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### A NOVEL SYNTHETIC APPROACH TO $\alpha$ -AMINOPHOSPHINE SULFIDE STRUCTURES: THE FIRST ADDITION OF DIMETHYL-PHOSPHINE SULFIDE TO 3-THIAZOLINES

Harald Gröger<sup>a</sup>; Jürgen Martens<sup>a</sup>; Jens R. Goerlich<sup>b</sup>; Reinhard Schmutzler<sup>b</sup>

<sup>a</sup> Fachbereich Chemie, Universität Oldenburg, Oldenburg, Germany <sup>b</sup> Institut für Anorganische und Analytische Chemie, Technische Universität, Braunschweig, Germany

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## A NOVEL SYNTHETIC APPROACH TO $\alpha$ -AMINOPHOSPHINE SULFIDE STRUCTURES: THE FIRST ADDITION OF DIMETHYLPHOSPHINE SULFIDE TO 3-THIAZOLINES

HARALD GRÖGER<sup>a</sup>, JÜRGEN MARTENS<sup>a\*</sup>, JENS R. GOERLICH<sup>b</sup> and  
REINHARD SCHMUTZLER<sup>b\*</sup>

<sup>a</sup>Fachbereich Chemie, Universität Oldenburg, Postfach 2503, 26111 Oldenburg, Germany; <sup>b</sup>Institut für Anorganische und Analytische Chemie, Technische Universität, Postfach 3329, 38023 Braunschweig, Germany

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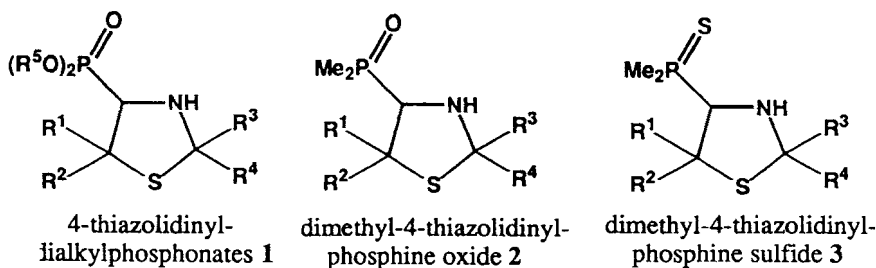
The addition of dimethylphosphine sulfide to the C=N double bond of heterocycles is described for the first time. The alkylation of the phosphine sulfide derivative was achieved via a new synthetic approach for this P-nucleophile. Starting from the S-containing, 5-membered 3-thiazolines the corresponding *N,S*-heterocyclic 3-thiazolidin-4-yl-dimethylphosphine sulfides **3** were prepared. The use of a chiral 3-thiazoline allowed investigations about the diastereoselectivity of the addition reaction with the phosphine sulfide nucleophile via 1,3-induction.

**Keywords:** 4-Thiazolidinylphosphine sulfides; Addition to the C=N double bond; Diastereoselectivity; Epimerization effect

### INTRODUCTION

$\alpha$ -Aminophosphonic acids and their derivatives are known to be physiologically active compounds.<sup>[1]</sup> They hold considerable interest due to possible medical applications. A versatile method widely used for the improvement of the properties of the compounds is the so-called *me-too* strategy. Using this, in the past we have synthesized analogues of  $\alpha$ -aminophosphonic acids by addition of P-nucleophiles to the C=N bond in acyclic and cyclic imines,<sup>[2,3]</sup> especially S-

\*Corresponding authors. E-Mail: martens@uni-oldenburg.de E-Mail: schmutzler@mac1.anchem.nat.tu-bs.de



containing phosphonic acid derivatives of type **1**, which are well known as pharmaceutically interesting compounds.<sup>[4]</sup>

