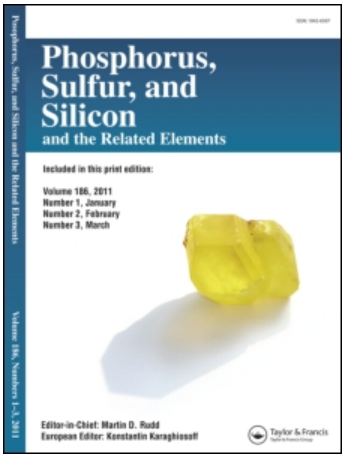


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

ADDITIONAL CYCLE FORMATION FROM 2-DIALKOXYPHOSPHONYLMETHYLTHIAZOLE

B. A. Baimashev[a]; N. A. Polezhaeva[a]; E. N. Klimovitskii[a]
[a] A.M. Butlerov Research Chemical Institute, Kasan State University, Kasan, RUSSIA

To cite this Article Baimashev, B. A. , Polezhaeva, N. A. and Klimovitskii, E. N.(1998) 'ADDITIONAL CYCLE FORMATION FROM 2-DIALKOXYPHOSPHONYLMETHYLTHIAZOLE', Phosphorus, Sulfur, and Silicon and the Related Elements, 132: 1, 251 — 257
To link to this Article: DOI: 10.1080/10426509808036990
URL: http://dx.doi.org/10.1080/10426509808036990

Phosphorus, Sulfur and Silicon, Vol. 132, pp. 251-257
Reprints available directly from the publisher
Photocopying permitted by license only

ADDITIONAL CYCLE FORMATION FROM 2-DIALKOXYPHOSPHONYLMETHYLTHIAZOLE

B.A. BAIMASHEV, N.A. POLEZHAEVA and E.N. KLIMOVITSKII*

A.M.Butlerov Research Chemical Institute, Kasan State University, Kremlevskaya Str. 18, Kasan 420008, RUSSIA

(Received 5 June, 1997)

Diisopropoxyphosphonyl-2-(4-methylthiazolyl)methane **I** reacts with carbonyl and α-halocarbonyl compounds by three routes. In the case of Knoevenagel or Horner-Wadsworth-Emmons reactions the corresponding ethylenes were produced, whereas employing α-halocarbonyls as partners resulted in pyrrolo[2.1b]thiazoles. 1-Phosphonyl-1-(2-thiazolyl)- ethylene undergoes smoothly [4+2] and [3+2] cycloaddition reactions.

Keywords: Dialkoxyphosphonyl-2-(4-methylthiazolyl)methanes; 1-phosphonyl-1-thiazolylethylenes; 6-dialkoxyphosphonylpyrrolo[2.1b]thiazoles; 3-methoxycarbonyl-5-dialkoxyphosphonyl-5-(4-methylthizol-2-yl)-2-pyrazoline; 5-dialkoxyphosphonyl-5-(4-methylthiazol-2-yl)-bicyclo[2.2.1]hept-2-ene

INTRODUCTION

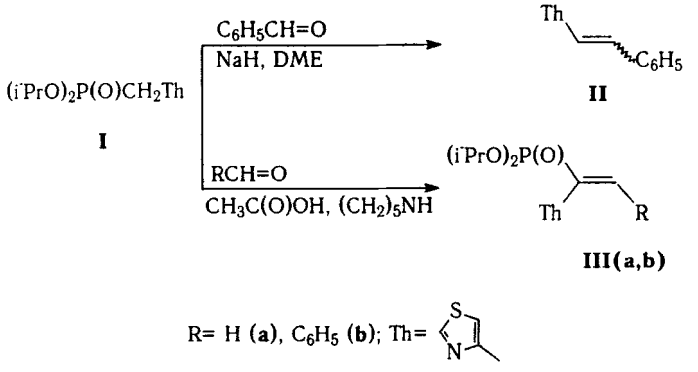
N-Containing heteroarylmethylphosphonates have received much attention due to their synthetic and biological utility.[1–4] In connection with this we have elaborated an approach to the dialkoxyphosphonylmethylthiazoles synthesis which incorporates Hantzsch reaction of C-phosphonylthioacetamide in the key stage.[5] These typical disubstituted methanes bearing activated methylene groups can react with carbonyl compounds to afford vinylthiazoles. Pyrrolo[2,1b]thiazoles could be obtained by using of α-halocarbonyls.[6] Gem- phosphonylthiazolylethylenes can also serve as useful substrates in [4+2], [3+2] cycloaddition and Michael reactions. One

* Corresponding Author.

must keep in mind that thiazolic cycle appears to be the synthetic equivalent of the formyl group.[7]

RESULTS AND DISCUSSION

It has been determined that depending upon the experimental conditions phosphonylthiazolylmethanes are being olefinated by aldehydes according to Knoevenagel or Horner-Wadsworth-Emmons reactions.



