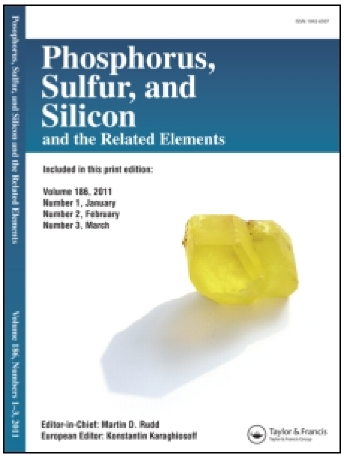

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 102. A CONVENIENT STEREOSPECIFIC SYNTHESIS OF DIALKYL 1-ALKYL(ARYL)-2-NITROETH-1-ENYLPHOSPHONATES

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 102

A Convenient Stereospecific Synthesis of Dialkyl 1-Alkyl(Aryl)-2-nitroeth-1-enylphosphonates

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Dialkyl 1-alkyl(aryl)-2-nitroeth-1-enylphosphonates were prepared by treatment of dialkyl 1-alkyl(aryl)-1-hydroxyl-2-nitroalkylphosphonates with thionyl chloride and pyridine. The dehydration process underwent stereospecifically providing exclusively the E-isomers. An E2 reaction mechanism was suggested.

Keywords: nitrovinylphosphonates; stereospecific dehydration; E2 mechanism

INTRODUCTION

Dialkyl 1-alkyl(aryl)-2-nitroeth-1-enylphosphonates(dialkyl 1-alkyl(aryl)-2-nitrovinylphosphonates for short) are the important intermediates for the synthesis of functionalized phosphonic acids owing to the presence of reactive alkene and nitro groups. It was expected that nucleophilic addition and subsequent reduction would result in 2-aminoalkylphosphonic acid derivatives as potential biolgically active molecules.[1] On the other hand, the conversion of a nitro group into a silylnitronate as a reactive 1,3-dipole provides a new synthetic route to phosphoryl isoxazoles.[2] Chemical investigation of the conjugated system containing vicinal nitro and phosphoryl groups separated by a double bond is interesting

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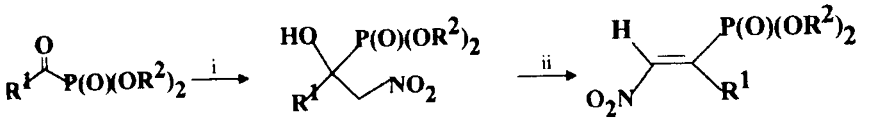
*Corresponding author.



1 2

i: CH_3NO_2, K_2CO_3/Bu_4NBr ii: $SOCl_2/NEt_3$

R^1=Me, Et, n-Pr, t-Bu, Ph, p-MeC_6H_4, m-MeC_6H_4, p-FC_6H_4, p-ClC_6H_4

both in organophosphorus chemistry and its potential utility as building block in organic synthesis.

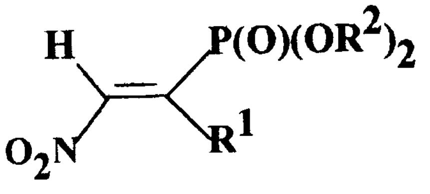
The classical Arbuzov rearrangement involving trimethyl phosphite and 2-bromonitropropene afforded a distereoisomeric mixture of dimethyl 1-isopropyl-2-nitrovinylphosphonate in 70% yield.[3] Baranov and Perekalin described the preparation of (E) dialkyl 1-alkyl-2-nitrovinylphosphonates from dialkyl 1-hydroxy-2-nitroalkylphosphonates by various approaches including the increase of the leaving ability of the hydroxyl group by converting it to the corresponding acetate or chloride. Nevertheless, direct dehydration with thionyl chloride in the presence of pyridine was successful in some cases.[4] The above method covered only a limited number of examples and the substrate was prepared by use of the highly toxic dinitrogen tetraoxide. This method is therefore not to be considered as a general synthetic route leading to the target molecule. Moreover, the stereochemistry involved in that transformation was not examined yet.

RESULTS AND DISCUSSION

A convenient synthesis of dialkyl 1-alkyl or 1-aryl 1-hydroxy-2-nitroethylphosphonates was described by us based on the nucleophilic addition of nitromethane to dialkyl acylphosphonate in the presence of potassium carbonate and tetrabutylammonium bromide.[5] It provided us a basis for the systematic study of the chemical conversion of this series of compounds during dehydration with thionyl chloride in the presence of pyridine. The results are illustrated in Scheme 1 and Table I.