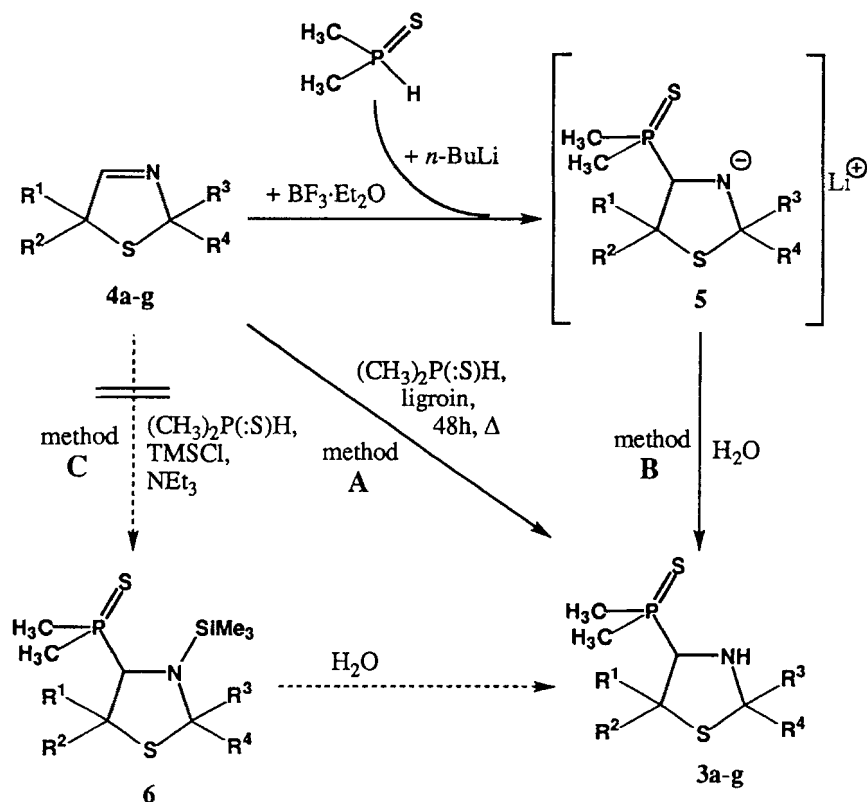
According to the *me-too* principle as a strategy in the development of optimized pharmaceuticals with improved structure-action relation, characteristic fragments of the pharmaceutically interesting 4-thiazolidinylphosphonates **1** were modified further (see Scheme 1). Therefore, we have recently described the preparation of dimethyl-(4-thiazolidinyl)phosphine oxides **2** by the reaction of various 3-thiazolines with dimethylphosphine oxide and species derived from the latter.<sup>[5]</sup> In these compounds (**2**), the phosphonic acid ester group was replaced by a dimethylphosphine oxide group.

Now we wish to report our attempts to make use of the same synthetic methods for the preparation of analogous 3-thiazolidinyl substituted dimethylphosphine sulfides of type **3**. Therein (compared to the phosphine oxides **2**), a S-Atom is replacing the O-atom in the P=O-double bond with preservation of the two methyl substituents at the P-atom. Moreover, these compounds seem to be interesting P=S analogues for the well known biologically active S-containing 4-thiazolidinylphosphonic acids and esters **1**.

To obtain these phosphine sulfides **3** we used - encouraged by previous investigations<sup>[3,5]</sup> - the *N,S*-heterocyclic 3-thiazolines **4** as starting components in addition reactions with dimethylphosphine sulfide under different reaction conditions.

## RESULTS AND DISCUSSION

As against the well investigated addition of dimethylphosphine sulfide to the C=O bond in carbonyl compounds,<sup>[6]</sup> information on the addition of phosphine sulfides to C=N bonds is rare. Until now, to the best of our knowledge, only the thermally induced addition of Me<sub>2</sub>P(:S)H to triazine as an imine synthon in the absence of a solvent has been described.<sup>[2]</sup> Although the acidity of Me<sub>2</sub>P(:S)H is 9.5 orders of magnitude higher than that of its oxygen analogue



SCHEME 2 Different synthetic methods in the preparation of 3-thiazolidines **3** ( $\text{R}^1\text{--R}^4$ : see Table I)

