feuer and Markofsky[5], in the reaction of alkali alkoxide with 2-nitroalkene generated in situ from 2-nitroalkyl acetate, the yield of 1-alkoxy-2-nitroalkane was improved markedly. Investigation of the nucleophilic addition of phosphorylated nitroalkene was encourageable. It concerns a compound bearing two electron-withdrawing nitro and phosphoryl groups separated by a double bond in a sterically hindered molecule. To the best of our knowledge, such a reaction has apparently not been reported in the literature.

RESULTS AND DISCUSSION

Diethyl 2-nitrovinyl-1-phosphonate underwent normal Michael addition with compounds bearing active methylene anion[1], while diethyl 1-aryl-2-nitrovinylphosphonate failed to react with acetylacetone anion[2]. In this paper we would like to report the performance of dialkyl 1-alkyl and/or 1-aryl-2-nitrovinyl-1-phosphonates toward non-carbon nucleophiles.

As expected, 1-alkyl-2-nitrovinylphosphonates gave normal Michael addition products with alkoxide anions (Scheme 1 and Table I)



SCHEME 1

TABLE I Synthesis of 1-alkyl-1-alkoxy-2-nitro-ethylphosphonates (2)

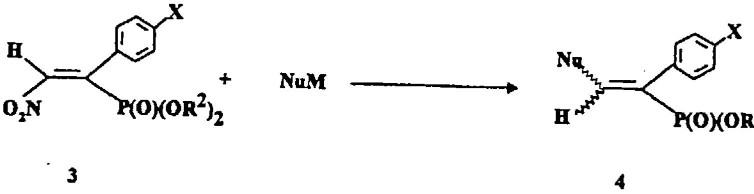
Entry	R^1	R^2	*Yields (%)*
2a	Me	$CH{=}CHCH_2$	61
2b	Me	Et	62
2c	Et	Me	56

The formation of 1-alkoxy derivative (2) can be rationalized by the charge density of α- and β- carbon calculated by the Grasateiger and Marsili method (Table II)[6]

TABLE II The partial charge density at α- and β- carbon atom in 2-nitrovinylphosphonate (2)

Entry	R^1	R^2	α	β
1	Et	Et	-0.014	-0.027
2	n-Pr	Et	-0.014	-0.027
3	Ph	Et	0.058	0.027
4	p-MeC_6H_4	Me	0.051	0.019
5	m-MeC_6H_4	Et	0.056	0.024
6	p-FC_6H_4	Et	0.054	0.022
7	p-ClC_6H_4	Et	0.060	0.029
8	Ph	i-Pr	0.058	0.027
9	p-MeC_6H_4	i-Pr	0.051	0.019

As shown in Table II, among the compounds studied, the α-carbon atom bear more positive charge than the β-carbon atom. Consequently, nucleophilic attack of alkoxy anion at α- position is reasonable.



X= H, F

Nu^-= MeO^- (a), EtO^- (b), $CH_2{=}CHCH_2O^-$ (c), $C_8H_{17}NH^-$ (d), $PhNH^-$ (e)

M^+= Na^+, Li^+

SCHEME 2

In case of 1-aryl-2-nitrovinylphosphonate, as found by us, diethyl 1-phenyl-2-nitrovinylphosphonate was inactive toward the allyloxy anion under the conventional reaction conditions. However, when the reaction temperature was raised to 5°C, to our surprise, diethyl-2-allyloxy-1-phenylphosphonate was formed. Obviously, this unexpected result arose from substitution of the nitro group by the allyloxy moiety. The geometry of the double bond in the starting alkene was reserved in the product as demonstrated by the magnitude of the coupling constant in the ^1H NMR spectrum. This unusual reaction motivated us to study the reaction of non-carbon nucleophiles namely oxygen and nitrogen nucleophiles with 1-aryl-2-nitrovinylphosphonates. The results are as shown in Scheme 2 and Table III.