Conversion of **1** to **2** under mild conditions by use of methanesulfonyl chloride/triethyl amine in tetrahydrofuran at −40°, provided, as a rule, a very low yield (< 17%) of the dehydration product. However, thionyl chloride/pyridine gives a higher yield (> 50%) of **2**. As found by us, this reaction undergoes

TABLE I Preparation of (E) dialkyl 1-alkyl(arkyl)-2-nitrovinyl phosphonates(**2**)



	R^1	R^2	*mp (°C) bp(mm)*	*Yield (%)*	*^{31}P NMR (δ, ppm)*	*^1H NMR (δ,ppm, 1H, = CH,J = Hz)*
2a	Me	Me	86–87(1)[4]	62	12.5	7.37 (J = 15.3)
2b	Me	Et	87–88(1)[4]	65	14.6	7.30 (J = 15.3)
2c	Me	i-Pr	85–86(1)[4]	57	15.0	7.37 (J = 15.3)
2d	Et	Et	oil	55	15.9	7.21 (J = 15.3)
2e	n-Pr	Et	oil	51	15.9	7.42 (J = 15.0)
2f	Ph	Et	88–90	63	11.8	7.45 (J = 15.3)
2g	p-MeC_6H_4	Me	52–56	59	15.0	7.59 (J = 15.0)
2h	m-MeC_6H_4	Et	45–47	61	12.0	6.90–8.00 (m,5H,Ph, = CH)
2i	p-FC_6H_4	Et	32–36	66	11.7	7.43 (J = 15.3)
2j	p-ClC_6H_4	Et	39–40	58	14.9	8.13 (J = 15.3)

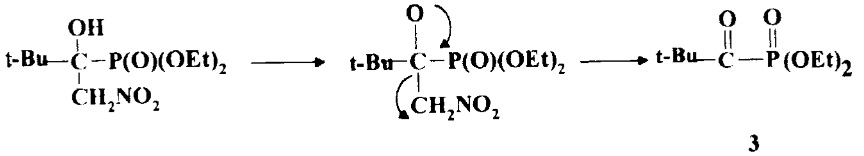
The preparation of **2a**, **2b** and **2c** was described by Baranov.[4] Other compounds in Table I are not published yet.

smoothly in boiling chlroform at about 60°C for a wide range of structures as indicated in Table I.

Since compounds **1** are unstable in alkaline medium due to C-C bond cleavage and the resultants **2** are easily polymerized at temperature higher than 65°C, care should be taken during the dehydration process by $SOCl_2$ /pyridine. The optimal reaction conditions are as follows: to an equimolar mixture of **1** and thionyl chloride in chloroform, two equimolar amounts of pyridine were added dropwise under vigorous stirring and refluxing of the reaction mixture. As indicated by the TLC, the dehydration reaction takes place as soon as the addition of pyridine starts. In order to eliminate side reactions, the reaction time should be limited to 15 min.

It should be pointed out that the presence of a bulky group will hinder the dehydration process and will provide the corresponding acylphosphonate (Scheme 2)

The fact that the dehydration products **2** showed only one peak in ^{31}P NMR spectra indicates stereospecific feature of the reaction showed. On the other hand, ^1H NMR of the product a doublet splitting for =CH with J = 15 Hz. This splitting is no doubt due to coupling with ^{31}P atom. According to the general conception, the magnitude of the $^3J_{PCCH}$ in this region is characteristic for E-



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isomer. As demonstrated by Benezra[6] vicinal $^3J_{PCCH}$ versus PCCH dihedral angles in phosphonates exhibit Karplus-like curves. The stable conformation of **1** is as shown in Scheme 3. Due to the fact that $^3J_{PCCH}$ of **1** are around 7, the two PCCH dihedral angles are about 60°.[7]

Based on the postulation of Evans,[8] Baranov suggested that the dehydration of **1** with $SOCl_2$ /pyridine proceeded through the formation of intermediate sulfonylpyridne-4-pyridinum chloride(**4**)

This intermediate **4** will provide a thermodynamically more stable E-isomer via the E1 mechanism. However, by this mechanism it is impossible to rationalize the experimental observations including the marked steric hindrance from bulky R^1 and the formation of the E conformer stereoselectively. It is important to note that the E-form is not always thermodynamically favorable according to the Maximum 2 molecular calculation (Table II))

Consequently, the experimental results allow us to postulate the following reaction mechanism (Scheme 3).