$\text{Me}_2\text{P}(\text{O})\text{H}$ ,<sup>[7]</sup> which means that in the tautomeric equilibrium the concentration of the active species  $\text{Me}_2\text{P-XH}$  is much higher for  $\text{X}=\text{S}$ , compared to  $\text{X}=\text{O}$ , previous investigations revealed that the addition of  $\text{Me}_2\text{P}(\text{O})\text{H}$  to  $\text{C}=\text{O}$  bonds proceeded much more smoothly than that of  $\text{Me}_2\text{P}(\text{S})\text{H}$ .<sup>[6]</sup> This may be due to the fact that  $\pi$ -interactions between P and S stabilize the  $\sigma^3$ -form  $\text{Me}_2\text{P-SH}$ . Furthermore, in the case of  $\text{Me}_2\text{P}(\text{O})\text{H}$  the direction of the reaction is shifted towards the addition product because of the thermodynamically favoured formation of the very strong  $\text{P}=\text{O}$  bond.

Nevertheless, the thermodynamically induced addition of  $\text{Me}_2\text{P}(\text{S})\text{H}$  to the reactive  $\text{C}=\text{N}$  bond of 3-thiazolines was possible although these electron-rich heterocycles normally exhibit low reactivity towards nucleophiles (Scheme 2/ Method A). The desired compounds **3a**, **e** and **3f** were obtained in 23 to 63% yield after 48 h of heating under reflux in ligroin. Addition under mild conditions

TABLE I Synthesis of racemic dimethyl-(4-thiazolidinyl)phosphine sulfides **3a–g** from thiazolines **4a–g**

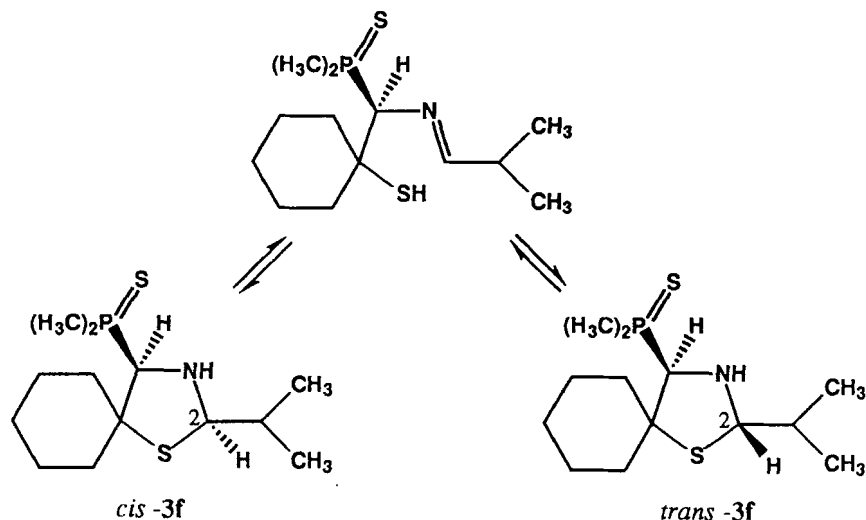
3[4 <sup>a</sup> ]	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	method <sup>b</sup>	yield <sup>c</sup>	dr <sup>d</sup>
a	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	A	63	—
					B(I)	34	—
					B(II)	78	—
b	CH <sub>3</sub>	CH <sub>3</sub>	—(CH <sub>2</sub> ) <sub>4</sub> —		B(II)	61	—
c	CH <sub>3</sub>	CH <sub>3</sub>	—(CH <sub>2</sub> ) <sub>5</sub> —		B(I)	32	—
					B(II)	56	—
d	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	B(I)	26	—
e	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	—(CH <sub>2</sub> ) <sub>4</sub> —		A	62	—
f	—(CH <sub>2</sub> ) <sub>5</sub> —		<i>i</i> Pr	H	A	23	66:34
					B(II)	49	69:31
g	—(CH <sub>2</sub> ) <sub>5</sub> —		—(CH <sub>2</sub> ) <sub>4</sub> —		B(II)	76	—