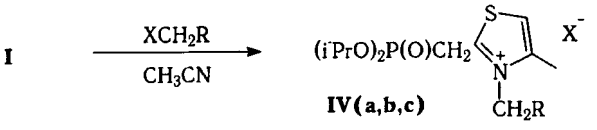
Thus phosphonate **I** and benzaldehyde condensation (NaH, DME) resulted in formation of 1-phenyl-2-(4-methylthiazol-2-yl)ethylene **II.** Since the olefinic protons in the ^{1}H NMR spectra of **II** can not be clearly discerned due to overlapping with aromatic ones the product configuration remains unsolved. Interestingly similar 2-vinylthiazoles can also be obtained by Peterson[8] and Wittig[7] reactions. Diastereoselectivity of the Knoevenagel reaction between **I** and benzaldehyde, on the contrary, was easily established. Preferential E-isomer formation of **IIIb** with d. e. >90% was provided by the ^{1}H, and ^{31}P NMR spectra comparison both of a reaction mixture and a pure product. For the purpose of stereochemical assignment olefine **IIIa** was also used.

The 300 MHz ^{1}H NMR spectra of **IIIa** reveals well separated signals of the geminal olefinic protons. The values of trans- and cis $^3J_{PH}$ constants were found to be 42.0 and 20.7 Hz, respectively. Vinyl proton **IIIb** is splitted by a phosphorus nuclei with a constant of 21Hz that permit unambiguous configurational assingment to be carry out. It must be pointed out that only the proton cis to the phosphonyl moiety of **IIIa** experiences stere-

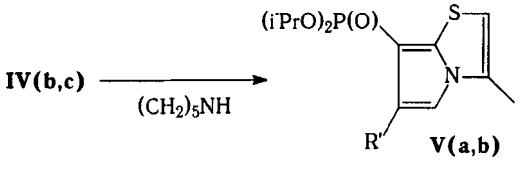
ospecific $^{6}J_{PH}$ long-range spitting of 0,5 Hz by a thiazole methine proton. The synthetic and ^{1}H, ^{13}C, ^{31}P NMR spectral data of **III** are given in a preliminary communication.[9]

During the synthesis of pyrrolo[2,1b]thiazoles from 2-alkylthiazoles and α-haloketones the condensation with participation of active methylene and carbonyl moieties also takes place, the initial quaternization being the first reaction stage.[10]

Thiazole **I** and bromoacetone (phenacyl bromide) were allowed to react in boiling toluene followed by piperidine and acetic acid addition. Such a procedure afforded pyrrolo[2.1b]thiazoles **V** with fairly low yields, around 15%.



R= H (**a**), C(O)CH$_3$ (**b**), C(O)C$_6$H$_5$ (**c**); X= J (**a**), Br (**b,c**)

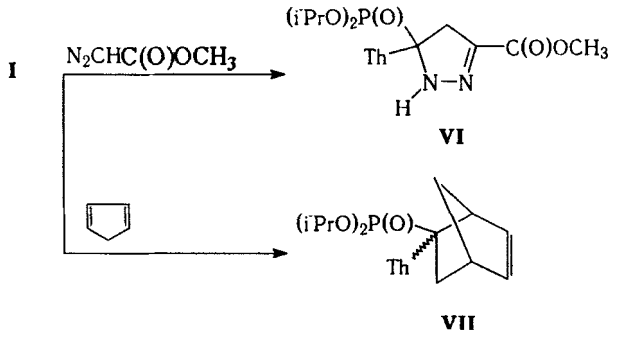


R'= CH$_3$ (**a**), C$_6$H$_5$ (**b**)

To achieve the yields of target bicycles **V** no less than 80% a two-step sequence must be involved with acetonitrile as a solvent for the preparation of the quaternary salts **IV**. To optimize the Menshutkin reaction step methyl iodide was chosen.

