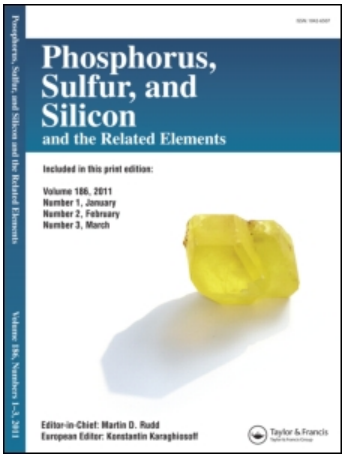


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Reactions of Nitrosovinylphosphonates with Electron-Rich Alkenes and Heterocycles

Emanuel Guimarães[a]; Américo Lemos[a]; Marta Lopes[a]
[a] Departamento de Química e Bioquímica, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Faro, Portugal

To cite this Article Guimarães, Emanuel , Lemos, Américo and Lopes, Marta(2007) 'Reactions of Nitrosovinylphosphonates with Electron-Rich Alkenes and Heterocycles', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 9, 2149 — 2155

To link to this Article: DOI: 10.1080/10426500701407425

URL: http://dx.doi.org/10.1080/10426500701407425

Phosphorus, Sulfur, and Silicon, 182:2149–2155, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701407425

Taylor & Francis
Taylor & Francis Group

Reactions of Nitrosovinylphosphonates with Electron-Rich Alkenes and Heterocycles

Emanuel Guimarães
Américo Lemos
Marta Lopes
Departamento de Química e Bioquímica, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus de Gambelas, Faro, Portugal

In the presence of a base, chlorohydroxyiminophosphonates are converted in situ into the corresponding transient nitrosovinylphosphonates, which react as heterodienes with electron-rich alkenes and heterocycles producing oxazines and open-chain oximes in moderate yields and good selectivity. This approach may be regarded as a new strategy for the synthesis of precursors of α-amino phosphonic acids.

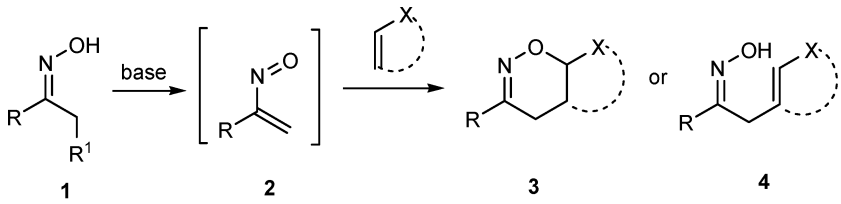
Keywords α-aminophosphonates; chloro-hydroxyiminophosphonates; Diels-Alder reactions; nitrosoalkenes; nitrosovinylphosphonates

INTRODUCTION

When treated with a base, halogen oximes **1** can generate in situ transient nitrosoalkenes **2**. These are intercepted by a wide range of electron rich alkenes and heterocycles, producing a variety of 1,2-oxazines **3** or open chain oximes **4**. The scope, versatility, and usefulness of the cycloaddition reactions of nitrosoalkenes with carbon-carbon double bonds over the last 20 years are well documented.[1,2] The efficiency of the cycloaddition is directly associated with the electron-withdrawing capacity of the 3-substituent and groups such trifluoromethyl, acyl, ethoxycarbonyl, or aryl have been used (Scheme 1).

The majority of these studies have been carried out with nitrosoalkenes bearing a 3-ethoxycarbonyl substituent. Reductive transformations of the C = N bond of the adducts and cycloadducts so formed

Received November 29, 2006; accepted March 18, 2007.
Thanks are due to Dr. T. L. Gilchrist for helpful discussions and Fundação Ciência e Tecnologia, UID 272/94, for financial support.
Address correspondence to Américo Lemos, Departamento de Química e Bioquímica, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus de Gambelas, 8000-810 Faro, Portugal. E-mail: alemos@ualg.pt