<sup>a</sup>The corresponding 3-thiazoline **4** was used as the starting imine component; <sup>b</sup>The methods A, B(I), and B(II) are described in detail in the experimental part; <sup>c</sup>Yield in %; <sup>d</sup>dr = diastereomeric ratio, determined from the <sup>31</sup>P-NMR spectra of the crude products.

took place when (i) the heterocycle was activated towards nucleophiles by treatment with the strong electron withdrawing Lewis acid boron trifluoride, and (ii) when the lithiated dimethylphosphine sulfide **5** was employed as the nucleophile (Scheme 2/ Method B). Numerous examples are known for the use of basic agents to catalyse this kind of addition,<sup>[8]</sup> but in contrast to observations on Me<sub>2</sub>P(:O)H<sup>[5]</sup> the generation of the corresponding anion **5** was only possible with *n*-butyl lithium at –50°C but not with potassium *t*-butylate. A disadvantage of pathway B is the considerably decreased yield (23–35%) when the reaction is carried out at low temperature (method B(I)). These yields were significantly increased, up to 78%, by heating the reaction mixture under reflux (method B(II)).

In the case of Me<sub>2</sub>P(:O)H another method for the generation of an active σ<sup>3</sup>-species is available by the transformation to its trimethylsilyl ester, which readily adds to C=O bonds,<sup>[6,9]</sup> as well as to the C=N bond of 3-thiazolines.<sup>[5]</sup> Attempts to make use of a highly reactive S-trimethylsilylated nucleophile, generated *in situ*, followed by hydrolysis of the resulting intermediate **6** led to the formation of the desired adducts only in poor yields (method (C); here the products were not isolated). This is presumably due to the low stability of the Si-S bond and to the formation of Me<sub>2</sub>P(:S)PMe<sub>2</sub> upon treatment of Me<sub>2</sub>P(:S)H with basic silylating agents.<sup>[10]</sup> The experimental data of the dimethyl-(3-thiazolidin-4-yl)phosphine sulfides **3a–g** are shown in Table I.

The compounds **3** are colorless solids, readily soluble in polar organic solvents but nearly insoluble in hexane or petroleum ether. The δ(<sup>31</sup>P)-values of **3a–3g** (36.30–38.40 ppm) are in the range expected for σ<sup>4</sup>P(V) compounds.<sup>[11]</sup> The difference between the δ(<sup>31</sup>P) values of **3a–3g** and those of the corresponding phosphine oxides<sup>[5]</sup> is small (ca. 3.5 ppm).



SCHEME 3 *cis/trans* Epimerization equilibrium of product **3f** (only one enantiomer each of the racemates *cis-3f* and *trans-3f* is shown)

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **3a–3g** prove the structures postulated. The doublets for the C4-H-proton with  $^2J(\text{P-H}) = 5.8\text{--}8.1$  Hz in the  $^1\text{H}$  NMR spectra of **3a–3g**, and the doublets for C4 with  $^1J(\text{P-C}) = 54.0\text{--}55.8$  Hz in the  $^{13}\text{C}$  NMR spectra are characteristic. The CI mass spectra of **3a–3g** show the protonated molecular ion  $[\text{M} + \text{H}]^+$  or characteristic fragments thereof (in case of **3e** and **3g**) as the base peak.

The addition of  $\text{Me}_2\text{P}(\text{:S})\text{H}$  to the  $\text{C}=\text{N}$  bond of the C2-chiral thiazoline **4f** provided information about the diastereoselectivity of the reaction *via* 1,3-induction. Surprisingly, the  $^{31}\text{P}$ -NMR spectrum of the crude product **3f** shows diastereoselectivity in nearly the same range around  $dr = 2:1$ , independent of the synthetic approach. This means that - at least - thermal activation as in method **A** as well as the boron trifluoride catalyzed method of preparation **B** led to the same diastereomeric ratios of the C2- and C4-chiral 3-thiazolidine derivative **3f** formed, in spite of the strongly different reaction conditions employed in this nucleophilic addition. Subsequently we investigated if, in addition to the kinetically controlled nucleophilic attack of the P-nucleophile to the  $\text{C}=\text{N}$  bond, a subsequent epimerization equilibrium at C2 would be possible, as is known from the ring-chain tautomerism of 3-thiazolidines.<sup>[3b,11]</sup> Such a postulated epimerization equilibrium - as shown in Scheme 3 - may be responsible for the similarity of the  $dr$  values.