Insertion of an electron withdrawing group in the α-position of vinylphosphonates was found to facilitate the reactivity of a double bond towards 1,3-dipoles and 1,3-dienes.[11,12] Vinylphosphonate **IIIa** (masked α-phosphonylacrolein) readily produces phosphonylsubstituted 2-pyrazoline **VI** with high chemoselectivity.

Phosphonylated norbornene **VII** can be obtained by the Diels-Alder reaction between **IIIa** and cyclopentadiene. It appeared that the diastereoselectivity of [4+2] addition is very poor.



EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra in $CDCl_3$ were recorded on a UNITY-300 spectrometer, operating at 299.95 MHz (^1H), 75.43 MHz (^{13}C) and 121.42 MHz (^{31}P). Hexamethyldisiloxane as an internal reference in ^1H and ^{13}C spectra and 85% H_3PO_4 as an external reference in ^{31}P NMR spectra were used. Thin-layer chromatography was conducted on Analtech GP silica gel plates and then was treated by iodine vapour. Column chromatography was conducted at ambient pressure utilizing silica gel (E. Merk, 100–160 mesh). Melting points were measured with a Kofler melting point apparatus and were uncorrected.

1-Phenyl-2-(4-methylthiazol-2-yl)-ethylene *(II)*

A mixture of **I** 0.5 g (1.80 mmol) NaH 0,04 g (1.87 mmol) and benzaldehyde 0 22 g (2.07 mmol) in 50 ml of DME was refluxed for 3 h, poured into 25 ml of H_2O and then extracted by 3 × 30 ml of methylene chloride, dried over $MgSO_4$, and concentrated. Yield: 0,34 g (82%), m.p. 86 °C (Et_2O-petroleum ether, 1:1). Found (%): C 71.10; H 5.51; N 6.96. Calcd. for $C_{12}H_{11}NS$ (%): C 71.78; H 5.61; N 6.85).

2-(Diisopropoxyphosphonylmethyl)-3,4-dimethylthiazolium iodide *(IVa)*

A mixture of **I** 0.5 g (1.80 mmol) and methyl iodide 0,3 g (2.11 mmol) in 50 ml of abs. CH_3CN was refluxed for 16 h. Concentration in *vacuo*

afforded a dark oil which was thoroughly washed with ether . Yield: 0,75 g (95%), Found (%): C 94.59; H 5.68; N 3.94; P 8.32. Calcd. for $C_{12}H_{23}JNO_3PS$ (%): C 94.99; H 5.59; N 3.34; P 7.99. ^{1}H-NMR δ: 1.27 (d, $^2J_{HH}$ 6,3 Hz, 3H, $\underline{CH_3}CH$); 1.30 (d, $^2J_{HH}$ 5,9 Hz, 3H, $\underline{CH_3}CH$); 2.59 (s, 3H, CH_3C=); 4.14 (d, $^2J_{PH}$ 21.0 Hz, 2H, CH_2) ; 4.14 (s, 3H, CH_3-N); 4.74 (m, 2H, $CH_3\underline{CH}$); 8.04 (s, 1H, H^5). ^{13}C-NMR δ: 15,38 ($\underline{CH_3}C$=); 23.80 ($\underline{CH_3}CH$); 32.17 (d, J_{PC}173.4 Hz, CH_2); 39.19 (s, CH_3-N); 73.0 and 73,11 ($CH_3\underline{CH}$; 120.30 (C^5); 145.96 (C^4); 165.47(C^2). ^{31}P-NMR δ: 14.33.

2-(Diisopropoxyphosphonylmethyl)-3-acetonyl-4-methylthiazolium bromide *(IVb)*

From **I** 1 g (3.61 mmol) and bromoacetone 0,6 g (4.38 mmol) in accordance with the previous protocol a thick dark oil was obtained. Yield: 1,4 g (90%), Found (%): C 40.01; H 6.13; N 3.75; P 7.82. Calcd. for $C_{14}H_{25}BrNO_4PS$ (%): C 40.61; H 6.09; N 3.38; P 7.48. ^{31}P-NMR δ: 14.8.

2-(Diisopropoxyphosphonylmethyl)-3-phenacyl-4-methylthiazolium bromide *(IVc)*

From **I** 1 g (3.61 mmol) and phenacylbromide 0,85 g (4.27 mmol) in accordance with the previous protocol viscosy dark oil was obtained. Yield: 1,7 g (89 %), Found (%): C 48.56; H 5.47; N 3.01; P 6.92. Calcd. for $C_{19}H_{27}BrNO_4PS$ (%): C 47.90; H. 5.71; N 2.34; P 6.50. ^{31}P-NMR δ: 15.1.

