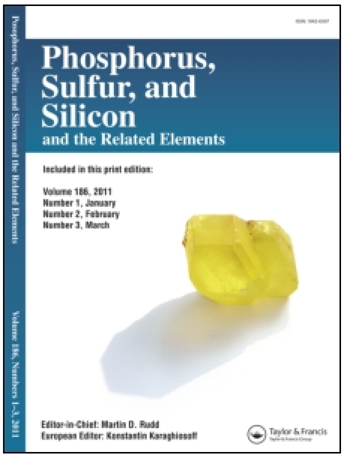

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Reactions of Azovinylphosphonates with Nucleophilic Alkenes and Heterocycles: Synthesis of Tetrahydropyridazine-3-phosphonate and 2-Substituted-1-hydrazonoethylphosphonate Derivatives

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Reactions of Azovinylphosphonates with Nucleophilic Alkenes and Heterocycles: Synthesis of Tetrahydropyridazine-3-phosphonate and 2-Substituted-1-hydrazonoethylphosphonate Derivatives

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Transient azovinylphosphonates, generated in situ by base induced dehydrohalogenation of the corresponding 2-bromo- and 2-chloro-acetylphosphonate- tert-butoxycarbonyl hydrazones are intercepted by electron rich alkenes and heterocycles in hetero Diels-Alder reactions, producing tetrahydopyridazine-3-phosphonates or open chain α-hydrazono phosphonates.

Keywords α-hydrazonophosphonates; 3-phosphono-1,2-diaza-1,3-butadienes; azovinylphosphonates; addition-elimination; cycloaddition; tetrahydropyridazine-3-phosphonates

INTRODUCTION

α-Aminophosphonic compounds are useful and important analogues of α-amino acids and exhibit biological activity.[1] Also α-hydrazino phosphonic acids and phosphonates are analogues of α-aminophosphonic acids and are effective protectors of crops from the phytoxic action of herbicides.[2]

Over the last decades a large number of heterocyclic systems have been obtained with great success using electron deficient 1,2-diaza-1,3-butadienes, either as Michael acceptors[3] or as heterodienes in inverse electron demand cycloaddition reactions,[4] with a vast range of nucleophilic olefins and heterocycles. However, literature reports of 1,2-diaza-1,3-butadienes carrying phosphorus substituents

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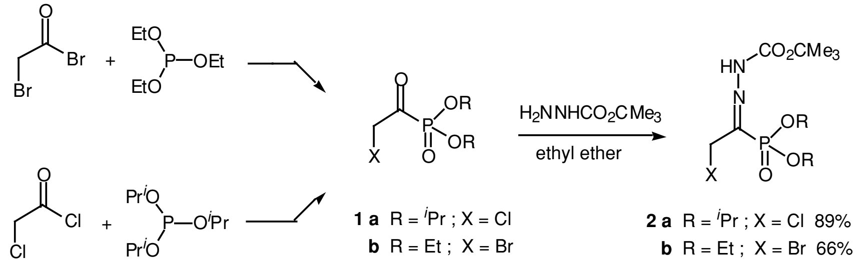
are scarce.[3g,4a,5] To the best of our knowledge, there is only one report describing the use of 4-phosphonyl- or 4-phosphinyl-1,2-diaza-1,3-butadienes in [4+2] cycloaddition reactions with alkenes and dihydrofuran.[4a]

We have recently described the first examples of cycloaddition reactions of nitrosovinyl-3-phosphonates, generated from the corresponding 2-chloro-1-hydroxyiminophosphonates.[6] As a continuation of our work we have extended this methodology to the synthesis of tetrahydopyridazine-3-phosphonates or open chain α-hydrazono phosphonates via the interception of transient 3-phosphono-1,2-diaza-1,3-butadienes, obtained from halogenated hydrazones, with electron rich heterocycles and olefins.

RESULTS AND DISCUSSION

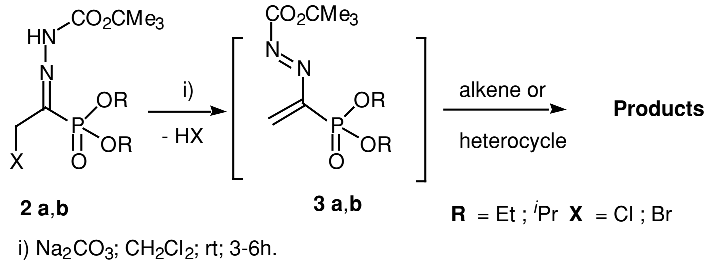
The acylphosphonates **1a**, **b** were obtained by the Arbuzov reaction of the respective haloacetyl halides and the corresponding alkylphosphite.[7] Further treatment with *tert*-butyl carbazate in ethyl ether, afforded the hydrazones **2a**, **b** in good yields (Scheme 1).