To prove this, fractional crystallization was carried out to give **3f** with the major diastereomer enriched to  $dr = 91:9$ . The product **3f** was dissolved in

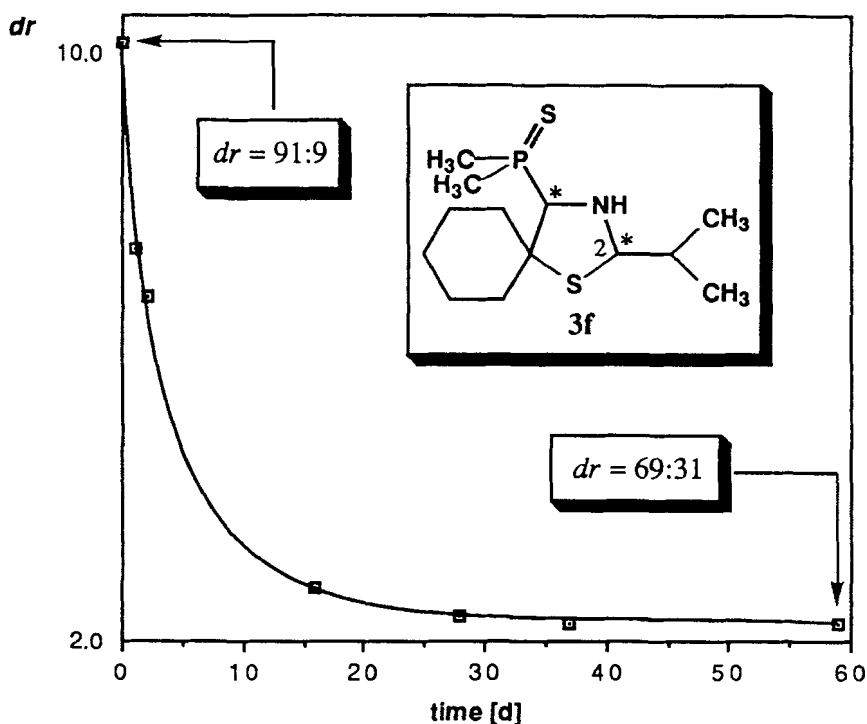


FIGURE 1 Time-epimerization correlation graph for **3f** (determined via  $^1\text{H}$ -NMR spectroscopy)

deuterated chloroform ( $\text{CDCl}_3$ ), stored at room temperature and  $^1\text{H}$  NMR spectra were recorded at different times. The observed *dr* values gave rise to the epimerization graph shown in Figure 1. Thereby, a strong decrease of the *dr*-values of **3f** from *dr* = 91:9 to *dr* = 69:31, caused by an epimerization effect at the C2 position, was found. The final *dr* values (*dr* = 69:31) were observed in the range of the *dr* values determined for the crude products **3f**. Consequently, a mechanistic model, which is schematically shown in Scheme 3, can be proposed. Thus, subsequently to the diastereoselective addition reaction forming **3f**, a thermodynamically controlled epimerization according to Scheme 3 led to the observed similar diastereoselectivities around *dr* = 2:1. So, the epimerization equilibrium is responsible for the similar *dr* values in both methods of preparation, in spite of the strongly dissimilar reaction conditions.

In summary, we have described a synthetic approach to dimethylphosphine adducts of 3-thiazolines **3** as interesting thio analogues of the well known biologically active 3-thiazolidin-4-ylphosphonates **1**. To the best of our knowledge, we are reporting, for the first time, the addition of dimethylphosphine sulfide to

imines, except for the case of triazine as a methylenimine synthon.<sup>[12]</sup> We obtained the products in satisfactory to good yields (up to 63% *via* method **A**, 78% *via* method **B**). A diastereoselective addition reaction with dimethylphosphine sulfide was carried out with the C2-chiral thiazoline **4f**, in order to investigate the 1,3-induction. In this case, *dr* values in the range of *dr* = 2:1 were observed independent of the experimental conditions. This could be explained by an epimerization equilibrium.