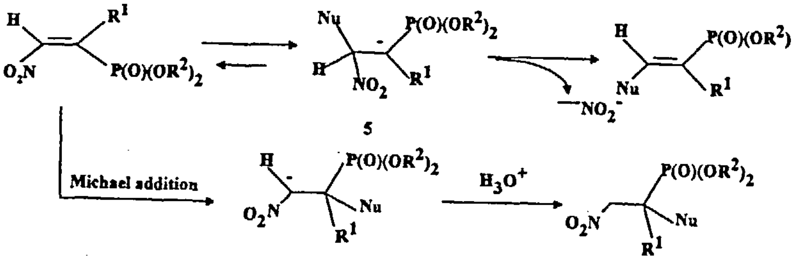
TABLE III The substitution reaction resulting between 1-aryl-2-nitrovinyl-1-phosphonate and oxygen and nitrogen nucleophiles

Product	*Substituent X*	*NuM*	*Yield(%)*	*E:Z*
4a	H	MeONa	45	100:0
4b	H	EtONa	54	100:0
4c	H	CH_2=$CHCH_2ONa$	47	100:0
4d	F	CH_2=$CHCH_2ONa$	46	100:0
4e	H	$C_8H_{17}NHLi$	42	84 :16
4f	H	PhNHLi	44	71:29

The oxygen nucleophiles were obtained by adding sodium hydride to the corresponding alcohol at room temperature and the nitrogen nucleophiles were prepared by introducing butyl lithium to the corresponding amine at –70°C. The configuration of the product was determined by using the coupling constant of the ethenylic proton to phosphorus ($^3J_{PCCH}$). The ratio of the E/Z forms were calculated from the integral ratio of the corresponding ^{31}P NMR shifts of the isomers.

The substitution reaction demonstrated by the experimental results, is fully unexpected due to the following structure factors. First of all, the nitro group is a good activator for alkene in Michael addition. It means that nitrovinylphosphonate is favourable to Michael addition. Besides this, the nitro group is a poor leaving group, particularly for that located on a sp^2 carbon atom. Finally the electron-withdrawing ability of the nitro group is better than that of the phosphoryl or even carbonyl group. Nucleophilic addition should take place on the α- position that is away from the nitro terminal as clearly demonstrated in Table III.

Due to the fact that the reaction proceeded by addition of the anion to 1-alkyl(aryl)-2-nitrovinylphosphonate and the formation of the characteristic color for ions, the substitution of the nitro group seemed to take place through the ionic process rather than a radical path way. Thus, a tentative reaction mechanism was suggested by us. (Scheme 3)

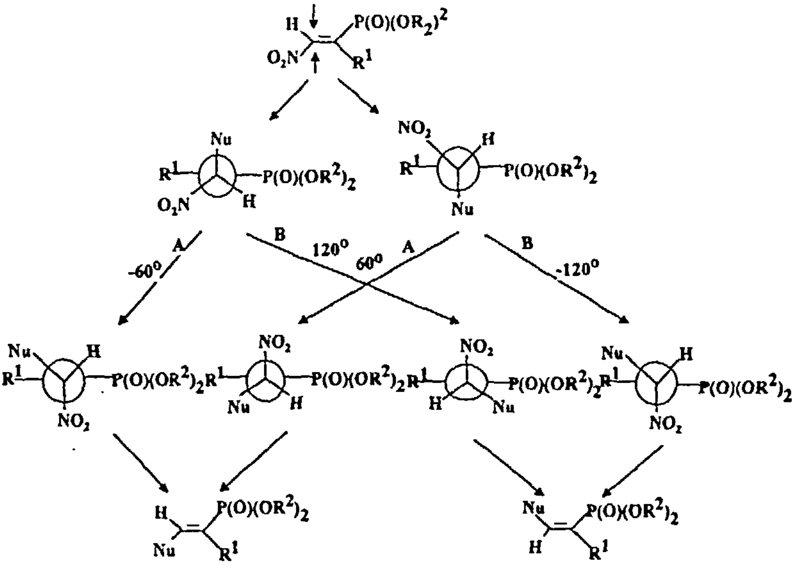


SCHEME 3

Formation of a dual stabilized ionic intermdiate 5, 1-aryl-2-nitrovinylphosphonate(R′=aryl) is favorable for an elimination pathway. However, in case of nitrostyrene or 1-alkyl-2- nitrovinylphosphonate, normal Michael addition reaction should take place.

The suggested reaction mechanism involves two steps consisting of addition and elimination. Our attempts to trap the anionic intermediate by adding ethanol as protic solvent to the system was unsuccessful. Furthermore no Wittig-Horner product could be formed by addition of propionaldehyde and 2-nitrovinylphosphonate to the resulting anionic species. These experimental results illustrate that elimination of the nitro group is a very fast process. This kinetic behavior could also serve as a basis for the stereochemistry involved in this reaction. (Scheme 4)

Since the rotation of the C-C bond is slower than the leaving of the NO_2 group, the reaction proceeds by pathway A and thus provides the E-isomer. Otherwise, the Z-isomer should result if pathway B is followed. In the present case, due to the rapid elimination of the nitro group, the reaction provides predominately E isomers.