SCHEME 1

When treated with sodium carbonate in dichloromethane at room temperature, the hydrazones **2a**, **b** were converted into the transient azovinylphosphonates **3a**, **b**. These transient species were trapped in situ by alkenes or heterocycles (Scheme 2), producing new 3-phosphonyl tetrahydropyridazines **4–7** or α-hydrazono phosphonates **8**, **9** (Table I).

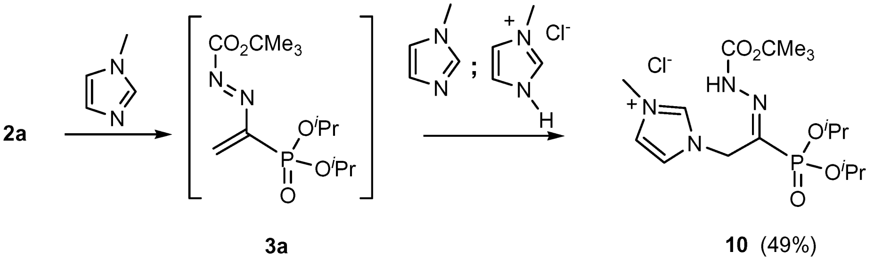
With alkenes, cycloadducts were produced. The efficiency of the reaction was directly associated with the properties of the dienophile, becoming less efficient with decreasing electron rich character of the dienophile. With heterocycles possessing lower aromatic or non aromatic character, such furan and 2,3-dihydrofuran, cycloadducts were isolated. With pyrrole and indole the open chain hydrazones were obtained, possibly, as a result of rearomatization of the primarily



SCHEME 2

formed cycloadducts.[8] The yields were, in general, somewhat better than those obtained in similar reactions with nitrosovinyl-3-phosphonates,[6] but lower than those obtained with 4-phosphonyl-1,2-diaza-1,3-butadienes[4a] and also with azoalkenes carrying the same alkoxycarbonylazo substituent, but having an ethoxycarbonyl group at the 3-position.[9] Although a direct comparative analysis of isolated product yields may be defective, these results may point out that the ethoxycarbonyl group may be a more effective electron withdrawing group than the phosphonate moiety; the phosphonate functionality may be more efficient at position 4 than at the position 3; azovinylphosphonates may be more electrophilic, and so more efficient, than nitrosovinylphosphonates.

We also explored the possibility to use the hydrazone **2a** as an alkylating agent for other azoles, thus attempting the synthesis of functionalised α-hydrazono phosphonates. Since it is known that 1-methylpyrazole is basic enough to promote the dehydrohalogenation of α-halogenated oximes,[10] this was used in the absence of base. The adduct **10** was isolated in 49% yield (Scheme 3).



SCHEME 3

In summary, we have developed a synthetic route to new tetrahydopyridazine-3-phosphonate and 2-substituted-1-hydrazonoethylphosphonate derivatives in moderate to good yields, either based on hetero Diels-Alder reactions of azovinylphosphonates derived from 2-halo-1-hydrazono phosphonates, or by elimination-addition reactions of one of these hydrazones. Established methods of reductive transformations at the C=N bond,[11] combined with the expected ease of removal of the *tert*-butoxycarbonyl group, will allow the access to a wide range of α-hydrazino and/or α–amino phosphonates.