R = CF_3; CHO; COR^2; CO_2R^3; C_6H_5; 4-$NO_2C_6H_4$
R^1 = Br; Cl

SCHEME 1

allow the access to α-amino esters, and thus to a great variety of non-proteinogenic aminoacids, proline analogues, and pyrroles.[2a,c,3]

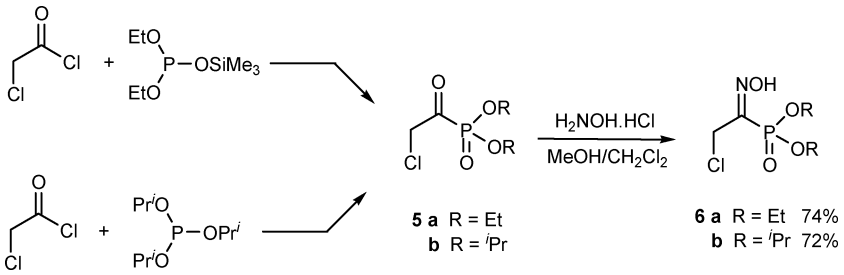
α-Amino phosphonic acids are considered as surrogates of α-amino acids and they exhibit biological activity[4] and applications as plant growth regulators,[5] inhibitors of certain enzymes,[6] HIV,[7] and antibacterial agents.[8] To the best of our knowledge there are no literature reports of Diels-Alder cycloaddition reactions involving the use of a 3-phosphonate substituent in nitrosoalkenes, which could mimic the carboxylic functionality. There are only a few reports, where a phosphonate or phosphinyl group was present in 1,2-diaza-1,3-butadienes, used in [4 + 2] cycloadditions.[9]

Here, we report the initial results of our investigation on the formation of transient nitrosovinylphosphonates, obtained from the corresponding chlorooximes, which act as heterodienes in Diels-Alder reactions with inverse electron demand, towards electron rich heterocycles and olefins.

RESULTS AND DISCUSSION

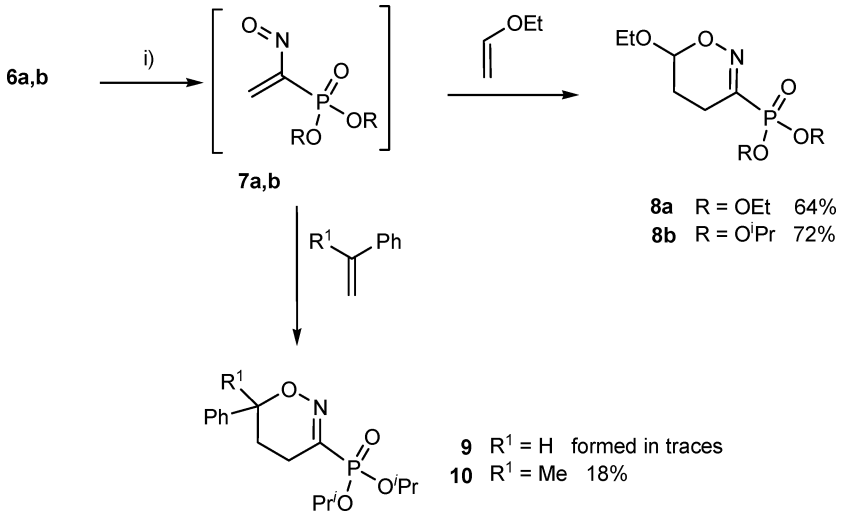
Initially we turned our attention to the preparation of the acyl phosphonate **5a**, obtained by the Arbuzov reaction of chloroacetyl chloride and diethyl trimethylsilyl phosphite.[10] Further treatment of the acylphosphonate with hydroxylamine hydrochloride in a mixture of methanol/dichloromethane afforded the desired oxime **6a** in 74% yield. As diethyl trimethylsilyl phosphite is an expensive reagent and because of the fact, that the oxime **6a** was an oil, we decided to perform similar experiments with triisopropyl phosphite. We isolated the oxime **6b** in a similar yield, which crystallized forming a nice colorless solid after a few days in the refrigerator (Scheme 2).