SCHEME 4

It should be emphasized that NO_2/alkyl substitution at the vinylic carbon was reported by Seebach et al[7]. More recently as described by Huang[8] similar substitution was observed with trialkyl gallium through a radical mechanism. The reaction illustrated in this paper served not only as a supplement of N_{O2} / alkyl substitution at the vinylic carbon atom of phosphoryl nitrostyrene with sodium alkoxides or lithium amides but in our opinion, it provides a convenient access to stereoselective phosphoryl enolates or enamines.

EXPERIMENTAL

The melting points are uncorrected. Infrared spectra were obtained on a Shimadzu-440 spectrometer. ^1H and ^{31}P NMR spectra were recorded on Varian XL-200 and a Joel FX 90Q spectrometers respectively using $CDCl_3$ as solvent. Chemical shifts for ^1H and 31P NMR are reported in ppm downfield from TMS and 85% H_3PO_4 as internal and external standard. Spectra for EI-MS were taken on a Finnigan 4201 mass spectrometer.

Diethyl 1-methyl-1-allyloxy-2-nitroeth-1-phosphonate (2a), Typical procedure

To a three-necked flask (100 mL) fitted with a septum cap, thermometer and a nitrogen-inlet was introduced freshly distilled anhydrous THE (20 mL) and then added from a syringe through a rubber cap redistilled allyl alcohol (0.28 mL, 4 mmol) followed by rapid addition of NaH (96 mg, 4 mmol). The reaction mixture was then stirred half an hour at ambient temperature. Evolution of hydrogen was observed. After that, a THF solution of diethyl 1-methyl-2-nitrovinylphophonate (446 mg, 2 mmol) was introduced by a syringe through a rubber cap, A pale yellow reaction mixture resulted in this stage. After being stirred over night at r.t., the reaction mixture turned dark brown. The resultant was neutralized with 1 N HCl and washed with brine. The separated organic solution was dried (Na_2SO_4) and filtered. The residue obtained upon removal of solvent in a rotatory evaporator was purified by column chromatography on silica gel using 95% EtOH:EtOAc (1:1) as eluent. 2a was obtained as a colorless liquid. Yield 346 mg or 61%

IR (film): 1560, 1380(NO_2), 1250(P=0, 10 20(P-O-C) cm^{-1}

^1H NMR(CCl_4) δ: (1.20(t, J=7, 6H, $2OCH_2CH_3$), 1.43(d, J=15, 3H,CH_3), 4.03(t-q, J=7,7, 4h, $2OC\underline{H}_2CH_3$), 4.26(d, J=7, 2H, CH_2NO_2),4.49(d, J=4, 2H, -$OC\underline{H}_2CH=CH_2$), 5.30(d-d, J=7,9,1H, $OCH_2CH=C\underline{H}_2$),5.86–5.96(m, 1H, OCH_2-$C\underline{H}=CH_2$)

^{31}P NMR ($CDCl_3$) : 20.3(s)

EIMS(m/e): 282$(M-H)^+$, 235(M^+-46), 179(m^+-C_3H_5),109(PO_3 Et^+-C_2H_4)

Anal. Calcd. for: $C_{10}H_{20}NO_6P$(281.25) C, 42.71 H, 7.17 N, 4.98%

Found: C, 42.35 H, 7.08 N, 4.51%.

1-methyl-1-ethoxy-2-nitroeth-1-phosphonate (2b)

Was prepared similarly as described for **2a** from 1-methyl-2-nitrovinylphosphonate and sodium ethoxide. **2b**was obtained as a colorless oily liquid. Yield 336 mg or 62%.

IR(film): 1560, 1360(NO_2), 1220(P=O), 1010(P-O-C) cm^{-1}

^1H NMR: (CCl_4) δ : 1.10 ~ 1.50(m, 12H, CH_3, $3OCH_2C\underline{H}_3$) ; 3.80 – 4.30(m, 8H, $3OC\underline{H}_2CH_3$, CH2NO_2)

EIMS(m/e): 270(M-H)$^+$, 224(M$^+$-NO$_2$), 121(M+-2C$_2$H$_4$-NO$_2$-C$_2$H$_5$ OH), 149(M$^+$-CH$_2$NO$_2$-CH3-OC2H5)

Anal. Calcd. for $C_9H_{20}NO_6P$ (269.24): C, 40.15 H, 7.49 N, 5.20%

Found: C, 40.20 H, 7.45 N, 5.29%.