## EXPERIMENTAL SECTION

The melting points were determined in an open capillary tube on a *Dr. Linström* instrument and are uncorrected. Elemental analyses were carried out on a Carlo Erba Stumentalione analyzer (MOD 1104). The <sup>1</sup>H-, <sup>13</sup>C- and <sup>31</sup>P-NMR spectra were recorded on a Bruker AM 300 spectrometer, in CDCl<sub>3</sub> as a solvent. Mass spectra were recorded on a Finnigan-MAT 212 spectrometer (Datasystem SS 300). The 3-thiazolines **4a**, **b**, **c**,<sup>[7]</sup> **4d–g**<sup>[12]</sup> were prepared according to the modified *Asinger* one pot synthesis method.

### Dimethyl-(4-thiazolidinyl)phosphine Sulfides **3**; General Procedures (GP)

**GP 1 (method A):** The 3-thiazoline **4** (2.5 mmol) and dimethylphosphine sulfide (2.5 mmol) were dissolved in 30 ml of ligroine and refluxed for 24 h. Subsequently, the hot reaction mixture was separated from the oily residue and was left to crystallize at -28°C. Crystals formed after several days, and were collected by filtration, washed with petroleum ether (40/60), and dried in vacuo.

**GP 2 (method B):** At 0°C *n*-butyllithium (3.5 mmol; 1.6 M solution in hexane) was added to a solution of dimethylphosphine sulfide **2** (3.5 mmol) in abs. THF (15 mL) via a syringe in an atmosphere of argon. The resulting solution was maintained at 0°C for 30 min; then the solution of the boron trifluoride-activated 3-thiazoline **4** (2.5 mmol **3**, dissolved in 10 mL of abs. THF) was added at this temperature. After the reaction mixture was allowed to warm up to room temperature the mixture was stirred for 5 days at room temperature (**method B(I)**), or refluxed for 4 hours (**method B(II)**) to complete the reaction and was hydrolysed with water (10 mL). After addition of methyl *t*-butyl ether (10 mL) the organic layer was separated, washed with water (2 × 10 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the crude product. The solid products crystallized from the crude products after several days at 4°C. The solids were filtered, washed with light petroleum and dried in vacuo (around 15 mbar).



**(±)-2,2,5,5-Tetramethyl-3-thiazolidin-4-yl-dimethylphosphine sulfide 3a**

mp.: 130–131 °C; IR (KBr):  $\nu = 3270 \text{ cm}^{-1}$  (N-H).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.45 - 1.88$  [m, 18H,  $6 \times \text{CH}_3$ ], 3.22 [d, 1H,  $^2J = 6.3 \text{ Hz}$ , C4-H].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 21.18$  [d,  $^1J = 53.1 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 22.45 [d,  $^1J = 55.5 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 28.68, 29.31 [ $\text{C}5(\text{CH}_3)_2$ ], 31.91, 33.15 [ $\text{C}2(\text{CH}_3)_2$ ], 62.89 [C5], 68.29 [d,  $^1J = 54.2 \text{ Hz}$ , C4], 72.98 [d,  $^3J = 19.6 \text{ Hz}$ , C2].  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 37.34$  [P]. MS (CI-isobutane):  $m/z$  (%) = 238 (100) [ $\text{MH}^+$ ].  $\text{C}_9\text{H}_{20}\text{NPS}_2$  (237.3): calc. C 45.54, H 8.49, N 5.90; found C 45.02, H 8.47, N 5.56.