3,5-Dimethyl-6-diisopropoxyphosphonyl-pyrrolo[2.1b]thiazole *(Va)*

The mixture of **IVb** 1 g (2.41 mmol) and piperidine 0,1 g (1.17 mmol) in 50 ml of abs. toluene was heated for 8 h at 80 °C with stirring. It was concentrated in *vacuo* and chromatographed (eluent ether/benzene, 1:9), R_F 0.33 (ethylacetate). Yield: 0,7 g (92 %), m.p. 89.5 °C. Found (%): C 52.95; H 7.52; N 9.99; P 10.25. Calcd. for $C_{14}H_{22}NO_3PS$ (%): C 53.31; H 7.04; N 9.83; P 10.17. ^{1}H-NMR δ: 1.17 and 1.30 (two m, 12H, $\underline{CH_3}CH$); 2.25 and 2.27 (two s, 6H, $\underline{CH_3}C$=); 4.56 (m, 2H, $CH_3\underline{CH}$); 6.25 (s, 1H, H^2); 6.83 (d, $^4J_{PH}$ 7.1 Hz, 1H, H^4). ^{13}C-NMR δ: 12,18 ($C^{3(5)}$); 12,66 ($C^{5(3)}$); 23.80, 23.87, 24.13, 24.17 ($\underline{CH_3}CH$); 69.75, 69.79 (CHO); 97.88 (d, J_{PC} 224.9 Hz, C^6); 106.75–156.19(other aromatic carbons). ^{31}P-NMR δ: 15.42.

3-Methyl-5-phenyl-6-diisopropoxyphosphonyl-pyrrolo[2,1b]thiazole *(Vb)*

From **IVc** 1 g (2.10 mmol) and piperidine 0,1 g (1.18 mmol) in accordance with a previous protocol. R_F 0.39 (ethylacetate). Yield: 0,72 g (91%), m.p. 125 °C. Found (%): C 60.12; H 6.83; N 3.91; P 8.19. Calcd. for $C_{19}H_{24}NO_3PS$ (%): C 60.53; H 6.41; N 3.71; P 8.21. ^{1}H-NMR δ: 1.01 and 1.21 (two m, 12H, $\underline{CH_3}CH$); 2.34 (s, 3H, CH_3C=); 4.55 (m, 2H, CHO); 6.35 (s, H^2); 7.14–7.30 (m, 5H, Ph); 7.65 (d, $^4J_{PH}$ 7.7 Hz, H^4). ^{13}C-NMR δ: 12,80 ($\underline{CH_3}$ -C=); 23.57, 23.62, 23.85 and 24.03 ($\underline{CH_3}CH$); 70.44 and 70.49 (CHO); 97.20 (d, J_{PC} 224.03 Hz,C^6); 108.50–153.0 (other aromatic carbons). ^{31}P-NMR δ : 15.68.

3-Methoxycarbonyl-5-diisopropoxyphosphonyl-5-(4-methylthiazol-2-yl) –2- pyrazoline *(VI)*

Methyl diazoacetate 0.35 g (3.46 mmol) was added to the solution of **IIIa** 1 g (3.46 mmol) in 50 ml abs. Et_2O. The mixture was stirred at room temperature for 20 h. The product was filtered, washed with Et_2O (10 ml), m.p. 112,5 °C. Yield: 1,1 g (83%), Found (%): C 46.21; H 6.15; N 10.95; P 7.83. Calcd. for $C_{15}H_{24}N_3O_5PS$ (%): C 46.27; H 6.21; N 10.80; P 7.95. ^{1}H-NMR δ: 1.02 and 1.07 (two d, $^2J_{HH}$ 6,0 Hz, 6H, $\underline{CH_3}CH$); 1.13 (d, $^2J_{HH}$ 6,0 Hz, 6H, $\underline{CH_3}$ CH); 2.37 (s, 3H, CH_3C=); 3.57 (m, 2H, CH_2) ; 3.79 (s, 3H, OCH_3), 4.71 (m, 2H, $CH_3\underline{CH}$) ; 6.89 (s, 1H, HC=); 7.47 (s, 1H, NH). ^{13}C-NMR δ: 16,65 ($\underline{C}H_3C$=); 23.20 (d, $^3J_{PC}$ 3.0 Hz, $\underline{CH_3}CH$); 23.39 (d, $^3J_{PC}$ 4.5 Hz, $\underline{CH_3}CH$); 23.76 and 24.04 ($\underline{C}H_3CH$); 42.27 (CH_2) ; 51.96 (OCH_3); 69.95 (d, J_{PC} 171.73 Hz, PC); 72.50 (d, J_{POC} 7.0 Hz, $CH_3\underline{C}H$); 73.02 (d, J_{POC} 6.54 Hz, $CH_3\underline{C}H$); 115.06 ($\underline{C}H$=C); 142.20 (d, J_{PC} 9.57 Hz, C=N); 152.14 ($CH_3\underline{C}$=); 161.83 (C=O); 176.33 (d, $^2J_{PC}$ 5.54 Hz, SC=N). ^{31}P-NMR δ: 15.95.