Diethyl 1-ethyl-1-methoxy-2-nitroeth-1-phosphonate (2c)

Was prepared similarly as described for **2a.** From 1-ethyl-2-nitrovinyl-1-phosphonate and sodium methoxide; **2c** was obtained as a colorless liquid, yield 300 mg or 56%.

IR(film): ν:1560, 1370(NO$_2$), 1210(P=O), 1010(P-O-C) cm^{-1}

^{1}H NMR(CCl$_4$) δ : 1.00 ~ 1.50(m, 11H, 2OCH$_2$C$\underline{H}_3$, C$\underline{H}_3$C$\underline{H}_2$),3.40 ~ 3.80(m, 9H, OCH$_3$, 2OCH$_2$CH$_3$,CH$_2$NO$_2$) EIMS(m/e): 268(M$^+$-1), 99(M$^+$-2CH3CH2CH-CH3OH-NO$_2$), 81(PO$_3$H$_2$$^+$)

Anal. Calcd. for $C_9H_{20}NO_6P$ (269.24): C, 40.15 H, 7.49 N, 5.20%

Found: C, 39.95 H, 7.55 N, 5.32%.

Diethyl 1-phenyl-2-methoxy-vinylphosphonate (4a)

Was prepared analogously as **2a** l.c. except petroleum ether: EtOAc (1:2) was used as eluent in column chromatographic separation starting from 1 -phenyl-2-nitrovinylphosphonate and sodium methoxide. **4a** was obtained as a pale yellow, oily liquid, yield 127 mg or 45%.

IR(film): ν: 1600(ph), 1220(P=0), 1030(P-O-C) cm^{-1}

^{1}HNMR (CCl$_4$) δ: 1.16(t, J=7, 6H, 2OCH$_2$C$\underline{H}_3$), 3.80(s,3H, OCH$_3$),3.96(t-q, J=7,7, 4H, 2OC$\underline{H}_2$CH$_3$), 6.90 ~ 7.40(m, 6H, ph, =H) ^{31} PNMR(CCDC13) δ: 21.3(s)

EIMS(m/e): 270(M$^+$), 225(M$^+$-CH$_3$), 199(M$^+$-C$_2$H$_4$-CH$_3$)

HRMS: 270.0992 Cacld. for $C_{13}H_{19}O_4P$ 270.2623

Diethyl 1-phenyl-2-ethoxy-vinylphosphonate (4b)

Was prepared analogously as **4a; 4b** was obtained as a pale yellow, oily liquid. Yield 54%

IR(film) ν:1620(Ph), 1220(P=O), 1020(P-O-C) cm^{-1}

^{1}H NMR(CCL$_4$) 6: 1.20(t, J=7, 6H, 2CH$_2$C$\underline{H}_3$), 1.27(t, J=7, 3H, OCH$_2$C$\underline{H}_3$), 3.73 ~ 4.23(m, 6H, 2P(O)OC$\underline{H}_2$CH$_3$, OC$\underline{H}_2$CH$_3$), 7,00 ~ 7,40(m, 5H, ph)

^{31}P NMR(CDCl$_3$) δ : 22.3 (s)

EIMS(m/e): 285(M+1$^+$), 255(M$^+$-C$_2$H$_5$), 199(M$^+$-C$_2$H$_5$-2C$_2$H$_4$) 102(M$^+$-OC$_2$H$_5$-2C$_2$H$_4$)

HRMS : 284.1220 Cacld. for C$_{14}$H$_{21}$O$_4$P 284.2913

Diethyl 1-phenyl-2-allyloxy-vinylphosphonate (4c)

Was prepared analogously as **4a; 4c** was obtained as a pale yellow, oily liquid. Yield 154 mg or 47%.