Reaction of the hydroxyl group with thionyl chloride is followed by addition of pyridine to form the easy leaving species sulfonylpyridinum chloride. At the same time, another molecule of pyridine attacks the hydrogen at the β-position and the leaving of the sulfonylpyridinium group forms a double bond. In this process, the C-C bond does not rotate, the conformation is kept. To sum up, a stereospecific (E) 2-nitrovinylphosphonate results.

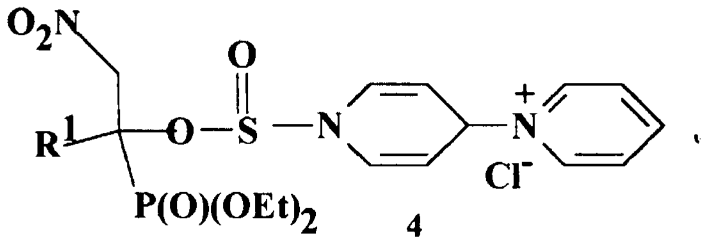

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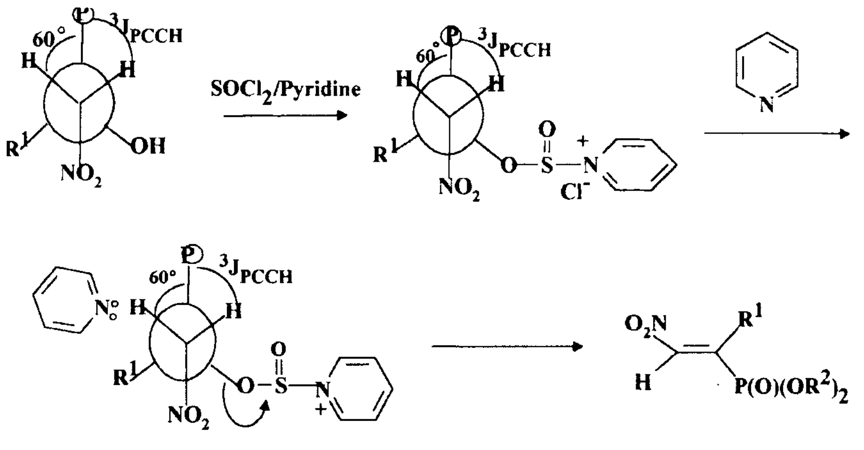
TABLE II Energy difference between E and Z forms of **2**

	*R^1^*	*R^2^*	*Energy (K cal/mol)*		
			E form	*Z form*	*E-Z*
2d	Et	Et	4.686	4.616	0.070
2e	n-Pr	Et	6.417	5.397	0.750
2f	Ph	Et	7.258	7.870	−0.612
2h	m-MeC_6H_4	Et	7.704	9.031	−1.327
2i	p-FC_6H_4	Et	6.975	7.820	−0.845
2j	p-ClC_6H_4	Et	6.539	5.897	0.642
2k	Ph	i-Pr	5.283	3.867	1.416
2l	p-MeC_6H_4	i-Pr	6.338	5.651	0.687

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 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 standards. Spectra for EI-MS were taken with a Finnigan 4201 mass spectrometer.

Trimethyl phosphite and triethyl phosphite were purchased from Fluka, Switzerland. Other reagents were obtained from local commercial sources. THF was freshly distilled from sodium benzophenone. Trichloromethane was dried over phosphorus pentaoxide. Pyridine was distilled from sodium hydroxide. Thionyl chloride was purified by distillation prior to use.



Diethyl 1-isopropyl-1-hydroxy-2-nitroethylphosphonates(1c)

To a mixture of diethyl isobutyryl phosphonate(0.03 mol), prepared by reaction of isobutyryl chloride with triethylphosphite via Arbuzov rearrangement,[9] and $MeNO_2$(20 ml) was added to a mixture of K_2CO_3 (0.5 g) and Bu_4NBr(0.5 g). The mixture was stirred at r.t. until no acylphosphoate could be detected on a TLC plate, The reaction mixture was worked as described for other diethyl 1-alkyl-1-hydroxy-2-nitroethylphosphonate.[5] Column chromatography on silica gel gave the product as a crystalline solid. mp 53°C. yield 70%

^1H NMR($CDCl_3$) δ: 1.00(d, J = 7, 7H, $2CH(CH_3)_2$), 1.23(t, J = 7, 6H, $2OCH_2CH_3$), 3.9–4.5(m, 7H, $2OCH_2CH_3$, CH_2NO_2 OH).

