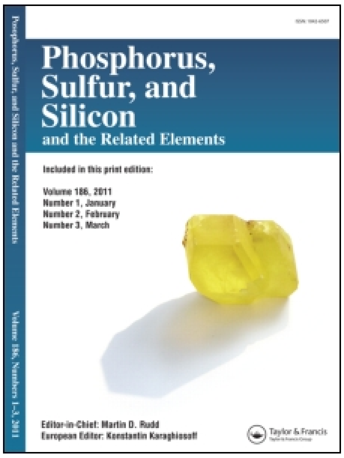

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Gröger, Harald , Goerlich, Jens R. , Schmutzler, Reinhard and Martens, Jürgen(2000) 'THE FIRST SYNTHESIS OF A 2H-1,4-BENZOTHIAZINE-BASED PHOSPHINE OXIDE AND SULFIDE', Phosphorus, Sulfur, and Silicon and the Related Elements, 166: 1, 253 — 259

To link to this Article: DOI: 10.1080/10426500008076546
URL: http://dx.doi.org/10.1080/10426500008076546

Phosphorus, Sulfur and Silicon, 2000, Vol. 166, pp. 253-259
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THE FIRST SYNTHESIS OF A 2H-1,4-BENZOTHIAZINE- BASED PHOSPHINE OXIDE AND SULFIDE

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(Received July 11, 2000)

The synthesis of a cyclic α-amino phosphine oxide and sulfide with an incorporated benzothiazine moiety is described. The products can be regarded as analogues of the biologically active thiazolidinylphosphonates, in which several characteristic functional groups have been modified.

Keywords: 3,4-Dihydrobenzothiazines; P nucleophiles; phosphine oxides; phosphine sulfides

INTRODUCTION

α-Aminophosphonic acids and derivatives thereof are efficient α-amino acid substitutes in physiological processes.[1] Their synthesis[2] has become an important topic in modern pharmaceutical chemistry. Among them, the thiazolidinylphosphonates **1**, which can be regarded as *N,S*-protected phosphonic acid analogues of the α-amino acid penicillamine, are described as biologically active compounds.[3] As an efficient strategy to design new pharmaceuticals with enhanced biological activity one can regard the selective transformation of functional groups while maintaining the characteristic molecular structure. In continuation of our research in

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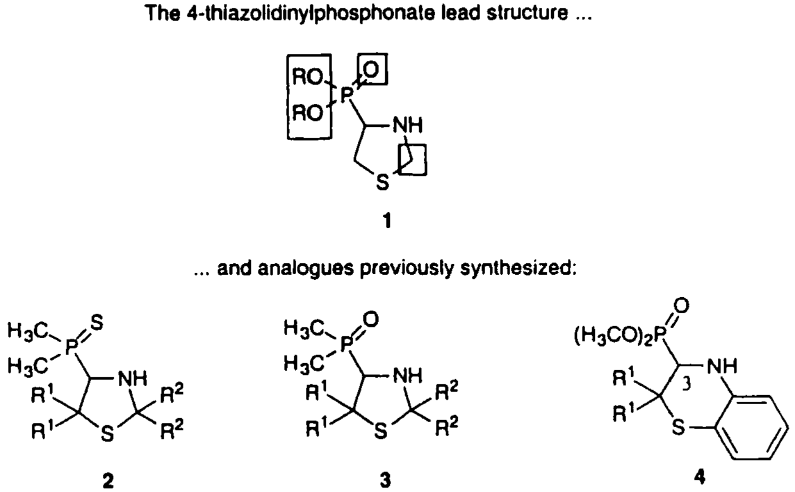
the field of thiazolidinylphosphonates[4,5] and derivatives[6–8] thereof, we have been interested in the synthesis of new analogues using the "modification potentials" shown in Scheme 1 as frames in **1**.