TABLE I Isolated Adducts and Cycloadducts

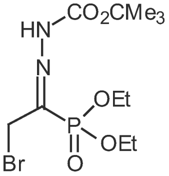
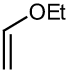
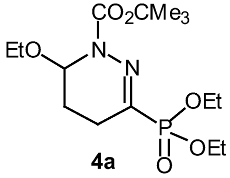
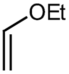
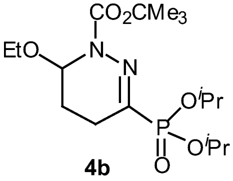
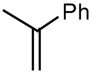
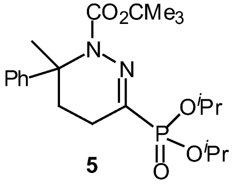
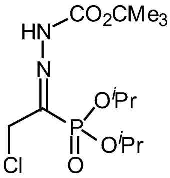
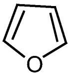
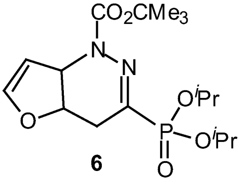
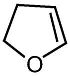
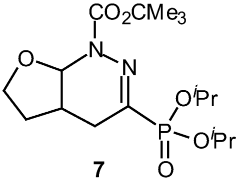
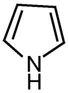
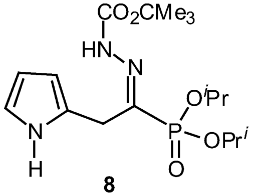
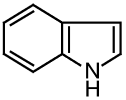
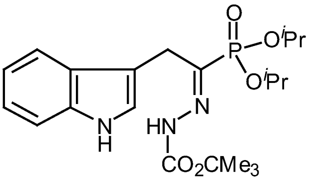
Hydrazone	Alkene or Heterocycle	Product	Yield (%)
		 **4a**	61
		 **4b**	67
		 **5**	22
		 **6**	44
		 **7**	33

TABLE I Isolated Adducts and Cycloadducts *(Continued)*

Hydrazone	Alkene or Heterocycle	Product	Yield (%)
		 **8**	38
		 **9**	36

EXPERIMENTAL

NMR and mass spectra were obtained at RIAIDT at Santiago de Compostela. ^{1}H NMR, ^{13}C NMR (75.47 MHz) and ^{31}P NMR spectra (121.47 MHz) were recorded with a Varian Unity Plus 300 (300 MHz) spectrometer or with a Bruker WM AMX spectrometer using $CDCl_3$ (except otherwise reported) as solvent and TMS (^{1}H and ^{13}C) or 85% phosphoric acid (^{31}P) as internal and external standards, respectively (chemical shifts (δ) in ppm, *J*in Hz). IR spectra were recorded with a Brucker FT-IR Tensor 27 instrument. Melting points were measured on a SRS MAP120 EZ-Melt melting point apparatus and are uncorrected.

Synthesis of the Hydrazono Phosphonates 2a,b—General Procedure

To the acylphosphonate **1a** or **1b** (12 mmol) in diethyl ether (30 mL) was added *tert*-butyl carbazate (12 mmol) and two drops of glacial acetic acid and the mixture was stirred at room temperature for 24 h. The insoluble material was then filtered and H_2O (30 mL) was added. The organic layer was separated, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was triturated with *n*-hexane and kept in the refrigerator. The hydrazono phosphonates separated as a solid (**2a**) or thick yellow oil (**2b**).

Diisopropyl 2-Chloro-1-(tert-butoxycarbonylhydrazono) ethylphosphonate (2a)

Yield 3.81 g (89%), white solid, mp 114.8−116.4 °C (from hexane/CH_2Cl_2). IR (KBr) $\nu_{max} = 3209, 2981, 1756, 1249, 997\ cm^{-1}$. ^1H NMR: $\delta = 1.35-1.38$ (m, 12H), 1.52 (s, 9H), 3.87 (d, $^3J_{PH} = 8.7$ Hz, 2H, CH_2), 4.61–4.82 (m, 2H, OCH), 11.42 (br, 1H). ^{13}C NMR: $\delta = 24.5$ (Me of *i*Pr), 24.6 (Me of *i*Pr), 28.7 (Me of *t*Bu), 34.1 (d, $^2J_{PC} = 19.5$ Hz, $\underline{C}H_2Cl$), 73.1 (OCH), 83.4 ($OCMe_3$), 141.4 (C=N), 151.6 (C=O). ^{31}P NMR: $\delta = 4.4$. HRMS (ESI) $[M+Na]^+$ calculated for $C_{13}H_{26}^{35}ClN_2NaO_5P$ 379.1160, found 379.1155.

Diethyl 2-Bromo-1-(tert-butoxycarbonylhydrazono) ethylphosphonate (2b)

Yield 2.96 g (66%), yellow oil. IR (KBr) $\nu_{max} = 3120, 2983, 1732, 1253, 1022\ cm^{-1}$. ^1H NMR: $\delta = 1.34-1.36$ (m, 3H), 1.38−1.41 (m, 12H), 3.94 (d, $^2J_{PH} = 11.4$ Hz, 2H, -CH_2Br), 4,39−4.78 (m, 2H, OCH), 11.38 (br, 1H).