When treated with a base, oximes **6a**,**b** were converted into the transient nitrosovinylphosphonates **7a**,**b**, which were intercepted by ethyl



SCHEME 2

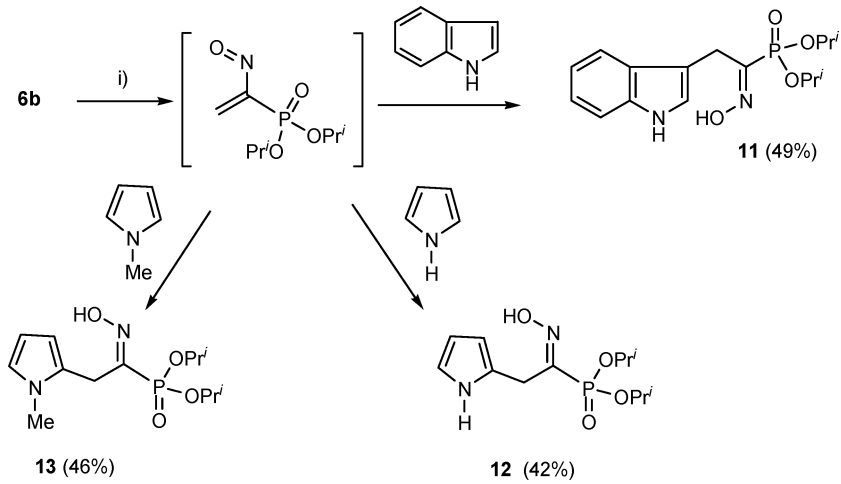
vinyl ether and α-methylstyrene affording the dihydrooxazines **8a**,**b** and **10**, respectively, as oils. As might be expected for a cycloaddition involving less electron rich alkenes, reaction with styrene failed to produce an isolable cycloadduct **9** (Scheme 3).



SCHEME 3

With indole, pyrrole and *N*-methylpyrrole, the open chain oximes **11–13** were obtained. Our efforts to intercept the nitrosovinylphosphonate with furan were unsuccessful; a very complicated and inseparable mixture of products was obtained (Scheme 4).

The yields, although not optimized, were quite good, and the reactions were found to be completely regioselective; no other isomers were detected or isolated from the reaction mixture. The ^{1}H NMR spectra were instructive, particularly the signal of 6-H, in compounds **8a**,**b** appeared as a perfect doublet of triplets at $\delta = 5.14$ (**8a**) and as a triplet



SCHEME 4 : i) Na_2CO_3; CH_2Cl_2; rt; 16 h

at $\delta = 5.15$ (**8b**). We postulate, by analogy with earlier work,[11] that all compounds are formed by [4 + 2] cycloaddition reactions of the nitrosovinylphosphonates **7a**,**b**, i.e., the cycloadduct will always be the primary product of the reaction. The open-chain oximes result from rearomatization by proton transfer and concomitant ring opening (the complications observed with furan may be partially associated with this kind of isomerization).

In summary, we report the first examples of Diels-Alder reactions of nitrosovinylphosphonates, generated in situ from the corresponding chlorooximes, with electron rich alkenes and heterocycles. The products are obtained with high selectivity and the yields are comparable with those reported for nitrosoalkenes bearing a 3-ethoxycarbonyl substituent.[12]

Since reductive transformations at the C = N bond of compounds like **11** allow an access to α-amino phosphonates and consequently to α-amino phosphonic acids,[13] which are considered surrogates or equivalents of α-amino acids, this strategy can be regarded as a new entry to this class of compounds.

Further studies of the reaction of these phosphonates, as well as other phosphorus derivatives, with electron rich alkenes and heterocycles, are in progress.