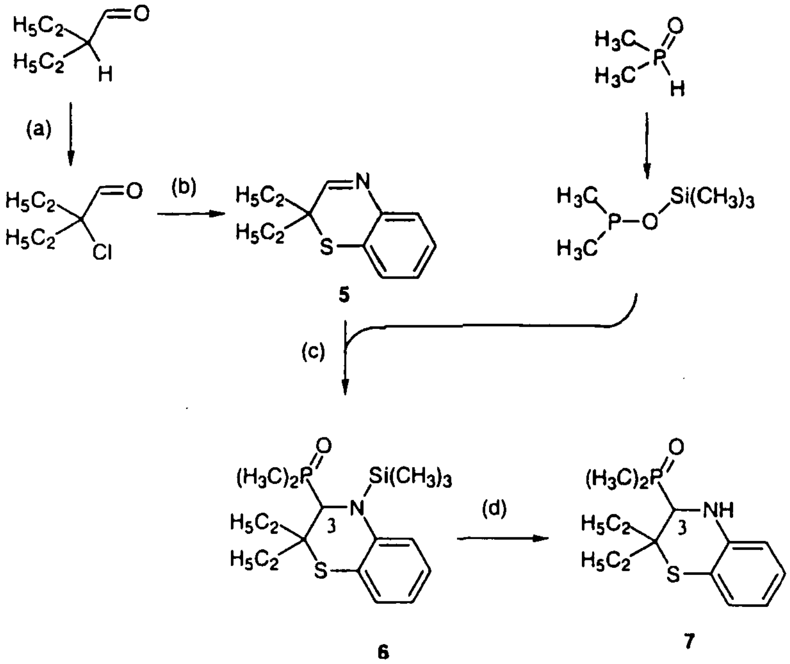
SCHEME 1 Thiazolidinylphosphonates **1** and derivatives thereof **2**, **3**, and **4**

In this connection, we already developed several routes for the preparation of phosphine sulfides **2** and phosphine oxides **3** as analogues of thiazolidinylphosphonates **1**.[6,7] In addition, the synthesis of 1,4-benzothiazinylphosphonates **4** has been reported.[8]

Such a 1,4-benzothiazine moiety is known to show significant biological activity.[9] Recent results[9] on anticancer activities of *N*-acylated 1,4-benzothiazines prompted us to communicate our results on the preparation of the novel 1,4-benzothiazine derivatives, **7** and **9** now. In these compounds, **7** and **9**, the benzothiazine heterocycle is combined with a phosphinoyl (in **7**) and a thiophosphinoyl group (in **9**).

RESULTS AND DISCUSSION

The synthesis of **7** was achieved by an economical three step route (Scheme 2). The starting materials are cheap and readily available, or are

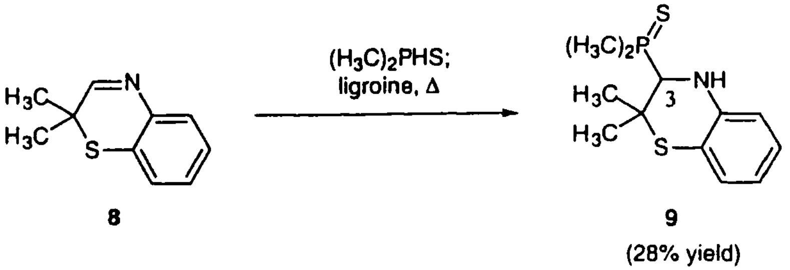


SCHEME 2 Synthesis of 3,4-dihydro-2*H*-1,4-benzothiazine-3-phosphine oxide 7 [(a) SO_2Cl_2; (b) 2-aminothiophenol, base [10]; (c) $(CH_3)_2PHO$, TMSCl; d) H_2O; 79 % (steps c and d)]

industrial waste materials, e.g. isobutyraldehyde. After preparing the α-chloro aldehyde starting from isobutyraldehyde, the *N*,*S*-heterocyclic imine **5** was obtained according to a procedure described by us earlier.[10] We were pleased to find that an addition of the trimethylsilyl derivative of dimethylphosphine oxide to the C=N double bond of **5** led to the desired aromatic *N*,*S*-heterocyclic phosphine oxide **7**. The first step of the reaction is the conversion of dimethylphosphine oxide into its trimethylsilyl derivative by adding trimethylsilylchloride to a solution of the phosphine oxide in dichloromethane at 0 °C. Subsequently, the imine **5** reacts with the silyl intermediate formed *in situ* to furnish the intermediate **6**. After hydrolysis the phosphine oxide adduct **7** was isolated in good yield (79%).