Anal. Cacld. for $C_9H_{20}NO_6P$(269.24): C 40.15 H 7.49 N 5.20 Found: C 40.34 H 7.52 N 5.31

Diethyl 1-t-butyl-1-hydroxy-2-nitroethylphosphonates(1d)

was prepared analogously as a crystalline solid, mp. 57°C, yield 71%

^1H NMR($CDCl_3$) δ:1.00(s, 9H, $C((CH_3)_3)$, 1.23(t, J = 7, 6H,$2OCH_2CH_3$), 4.73(m, 3H, CH_2NO_2 OH)

Anal. Cacld. for $C_{10}H_{20}NO_6P$(283.27): C 42.40 H 7.82 N 4.75 Found: C 41.95 H 7.53 N 4.31

Diethyl 1-phenyl-2-nitrovinylphosphonate (2f) General procedure

A solution of diethyl 1-phenyl-1-hydroxy-2-nitroethylphosphonate (1.5 g, 5 mmol) in $CHCl_3$(40 ml) was heated to reflux under nitrogen. Under vigorous stirring, thionyl chloride (0.37 ml, 5mmol) was added slowly and then followed by addition of pyridine(0.81 ml, 10 mmol) dropwise. After 15 min reaction, the mixture was cooled and then washed with brine until pH 7. The organic layer was dried(Na_2SO_4) and concentrated to provide the crude product which was then purified by column chromatography on silica gel using EtOAc/petroleum (1:1) as eluent. A slightly yellow solid with mp. 88–90°C and 63% yield was obtained.

IR(KBr)ν: 1600(=), 1540, 1380(NO_2), 1260(P=O), 1010(P-O-C) cm^{-1}

^1H NMR ($CDCl_3$): δ: 1.12(t, J = 7, 6H, $2OCH_2CH_3$), 3.95(d-q, J = 7, 7, 4H, $2OCH_2CH_3$), 7,18(S, 5H,ph), 7.45(d, 1H, J = 15.3, =CH)

^{31}P NMR ($CDCl_3$): δ: 11.8(S)

EIMS: 286$(M + 1)^+$, 102(M^+-NO_2-PO_3Et), 109(PO_3Et^+), 81(PO_3^+)

Anal. Calcd. for $C_{12}H_{16}NO_5P$(285.24): C 50.53 H 5.65 N 4.91 Found: C 50.51 H 6.28 N 5.03

Diethyl 1-ethyl-2-nitrovinylphosphonate(2d)

was prepared similar to the method described for **2f**. **2d** was obtained as a pale yellow liquid, 0.56 g or 55% yield.

IR(film) ν: 1350, 1550(NO_2), 1250(P=O),1050(P-O-C) cm^{-1}

^1H NMR (CCl_4): δ: 1.00–1.43(m, 9H, CH_3CH_2, $2OCH_2CH_3$), 2.23–2.83(d-q, J = 18,7,2H, CH_3CH_2), 3.82–4.23(d-q, 4H, CH_2O), 7.21(d, J = 15.3, 1H, =CH) ^{31}P NMR ($CDCl_3$): δ: 15.9(S)

Diethyl 1-propyl-2-nitrovinylphosphonate(2e)

was prepared similar to the method described for **2f**. **2e** was obtained as a pale yellow liquid, 0.64g or 57% yield.

IR(film)ν: 1350, 1550(NO_2), 1260(P=O), 1050(P-O-C) cm^{-1}

^1H NMR (CCl_4)δ: 0.9–1.8(11H, m, OCH_2CH_3, $CH_2CH_2CH_3$), 2.4–2.9(d-t, J = 18,7,2H, CH_3CH_2), 4.20(d-q, J = 7,7, 4H, $2OCH_2CH_3$), 7.42(d, J = 15.0, 1H, =CH)

^{31}P NMR ($CDCl_3$): δ: 15.9(S)

EIMS: 252$(M + 1)^+$, 149(M^+-NO_2-$2C_2H_4$), 223(M^+-C_2H_4)

Anal. Calcd. for $C_9H_{18}NO_5P$(251.22): C 43.03 H 7.22 N 5.58 Found: C 42.44 H 7.08 N 4.51

Dimethyl 1-p-totyl-2-nitrovinylphosphonate (2g)

was prepared by dehydrating dimethyl 1-p-tolyl-1-hydroxy-2-nitroethylphosphonate similar to the method described for **2f**. **2g** is a slightly yellow crystalline solid, mp 52–56°C, yield 0.8g or 59%.