EXPERIMENTAL

^{1}H NMR and mass spectra were performed by RIAIDT at Santiago de Compostela. ^{1}H NMR spectra were recorded with a Bruker AMX

300 spectrometer. Deuteriochloroform was used as a solvent and TMS was used as an internal reference. The chemical shifts are given in δ (ppm) and the coupling constants J in Hz. IR spectra were recorded on a Brucker FT-IR Tensor 27 instrument. Melting points were measured on a Stuart Scientific SMP3 melting point apparatus and are uncorrected.

Synthesis of the Phosphonates 6a,b—General Procedure

Hydroxylamine hydrochloride (20 mmol) and the acylphosphonate (**5a** or **5b** 16.8 mmol) were added to the mixture of $MeOH/CH_2Cl_2$ (60/20 mL) and stirred at room temperature for 16 h. The solvents were then evaporated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2/H_2O (50/40 mL). The organic layer was separated, washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent afforded the phosphonates **6a**,**b**.

Diethyl 2-Chloro-1-(hydroxyimino)ethylphosphonate (6a)

Yield 2.50 g (74%), oil, IR (neat) ν_{max} = 3598–3300, 2989, 1249, 1024 cm^{-1}. ^1H NMR: δ = 1.36 (dt, J = 6.9 and 1.3 Hz, 6H), 4.18–4.21 (m, 4H), 4,30 (d, J_{PH} = 12,9 Hz, 2H), 10.5 (br, 1H). HRMS calculated for $C_6H_{13}NO_4P^{35}Cl$ 229.027074, found 229.027635; calculated for $C_6H_{13}NO_4P^{37}Cl$ 231.024124, found 231.024339.

Diisopropyl 2-Chloro-1-(hydroxyimino)ethylphosphonate (6b)

Yield 3.12 g (72%), colorless solid, mp 57.6-59.2°C (from hexane/CH_2Cl_2). IR (KBr) ν_{max} = 3451, 3145, 2983, 1255, 1220, 1002 cm^{-1}. ^1H NMR: δ = 1.37 (dd, J = 7.0 and 6.6 Hz, 12H) , 4.29 (d, J_{PH} = 12,6 Hz, 2H), 4,74–4.85 (2 H, m), 10.6 (1H, br). MS (CI): m/z(%) = 260 (13), 258 (43), 218 (12), 216 (40), 176 (33), 174 (100). HRMS calculated for $C_8H_{18}NO_4P^{35}Cl$ 258.066199, found 258.066271; calculated for $C_8H_{18}NO_4P^{37}Cl$ 260.063249, found 260.062837.

Synthesis of the Phosphonates 8, 10–13—General Procedure

A mixture of the oxime (**6a** or **6b**, 2.2 mmol), Na_2CO_3 (11 mmol) and the dienophile (22 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 16 h. Filtration of the insoluble material and evaporation of the solvent followed by dry-flash chromatography gave the phosphonates **8**, **10**–**13**.

Diethyl 6-Ethoxy-5,6-dihydro-4H-1,2-oxazin-3-yl-phosphonate (8a)

From oxime **6a** and ethyl vinyl ether, yield 0.372 g, (64%), oil, IR (neat) $\nu_{max} = 2983, 1263, 1224, 1026\ cm^{-1}$. ^1H NMR: $\delta = 1.16$-1.24 (m, 6H), 1.35 (t, $J = 7.1$ Hz, 3H), 1.82–2.03 (m, 2H, 5′ and 5-H), 2.28–2.45 (m, 2H, 4′ and 4-H), 3.61 (dq,$J = 11.0$ and 8.0 Hz, 1H, MeCHHO), 3.85 (dq, $J = 10.7$ and 8.0 Hz, 1H, MeCHHO), 4.07–4.25 (m, 4H), 5.14 (dt, $J =$ 5.3 and 2.6 Hz, 1H, 6-H). MS (EI): $m/z(\%) = 265$ (9), 248 (36), 221 (100). HRMS calculated for $C_{10}H_{20}NO_5P$ 265.107911, found 265.107861.