In order to prepare the corresponding thia derivative **9**, another synthetic route was chosen. In earlier investigations on the addition of dimethylphosphine sulfide to thiazolines we found that the route via a trimethylsilyl intermediate formed *in situ* (as in the case of **6**) is not suitable for the preparation of the dimethylphosphine sulfide adduct **9**.[6]

As an alternative preparative strategy a thermally activated addition of dimethylphosphine sulfide to the imine **8** was carried out to give the desired aromatic *N,S*-heterocyclic phosphine sulfide **9** (Scheme 3). Interestingly, there is no need for a catalyst for this addition reaction. However, the yield (28%) has been remarkably lower in the case of the less nucleophilic phosphine sulfide. Thus, replacing dimethylphosphine oxide by the less reactive dimethyl phosphine sulfide as a starting material led to a lower conversion rate. Accordingly, the yields depend strongly on the type of the phosphorus nucleophile.



SCHEME 3 Synthesis of 3,4-dihydro-2*H*-1,4-benzothiazine-3-phosphine sulfide **9**

Compared to the biologically active amino phosphonates **1**, in the structure of compound **9** the alkoxide group is replaced by an alkyl group. In addition, the P=O double bond was substituted by a P=S double bond, and the *N,S*-acetalic C-atom has been "changed" to an incorporated aromatic ring system. Thus, with the formation of the thiazolidinyl "analogue" **9** we succeeded in making use of all of the possible transformations shown in Scheme 1 (see frames in structure **1**).

In conclusion, we have reported the synthesis of the 2*H*-1,4-benzothiazine-3-phosphine oxide **7** and its sulfide analogue **9**, respectively. These compounds include a benzothiazine framework in combination with a phosphinoyl moiety. Caused by the fact that acylated derivatives are known to possess cytotoxic activity, the non-acylated compounds **7** and **9** further offer an access to new pharmaceutically interesting *N*-acylated structures.

EXPERIMENTAL SECTION

The melting points were determined in an open capillary tube on a *Dr. Linström* instrument and are uncorrected. The ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded on a Bruker AM 300 spectrometer, in $CDCl_3$ as a solvent. Mass spectra were recorded on a Finnigan-MAT 212 spectrometer. Elemental analyses were carried out on a Carlo Erba Stumentalione analyzer (MOD 1104) and were in accord with the calculated data (±0.4%). The 2*H*-1,4-benzothiazines **5** and **8** were prepared as described earlier.[10]

(±)-2,2-Diethyl-3,4-dihydro-2H-1,4-benzothiazin-3-yl dimethylphosphine oxide 7

To a solution of 0.20 g of dimethylphosphine oxide (2.5 mmol) and 0.39 ml of triethylamine (2.75 mmol) in 50 ml of abs. dichloromethane are added 0.35 ml of trimethylsilylchloride (2.75 mmol) at 0 °C under argon atmosphere (the reaction temperature should not exceed 5 °C!). After stirring the reaction mixture for 15 min 0.51 g 2,2-diethyl-2*H*-1,4-benzothiazine **5** (2.5 mmol), dissolved in 10 ml of abs. dichloromethane, were added dropwise. After the reaction mixture was allowed to warm up to room temperature the mixture was stirred for 8 h at room temperature to complete the reaction and was hydrolysed with water (50 mL). The organic layer was separated, and the aqueous layer was washed with dichloromethane (2 × 15 mL). The collected organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the crude product (as a solid). The solid product was filtered, washed with light petroleum and dried in vacuo (ca. 15 mbar).