IR(KBr): ν: 1530, 1360(NO_2), 1230(P=O), 1050(P-O-C) cm^{-1}

^1H NMR ($CDCl_3$): δ: 2.37(S, 3H, CH_3), 3.77(d, J = 12,6H,$2OCH_3$), 7,19(m, 4H,ph), 7,59(d, J = 15, 1H, =CH)

^{31}P NMR ($CDCl_3$): δ: 15.0(S)

EIMS: 271$(M + 1)^+$, 109$(PO_3Et)^+$, 115(M^+-PO_3Me_2-NO_2-H)

Anal. Calcd. for $C_{11}H_{14}NO_5P$(271.22): C 48.72 H 5.20 N 5.17 Found: C 48.68 H 4.93 N 4.81

Diethyl 1-m-totyl-2-nitrovinylphosphonate (2h)

was prepared by dehydrating diethyl 1-m-tolyl-1-hydroxy-2-nitroethylphosphonate similar to the method described for **2f**. **2h** is a slightly yellow crystalline solid, mp. 45–47°C, yield 0.91g or 61%

IR(KBr) ν: 1520, 1380(NO_2), 1220(P=O), 1050(P-O-C) cm^{-1} ^1H NMR ($CDCl_3$) δ: 1.20(t, J = 7,6H, $2OCH_2CH_3$), 2.30(S, 3H,CH_3),4.00(d–q, J = 7,7, 4H, $2OCH_2CH_3$), 6.90–8.00(M, 5H,ph, =CH)

^{31}P NMR ($CDCl_3$): δ: 12.0(S)

EIMS: 300(M + 1)$^+$, 115(M^+-NO_2-PO_3Et-H), 109(PO_3Et^+-C_2H_4)

Anal. Calcd. for $C_{13}H_{18}NO_5P$(299.26): C 52.18 H 6.66 N 4.68 Found: C 52.17 H 7.04 N 4.18

Diethyl 1-(p-fluorophenyl)-2-nitrovinylphosphonate (2i)

was prepared by dehydrating diethyl 1-p-fluorophenyl-hydroxy-2-nitroethylphosphonate similar to the method described for **2f**. **2i** is a slightly yellow crystalline solid, mp. 32–36°C, yield 1.00g or 66%

IR(KBr) 7nu;: 1600(=), 1540, 1380(NO_2), 1250(P=O), 1010(P-O-C) cm^{-1}

^1H NMR ($CDCl_3$): δ: 1.20(t, 6H, J = 7, $2OCH_2CH_3$), 4.00(d–q, 4H, J = 7, 7,OCH_2CH_3), 7,30–6.80(m, 4H, ph), 7,43(d, J = 15.3, 1H,=CH)

^{31}P NMR ($CDCl_3$): δ: 11.7(S)

EIMS: 304(M + 1)$^+$, 201(M^+-NO_2-C_2H_4), 120(M^+-NO_2-PO_3Et), 109(PO_3Et^+), 81(PO_3^+)

Anal. Calcd. for $C_{12}H_{15}NO_5PF$(303.23): C 47.53 H 4.99 N 4.62 Found: C 47.34 H 4.81 N 4.35

Diethyl 1-(p-chlorophenyl)-2-nitrovinylphosphonate (2j)

was prepared by dehydrating diethyl 1-p-chlorophenyl-1-hydroxy-2-nitroethylphosphonate similar to the method described for **2f**. **2j** is a slightly yellow crystalline product, mp 39–40°C yield 0.92g or 58%

IR(KBr) ν: 1530(NO_2), 1250(P=O), 1050(P-O-C) cm^{-1}

^1H NMR ($CDCl_3$): δ: 1.43(t, J = 7, 6H, $2OCH_2CH_3$), 4.13(d–q, J = 7, 7, 4H,$2OCH_2CH_3$), 7.1–7.5(m, 4H,ph), 8.13(d, J = 15.3, 1H,=CH) ^{31}P NMR ($CDCl_3$): δ: 14.9(S)

EIMS: 319(M + 1)$^+$, 111($ClC_6H_4^+$)

Anal. Calcd. for $C_{12}H_{15}NO_5PCl$(319.69): C 45.09 H 4.73 N 4.38 Found: C 45.28 H 4.83 N 3.75

Acknowledgements

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