Diisopropyl 6-Ethoxy-5,6-dihydro-4H-1,2-oxazine-3-yl-phosphonate (8b)

From oxime **6b** and ethyl vinyl ether, yield 0.471 g, (72%), oil, IR (neat) $\nu_{max} = 2981, 1255, 1109, 1001\ cm^{-1}$. ^1H NMR: $\delta = 1.18$ (t, $J =$ 7.0 Hz, 3H), 1.33–1.36 (m, 12H), 1.83-2.10 (m, 3H, 5′-H, 5-H and 4-H), 2.34–2.42 (m, 1H, 4′-H), 3.62 (dq, $J = 10.8$ and 7.9 Hz, 1H, MeC<u>H</u>HO), 3.86 (dq, $J = 10.9$ and 7.9 Hz, 1H, MeCH<u>H</u>O), 4.70-4.82 (m, 2H), 5.15 (t, $J = 2.4$ Hz, 6-H, 1H).

Diisopropyl 6-Methyl-6-phenyl-5,6-dihydro-4H-1,2-oxazine-3-yl-phosphonate (10)

From oxime **6b** and α-methylstyrene, yield 0,134 g, (18%), oil, IR (neat) $\nu_{max} = 2927, 2856, 1465, 1267, 1001\ cm^{-1}$. ^1H NMR: $\delta = 1.22$–1.34 (m, 12H), 1.45 (s, 3H), 1.98–2.13 (m, 3H, 5′-, 5-H and 4-H), 2.25–2.28 (m, 1H, 4′-H), , 4.64–4.82 (m, 2H), 7.25–7.68 (m, 5H).

Diisopropyl 1-(Hydroxyimino)-2-(1H-indol-3-yl)ethylphosphonate (11)

From oxime **6b** and indole, yield 0.365 g, (49%), light yellow solid, mp 148.6–150.2°C, IR (KBr) $\nu_{max} = 3546, 3413, 1639, 1618, 1209, 1010\ cm^{-1}$. ^1H NMR: $\delta = 1.06$ (d, $J = 7.0$ Hz, 6H), 1.23 (d,$J = 7.1$ Hz, 6H), 4.03 (d, $J_{PH} = 14{,}1$ Hz, 2H), 4.59–4.63 (m, 2H), 7.05–7.22 (m, 3H), 7.36 (d, $J = 7.6$ Hz, 1H); 7.78 (d, $J = 8.6$ Hz, 1H), 8.2 (br, 1H), 9.2 (br, 1H). MS (EI): $m/z(\%) = 338$ (37), 237 (96), 236 (100), 156 (22), 155 (18), 130 (29). HRMS calculated for $C_{16}H_{23}N_2O_4P$ 338.139546, found 338.139120.

Diisopropyl 1-(Hydroxyimino)-2-(1H-pyrrol-2-yl)ethylphosphonate (12)

From oxime **6b** and pyrrole, yield 0.266 g (42%), oil, IR (neat) $\nu_{max} =$ 3255, 3176, 2981, 1454, 1387, 1242, 999 cm^{-1}. ^1H NMR: $\delta = 1.30$–1.37 (m, 12H), 3.83 (d, $J_{PH} = 14{,}1$ Hz, 2H), 4.58–4.64 (m, 2H), 6.00–6.05 (m, 2H), 6.64–6.65 (m, 1H), 9.2 (br, 1H), 10.8 (br, 1H). MS (CI): $m/z(\%)$

= 289 (100) [M^++1]. HRMS calculated for $C_{12}H_{21}N_2O_4P$ 288.123444, found 288.123896.

Diisopropyl 1-(Hydroxyimino)-2-(1-methyl-1H-pyrrol-2-yl)ethylphosphonate (13)

From oxime **6b** and *N*-methyl pyrrole, yield 0.306 g (46%), oil, IR (neat) $\nu_{max} = 3220, 2981, 1386, 1240, 1012\ cm^{-1}$. ^1H NMR: $\delta = 1.19$-1.37 (m, 12H), 3.59 (s, 3H), 3.85 (d, J_{PH} = 13,8 Hz, 2H), 4.59–4.68 (m, 2H), 5.96–6.07 (m, 2H), 6.58–6.61 (m, 1H), 10.5 (br, 1H). MS (CI): *m/z*(%) = 303 (100) [M^++1], 94 (100). HRMS calculated for $C_{13}H_{23}N_2O_4P$ 302.139546, found 302.139344.