Yield: 79 %. mp.: 175 °C. ^{1}H-NMR ($CDCl_3$): $\delta = 0.88$ [t, $^3J = 7.2$ Hz, 3H, $CH_2C\underline{H}_3$], 1.04 [t, $^3J = 7.3$ Hz, 3H, $CH_2C\underline{H}_3$], 1.55 [d, $^2J = 12.0$ Hz, 6H, $(CH_3)_2PO$], 1.56 – 1.79 [m, 2H, $C\underline{H}_2CH_3$], 2.00 – 2.26 [m, 2H, $C\underline{H}_2CH_3$], 3.73 [dd, $^3J = 6.6$ Hz, $^2J = 10.0$ Hz, 1H, C3-H], 4.94 – 5.00 [m, 1H, NH], 6.54 – 6.96 [m, 4H, aromat. C-H]. ^{13}C-NMR ($CDCl_3$): $\delta = 7.66$, 8.09 [2 × $CH_2\underline{C}H_3$], 15.99 [d, $^1J = 78.0$ Hz, CH_3PO], 16.87 [d, $^1J = 85.6$ Hz, CH_3PO], 26.00 [$\underline{C}H_2CH_3$], 28.85 [d, $^3J = 5.1$ Hz, $\underline{C}H_2CH_3$], 48.19 [C2], 58.31 [d, $^1J = 82.7$ Hz, C3], 115.15 – 138.23 [aromat. C]. MS (CI-Isobutane): m/z (%) = 284 (58) [MH^+], 206 (100) [$MH^+ - H(O)P(CH_3)_2$].

(±)-2,2-Dimethyl-3,4-dihydro-2H-1,4-benzothiazin-3-yl dimethylphosphine sulfide 9

In 30 ml of ligroine 0.29 g of 2,2-dimethyl-2*H*-1,4-benzothiazine **8** (1.6 mmol) and 0.19 g of dimethylphosphine sulfide (2 mmol) were dissolved and refluxed for 20 h. Subsequently, the hot reaction mixture was separated from the oily residue and the organic solvents were evaporated *in vacuo*. After dissolving the oily residue in a small amount of diethyl ether, the mixture was left to crystallize at −28 °C. Crystals formed after several days were collected by filtration, washed with petroleum ether (40/60), and dried in vacuo.

Yield: 28 %. mp.: 128 °C. ^{1}H-NMR ($CDCl_3$): $\delta = 1.57, 1.74$ [2s, 6H, $C(C\underline{H}_3)_2$], 1.81 [d, $^2J = 12.5$ Hz, 3H, CH_3P], 1.88 [d, $^2J = 12.4$ Hz, 3H, CH_3P], 3.69 [d, $^2J = 4.0$ Hz, 1H, C3-H], 5.08 – 5.39 [m, 1H, NH], 6.65 – 6.96 [m, 4H, aromat. C-H]. ^{13}C-NMR ($CDCl_3$): $\delta = 21.23$ [d, $^1J = 53.13$ Hz, CH_3P], 21.34 [d, $^1J = 48.0$ Hz, CH_3P], 27.41 [C2-$\underline{C}H_3$], 32.41 [d, $^3J = 4.8$ Hz, C2-$\underline{C}H_3$], 42.37 [C2], 64.72 [d, $^1J = 52.1$ Hz, C3], 116.02 – 137.62 [aromat. C]. ^{31}P-NMR ($CDCl_3$): $\delta = 46.19$ [P]. MS (CI-Isobutane): m/z (%) = 272 (28) [MH^+], 178 (100) [$MH^+ - (CH_3)_2PHS$].

Acknowledgements

Thanks are due to the *Heinz Neumüller Stiftung* for a Ph. D. course grant to *H. Gröger*, and to *Hoechst A.G.* for providing dimethylphosphine oxide. Also, the ongoing support of the *Fonds der Chemischen Industrie* is gratefully acknowledged.

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