**(±)-2,2-Dimethyl-1-thia-4-aza-spiro[4.4]non-3-yl-dimethylphosphine sulfide 3b**

mp.: 114–116 °C; IR (KBr):  $\nu = 3290 \text{ cm}^{-1}$  (N-H).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.24 - 2.03$  [m, 20H,  $\text{C}2(\text{CH}_3)_2$ ,  $-(\text{CH}_2)_4-$  ( $\text{CH}_3$ ) $_2\text{PS}$ ], 2.09–2.21 [m, 1H, NH], 3.08 [d, 1H,  $^1J = 6.3 \text{ Hz}$ , C3-H].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 21.30$  [d,  $^1J = 52.8 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 22.36 [d,  $^1J = 55.3 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 23.67, 24.20, 41.06, 43.98 [ $-(\text{CH}_2)_4-$ ], 28.62, 29.56 [ $\text{C}2(\text{CH}_3)_2$ ], 61.45 [C2], 68.92 [d,  $^1J = 54.3 \text{ Hz}$ , C3], 82.00 [d,  $^3J = 19.5 \text{ Hz}$ , C5].  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 36.30$  [P]. MS (CI-isobutane):  $m/z$  (%) = 264 (100) [ $\text{MH}^+$ ].  $\text{C}_{11}\text{H}_{22}\text{NPS}_2$  (263.3): calc. C 50.16, H 8.42, N 5.32; found C 50.01, H 8.20, N 4.96.

**(±)-2,2-Dimethyl-1-thia-4-aza-spiro[4.5]dec-3-yl-dimethylphosphine sulfide 3c**

mp.: 134–135 °C; IR (KBr):  $\nu = 3280 \text{ cm}^{-1}$  (N-H).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.15 - 2.20$  [m, 22H,  $\text{C}2(\text{CH}_3)_2$ ,  $-(\text{CH}_2)_5-$  ( $\text{CH}_3$ ) $_2\text{PS}$ ], 2.86 [br s, 1H, NH], 3.22 [d, 1H,  $^1J = 5.8 \text{ Hz}$ , C3-H].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 21.27$  [d,  $^1J = 53.4 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 22.48 [d,  $^1J = 55.4 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 23.55, 25.15, 25.41, 41.37, 41.47 [ $-(\text{CH}_2)_5-$ ], 28.84, 29.25 [ $\text{C}2(\text{CH}_3)_2$ ], 60.36 [C2], 67.42 [d,  $^1J = 54.2 \text{ Hz}$ , C3], 78.48 [d,  $^3J = 19.3 \text{ Hz}$ , C5].  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 37.75$  [P]. MS (CI-isobutane):  $m/z$  (%) = 278 (100) [ $\text{MH}^+$ ].  $\text{C}_{12}\text{H}_{24}\text{NPS}_2$  (277.4): calc. C 51.95, H 8.72, N 5.05; found C 51.48, H 8.70, N 4.94.

**(±)-2,2,5,5-Tetraethyl-3-thiazolidin-4-yl-dimethylphosphine sulfide 3d**

mp.: 67–68 °C; IR (KBr):  $\nu = 3270 \text{ cm}^{-1}$  (N-H).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 0.84 - 1.11$  [m, 12H,  $4 \times \text{CH}_2\text{CH}_3$ ], 1.58–2.01 [m, 14H,  $(\text{CH}_3)_2\text{PS}$ ,  $4 \times \text{CH}_2\text{CH}_3$ ], 2.74 [br s, 1H, NH], 3.34 [d, 1H,  $^2J = 7.8 \text{ Hz}$ , C4-H].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 9.40, 9.62, 9.69, 9.94$  [ $4 \times \text{CH}_2\text{CH}_3$ ], 21.20 [d,  $^1J = 53.3 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 22.49 [d,  $^1J = 55.6 \text{ Hz}$ ,  $\text{CH}_3\text{PS}$ ], 27.36, 32.25, 32.44, 34.64 [ $4 \times \text{CH}_2\text{CH}_3$ ],

62.57 [d,  $^1J = 54.3$  Hz, C4], 70.96 [C5], 81.47 [d,  $^3J = 18.8$  Hz, C2].  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 37.73$  [P]. MS (CI-isobutane):  $m/z$  (%) = 294 (100) [ $\text{MH}^+$ ].  $\text{C}_{13}\text{H}_{28}\text{NPS}_2$  (293.4): calc. C 53.21, H 9.62, N 4.77; found C 53.12, H 9.61, N 4.32.