Reactions of the Hydrazono Phosphonates 2a,b—General Procedure

A mixture of the hydrazone **2a** or **2b** (2.2 mmol), Na_2CO_3 (11 mmol) and the alkene or heterocycle (22 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature until the disappearance (TLC) of the hydrazone (3 to 6 h). Filtration of the insoluble material and evaporation of the solvent followed by dry-flash chromatography gave the phosphonates **4–9**.

1-tert-Butoxycarbonyl-3-diethylphosphono-6-ethoxy-5,6-dihydro-4H-pyridazine (4a)

From **2b** and ethyl vinyl ether, yield 0.49 g, (61%), oil. IR (neat) $\nu_{max} = 2979, 2929, 1732, 1249, 1151, 1014\ cm^{-1}$. ^1H NMR: $\delta = 1.18$ (t, $J = 7.0$ Hz, 3H), 1.35−1.44 (m, 15H), 1.84−2.06 (m, 2H, 5' and 5-H), 2.26−2.49 (m, 2H, 4′ and 4-H), 3.46 (dq,$J = 8.0, 3.0$ Hz, 1H, MeC*H*HO), 3.83 (dq, $J = 8.0, 2.7$ Hz, 1H, MeCH*H*O), 4.74−4.82 (m, 2H, OCH), 5.18 (dt, $J = 3.0, 2.7$ Hz, 1H, 6-H).

1-tert-Butoxycarbonyl-3-diisopropylphosphono-6-ethoxy-5,6-dihydro-4H-pyridazine (4b)

From **2a** and ethyl vinyl ether, yield 0.58 g, (67%), oil. IR (neat) $\nu_{max} = 2980, 2933, 1738, 1389, 1248, 115, 999\ cm^{-1}$. ^1H NMR: $\delta = 1.16$ (t, $J = 7.0$ Hz, 3H), 1.32−1.38 (m, 12H), 1.43 (s, 9H), 1.80−2.10 (m, 2H, 5′

and 5-H), 2.42 - 2.49 (m, 2H, 4′ and 4-H), 3.51–3.57 (m, 1H, MeC*H*HO), 3.79–3.85 (m, 1H, MeCH*H*O), 4.41–4.75 (m, 2H, OCH), 5.22 (bs, 1H, 6-H). MS (CI): *m*/*z*(%) = 393 [M+H]$^+$ (62), 374 (34), 337 (54), 247 (61), 163 (100), 155 (57), 117 (46), 57 (46). HRMS: calculated for $C_{17}H_{34}N_2O_6P$, 393.21545; found 393.21457.

1-tert-Butoxycarbonyl-3-diisopropylphosphono-6-methyl-6-phenyl-5,6-dihydro-4H-pyridazine (5)

From **2a** and α-methylstyrene, yield 0.21 g, (22%), oil. IR (neat) $\nu_{max} = 2979, 2933, 1726, 1372, 1250, 1000\ cm^{-1}$. ^1H NMR: $\delta = 1.32–1.42$ (m, 21H), 1.51 (s, 3H), 1.61–1.93 (m, 2H, 5' and 5-H), 2.12–2.37 (m, 2H, 4' and 4-H), 4.71–4.84 (m, 2H, OCH), 7.19–7.34 (m, 5H). MS (CI): *m*/*z*(%) = 439 [M+H]$^+$ (100%). HRMS: calculated for $C_{22}H_{36}N_2O_5P$ [M+1], 439.23564; found 439.23619.

1-tert-Butoxycarbonyl-3-diisopropylphosphono-1,4,4a,7a-tetrahydrofuro[3,2-c]-pyridazine (6)

From **2a** and furan, yield 0.38 g, (44%), oil. IR (neat) ν_{max} = 2981, 2935, 1755, 1369, 1249, 998 cm^{-1}. ^1H NMR: δ = 1.31–1.39 (m, 12H), 1.49 (s, 9H), 2.32 (dd, *J* = 14.0, 4.2 Hz, 1H, H-4), 3.36 (m, 1H, H-4'), 4.69–4.78 (m, 2H, OCH), 5.02–5.13 (m, 3H, H-4a, H-7, H-7a), 6.33 (d, *J* = 6.0 Hz, 1H, H-6). HRMS (FAB): calculated for $C_{17}H_{30}N_2O_6P$, 389.18360 [M+1]; found 389.18291.