5-Diisopropoxyphosphonyl-5-(4-methylthiazol-2-yl-) bicyclo[2.2.1]hept-2–ene *(VII)*

IIIa 0.5 g (1.73 mmol) and cyclopentadiene 0.15 g (2.27 mmol) in 10 ml of abs. Et_2O was allowed to react at room temperature for 24 h. The solvent and unreacted cyclopentadiene were removed in *vacuo*. Yield: 0,54 g of dark oil (89%), Found (%): C 57.46; H 7.32; N 3.94; P 8.73. Calcd. for $C_{17}H_{26}NO_3PS$ (%): C 57.41; H 7.29; N 4.01; P 6.83. ^{13}C-NMR (diastere-

omeric mixture,~1:1), δ: 16,97 ($\underline{CH_3}C=$); 23.57 and 23.88 ($\underline{CH_3}CH$); 45.53 (d, J_{PC} 76.6 Hz, PC); 53.57 (d, J_{PC} 140.4 Hz, PC); 34.51, 35.70, 41.05, 42.63, 47.31, 50.16, 51.11, 54.63 (C^1, C^3, C^4, C^7 of carbocycle); 71.00, 71.10 and 71.21 (CH_3 $\underline{CH}$); 113.35 and 113.63 (C^5 of thiazole); 131.88, 131.93, 132,16, 135.80, 135.88, 136,04 and 137.64 (C^5 and C^6 of carbocycle); 150.70 and 150.73 (C^4 of thiazole); 171.10 and 171.16 (C^2 of thiazole). ^{31}P-NMR δ: 26.35.

References

[1] G. Sturtz, G. Appere, K. Breistol, O. Fodstad, G. Schwartsmann, H. R. Hendriks, Eur. J. Med. Chem., **27,** 825 (1992).

[2] G. Sturtz, H Couthon, O. Fabulet, M. Mian, S. Rosini, Eur. J. Med. Chem., **28,** 899 (1993).

[3] P. Page, M.-R. Mazieres, J. Bellan, M. Sanchez, B. Chaudret, Phosphorus, Sulfur and Silicon, **70,** 205 (1992).

[4] T. Minami, M. Nakayama, K. Fujimoto, S. Matsuo, Phosphorus, Sulfur and Silicon, **75,** 135 (1993).

[5] B. A. Baimashev, N. A. Polezhaeva, B. A. Arbusov, Zhur : Obshch. Khim., **63,** 219 (1993).

[6] The chemistry of heterocyclic compounds, (ed. R.C. Elderfild) John Wiley & Sons, **V,** (1956).

[7] A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, Tetrahedron, **44,** 2021 (1988).

[8] E. J. Corey, D. L. Boger, Tetrahedron Lett., 4041 (1976).

[9] B. A. Baimashev, S. V. Grigor'ev, N.A. Polezhaeva, E. N. Klimovitskii, Zhur. Obshch. Khim., **65,** 522 (1995).

[10] G. Vernin, in: The Chemistry of Heterocyclic Compounds, (ed. J. V. Metzger) Vol. 34, Part III: General Synthetic Methods for Thiazole and Thiazolium Salts, John Wiley & Sons., 165 (1979).

[11] R. A. Nugent, M. Murphy, S. T. Schlachter, C. J. Dunn, R. J. Smith, N. D. Staite, L. A. Galinet, S. K. Shields, D. G. Aspar, K. A. Richard, N. A. Rohloff, J. Med. Chem., **36,** 134 (1993).

[12] M. Mikolajczyk, W. H. Midura, Tetrahedron: Asymmetry, **3,** 1515 (1992).