REFERENCES AND NOTES

[1] Reviews: a) P. G. Tsoungas, *Heterocycles*, **57,** 1149 (2002); b) I. M. Lyapkalo and S. Ioffe, *Russ. Chem. Rev*., **67,** 467 (1998); c) T. L. Gilchrist and J. E. Wood, *In Comprehensive Heterocyclic Chemistry II*, (A. J. Boulton, Pergamon Press: Oxford, 1996) Vol. 6, pp. 279–299.

[2] Recent contributions: a) J. K. Gallos, V. C. Sarli, Z. S. Massen, A. C. Varvogli, C. Z. Papadoyanni, S. D. Papaspyrou, and N. G. Argyropoulos, *Tetrahedron*, **61,** 565 (2005); b) T. C. Wabnitz, S. Saaby, and K. A. Jorgensen, *Org. Biomol. Chem*., **2,** 828 (2004); c) S. Hegazi, S. L. Titouani, M. Soufiaoui, and A. Tahdi, *Tetrahedron*, **60,** 10793 (2004); d) J. K. Gallos, V. C. Sarli, A. C. Varvogli, C. Z. Papadoyanni, S. D. Papaspyrou, and N. G. Argyropoulos, *Tetrahedron Lett*., **44,** 3905 (2003); e) A. Tahdi, L. S. Titouani, M. Soufiaoui, N. Komiha, O. K. Kabbaj, S. Hegazi, A. Mazzah, and A. Eddaif, *Tetrahedron*, **58,** 1507 (2002); f) R. Zimmer, B. Orschel, S. Scherer, and H.-U. Reissig, *Synthesis*, 1553 (2002).

[3] a) R. Henning, U. Lerch, and H. Urbach, *Synthesis*, 625 (1989); b) C. Hippeli and H.-U. Reissig, *Liebigs Ann. Chem*., 475 (1990); c) C. Hippeli, R. Zimmer, and H.-U. Reissig, *Liebigs Ann. Chem*., 469 (1990).

[4] Reviews: a) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur, and Silicon*, **63,** 193 (1991); b) V. P. Kukhar and H. R. Hudson, Eds, *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity* (Wiley, Chichester, 2000).

[5] a) F. A. Hartman, U.S. Patent, 3,894,861 (1975); b) I. A. Natchev, *Liebigs Ann. Chem.*, 861 (1988).

[6] W. Smith and P. Bartlett, *J. Am. Chem. Soc*., **120,** 4622 (1998) and references cited therein.

[7] H. Dieter and H. Jutta, European Patent Application, EP, 472,077 (1992).

[8] a) P. S. Ringrose, *Nature*, 272 (1978); b) F. R. Atherton, C. H. Hassal, and R. W. Lambert, *J. Med. Chem.*, **29,** 29 (1986).

[9] a) F. Palacios, D. Aparicio, Y. López, J. M. de los Santos, and C. Alonso, *Tetrahedron,* **62,** 1095 (2006); b) F. Palacios, D. Aparicio, Y. López, J. M. de los Santos, and C. Alonso, *Eur. J. Org. Chem*., 1142 (2005).

[10] D. R. Brittelli, *J. Org. Chem*., **50,** 1845 (1985).

[11] T. L. Gilchrist and A. Lemos, *J. Chem. Soc., Perkin Trans. I*, 1391 (1993).

[12] T. L Gilchrist and T. G. Roberts, *J. Chem. Soc., Perkin Trans. I*, 1283 (1983).

[13] R. S. Rogers and M. K. Stern, *Synlett*., 708 (1992); b) W. Subotkowski, J. Kowalik, R. Tyka, and P. Mastalerz, *Pol. J. Chem*., **55,** 853 (1981).