IR(film) ν: 1600(Ph), 1240(P=O), 1020(P-O-C) cm^{-1}

^{1}HNMR (CCl$_4$) δ : R (CCl$_4$): 6 : 1.25(t,, J=7, 6H, 2OCH$_2$C$\underline{H}_3$), 4.08(t-q, J=7, 7, 2OC$\underline{H}_2$CH$_3$), 4.49(d, J=4, O-C$\underline{H}_2$-CH=CH$_2$, 2OC$\underline{H}_2$CH$_3$), 5.03(d-d, 2H, OCHCH=C$\underline{H}_2$, J=7, 9 Hz), 5.86–5.96 (m, 1H, OCH$_2$-C$\underline{H}$=CH$_2$), 7.23–7.34(m, 4H, Ph), 7.46–7.48 (m, 2H, Ph) ^{31}P NMR(CDCl$_3$) δ : 24.7(s)

EIMS (m/e): 296(M$^+$), 268 (M$^+$-C$_2$H$_4$), 199(M$^+$-2C$_2$H$_4$-C$_3$H$_5$)

HRMS: 296.1145; Cacld for C$_{15}$H$_{21}$O$_4$P 296.3023

Diethyl 1-p-fluorophenyl-2-allyloxy-vinylphosphonae (4d)

Was obtained analogously as **4a**, starting from diethyl 1 -(fluorophenyl)-2-nitrovinylphosphonate (285 mg, 1 mmol) and sodium allyloxide as a pale yellow, oily liquid, yield 144 mg or 46%.

IR (film) ν: 1560(Ph), 1220(P=0), 1020(P-O-C) cm^{-1}

^{1}H NMR(CCl$_4$) δ : 1.20(t, J=7, 6H, 2OCH$_2$C$\underline{H}_3$), 3.96(t-q, J=7,7, 4H, 2OC$\underline{H}_2$CH$_3$), 4.40(d, J=4, 2H, -OC$\underline{H}_2$CH=CH$_2$), 5.23(d-d, J=7, 9, 2H,-OCH$_2$CH=C$\underline{H}_2$),5.53–6.03(m, 1H, -OCH$_2$C$\underline{H}$=CH$_2$).6.70–7,50(m, 5H, ph, =H)

^{31}P NMR δ : 21.4(s)

19F NMR 6 : –38.0(s)

EIMS (m/e): 314(M$^+$), 286(M$^+$-C$_2$H$_4$), 217(M$^+$-C$_3$H$_5$-2C$_2$H$_4$)

HRMS: 314.1080 Calcd. For C$_{15}$H$_{21}$PO$_4$F 315.3009

Diethyl 1-phenyl-2-octylaminevinylphosphonate (4e)

Was prepared analogously as **4a.** Starting from diethyl 1-phenyl-2-nitrovinylphosphonate and lithium octylamide prepared from n-octylamine (0.34 mL 2 mmol) and a hexane solution of n-butyl lithium (1.4 M hexane solution 1.44 mL, 2 mmol) at –70°C. After column chromatography on silica gel(petroleum ether: EtOAC=1:2 as eluent, if **4f** was obtained in 42% yields. IR(film) ν:1600(Ph), 1260(P=0), 1010(P-O-C) cm^{-1}

^1H NMR (CCl_4) δ : 0.67–1.77(m, 23H, $20CH_2C\underline{H}_3$,$C_8\underline{H}_{17}$),

2.87 ~ 3.17(m, 1H, NH), 3.82(t-q, J=7,7, 4H, $20C\underline{H}_2CH_3$)6.87 ~ 7,53(m, 5H, ph, =CH)

^{31}P NMR ($CDCl_3$) δ: 15.7,16.0

EIMS(m/e): 367(M^+), 268(M^+-C_3H_7-$2C_2H_4$)

Anal.Calcd.for $C_{20}H_{34}NO_3P$ (367.26) : C, 65.37 H, 9.33 N, 3.81% Found: C, 65.02 H, 9.09 N, 3.76%.

Diethyl 1-phenyl-2-phenylvinylphosphonate (4e)

Was prepared analogously as **4a.** Starting from diethyl 1-phenyl-2-nitrovinylphosphonate and lithium phenylamide prepared from aniline and n-butyl lithium. **4f** was obtained as a pale yellow, oily liquid. Yield 44%

IR(film) ν: 1550(Ph),1220(P=O),1010(P-O-C),3200(NH) cm^{-1}

^1H NMR(CCl_4) δ: 1.33(t, J=7, 6H, $20C\underline{H}_2C\underline{H}_3$), 4.03(m, 5H, $2OC\underline{H}_2CH_3$,NH),6.80–7.50(m, 11H, Ph, NHPh, =CH)

^{31}P NMR ($CDCl_3$) δ: 21.4,22.0

EMS (m/e) : 331(M^+), 193(M^+-PO_3EtH)

Anal.Calcd.for $C_{18}H_{22}NO_3P$(331.35) : C, 65.28 H, 6.69 N, 4.23% Found: C, 65.73 H, 6.58 N, 4.45%.

Acknowledgements

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