1-tert-Butoxycarbonyl-3-diisopropylphosphono-1,4,4a,6,7,7a-hexahydrofuro[3,2-c]-pyridazine (7)

From **2a** and 2,3-dihydrofuran, yield 0.28 g, (33%), colorless oil, IR (neat) $\nu_{max} = 2981, 2935, 1722, 1252, 999\ cm^{-1}$. ^1H NMR: $\delta = 1.22–1.40$ (m, 12H), 1.51 (s, 9H), 1.82–2.56 (m, 4H, H-4, H-4′, H-7, H-7′), 3.83–4.26 (m, 4H, H-4a, H-6, H-6′, H-7a), 4.68–4.81 (m, 2H, OCH). MS (CI): *m*/*z*(%) = 391 [M+H]$^+$ (100%). HRMS: calculated for $C_{17}H_{32}N_2O_6P$, 391.1998 [M+1]$^+$; found 389.1989.

Diisopropyl 1-tert-butoxycarbonylhydrazono-2-(1H-pyrrol-2-yl)ethylphosphonate (8)

From **2a** and pyrrole, yield 0.32 g (38%), oil. IR (neat) ν_{max} = 3219, 2980, 1728, 1371, 1250, 1143, 1001. ^1H NMR: δ = 1.32–1.53 (m, 21H), 3.99 (d, J_{PH} = 13,8 Hz, 2H), 4.61–4.66 (m, 2H, OCH), 6.08–6.15 (m, 2H, H-3, H-4), 6.60–6.71 (m, 1H, H-5), 9.65 (br, 1H), 11.19 (br, 1H). MS (CI): *m*/*z*(%) = 388 (100) [M$^+$+1]. HRMS: calculated for $C_{17}H_{30}N_3O_5P$, 388.19925; found 288.19966.

Diisopropyl 1-tert-butoxycarbonylhydrazono-2-(1H-indol-3-yl)ethylphosphonate (9)

From **2a** and indole, yield 0.35 g, (36%), light yellow oil. IR (neat) $\nu_{\max} = 3.381, 2981, 2935, 1722, 1252, 997\ \text{cm}^{-1}$. ^{1}H NMR: $\delta = 1.32-1.38$ (m, 12H), 1.49 (s, 9H), 4.08 (d, $^3J_{PH} = 13.5$ Hz, 2H, CH_2), 4.49–4.60 (m, 2H, OCH), 7.05–7.71 (m, 5H, arom-H), 8.39 (br, 1H, NH-indole), 11.38 (br, 1H, NH-hydrazone). ^{13}C NMR: $\delta = 23.2$ (Me of *i*Pr), 23.9 (Me of *i*Pr), 28.2 (Me of *t*Bu), 32.1 (d, $^2J_{PC} = 19.7$ Hz, CH_2), 64.2 (OCH), 82.4 (O*C*Me$_3$), 119.4, 110.1, 116.6, 117.1, 119.7, 121.2, 125.8, 134.9, 143.2 (d, $^1J_{PC} = 37$ Hz, C=N), 152.5 (C=O). ^{31}P NMR: $\delta = 6.5$. MS (CI): *m/z(%)* = 438 (15) $[M+1]^+$, 392 (100). HRMS: calculated for $C_{21}H_{33}N_3O_5P$, 438.21576; found 438.21635.

3-((2-tert-Butoxycarbonylhydrazono)-2-diisopropylphosphonoethyl)-1-methylimidazo-lium Chloride (10)

To **2a** (0.78 g, 2.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise 1-methylimidazole (0.36 g, 4.4 mmol). After the addition was complete the mixture was stirred for further 15 min. Evaporation of the solvent followed by addition of hexane resulted in the formation of a very hygroscopic yellow solid 0.47 g (49%). IR (neat) $\nu_{\max} = 3155, 2979, 1728, 1371, 1273, 1252, 1159, 988\ \text{cm}^{-1}$. ^{1}H NMR (DMSO-d$_6$): $\delta = 1.11$ (d, $J = 6.7$ Hz, 6H), 1.17 (d, $J = 6.7$ Hz, 6H), 1.51 (s, 9H), 4.60 (s, 3H), 4.62–4.69 (m, 2H), 5.02 (d, $^2J_{PH} = 11.0$ Hz, 2H), 7.37 (dd, $J = 6.7, 3.3$ Hz, 2H), 8.71 (s, 1H), 11.40 (bs, 1H).

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