**(±)-2,2-Dimethyl-1-thia-4-aza-spiro[4.4]non-3-yl-dimethylphosphine sulfide**  
**3e**

mp.: 70–71 °C; IR (KBr):  $\nu = 3280$   $\text{cm}^{-1}$  (N-H).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 0.98$  [t,  $^3J = 7.2$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ], 1.06 [t,  $^3J = 7.3$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ], 1.62–2.15 [m, 12H,  $-(\text{CH}_2)_4-$ ,  $2 \times \text{CH}_2\text{CH}_3$ ], 1.76 [d,  $^2J = 12.6$  Hz, 3H,  $\text{CH}_3\text{PS}$ ], 1.81 [d,  $^2J = 12.8$  Hz, 3H,  $\text{CH}_3\text{PS}$ ], 2.81 [br s, 1H, NH], 3.22 [d,  $^2J = 8.1$  Hz, 1H, C3-H].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 9.85, 9.96$  [ $2 \times \text{CH}_2\text{CH}_3$ ], 21.32 [d,  $^1J = 54.1$  Hz,  $\text{CH}_3\text{PS}$ ], 22.25 [d,  $^1J = 55.2$  Hz,  $\text{CH}_3\text{PS}$ ], 23.76, 24.23, 40.90, 43.81 [ $-(\text{CH}_2)_4-$ ], 27.74, 32.58 [ $\text{C}2(\text{CH}_3)_2$ ], 63.89 [d,  $^1J = 54.8$  Hz, C3], 71.90 [C2], 81.15 [d,  $^3J = 18.5$  Hz, C5].  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 36.96$  [P]. MS (CI-isobutane):  $m/z$  (%) = 292 (68) [ $\text{MH}^+$ ], 198 (100) [ $\text{MH}^+ - (\text{CH}_3)_2\text{PHS}$ ].  $\text{C}_{13}\text{H}_{26}\text{NPS}_2$  (291.4): calc. C 53.57, H 8.99, N 4.81; found C 53.25, H 8.78, N 4.53.

**(±)-2-Isopropyl-1-thia-3-aza-spiro[4.5]dec-4-yl-dimethylphosphine sulfide 3f**  
**(mixture of diastereomers)**

mp.: 107–109 °C (method A); mp.: 99–102 °C (method B(II)); IR (IBr):  $\nu = 3270$   $\text{cm}^{-1}$  (N-H);  $^1\text{H}$  NMR (major diastereomer) ( $\text{CDCl}_3$ ):  $\delta = 0.80 - 2.17$  [m, 23H,  $(\text{CH}_3)_2\text{PS}$ ,  $-(\text{CH}_2)_5-$ ,  $\text{CH}(\text{CH}_3)_2$ ], 2.83 [d,  $^2J = 6.8$  Hz, 1H, C4-H], 4.35 [d,  $^2J = 6.6$  Hz, 1H, C2-H];  $^1\text{H}$  NMR (minor diastereomer) ( $\text{CDCl}_3$ ):  $\delta = 0.80 - 2.17$  [m, 23H,  $(\text{CH}_3)_2\text{PS}$ ,  $-(\text{CH}_2)_5-$ ,  $\text{CH}(\text{CH}_3)_2$ ], 2.93 [d,  $^2J = 6.0$  Hz, 1H, C4-H], 4.17 [d,  $^2J = 8.8$  Hz, 1H, C2-H];  $^{13}\text{C}$  NMR (major diastereomer) ( $\text{CDCl}_3$ ):  $\delta = 19.57, 20.46$  [ $\text{CH}(\text{CH}_3)_2$ ], 21.75 [d,  $^1J = 54.2$  Hz,  $\text{CH}_3\text{PS}$ ], 22.22 [d,  $^1J = 54.8$  Hz,  $\text{CH}_3\text{PS}$ ], 23.56, 25.47, 27.55, 37.08, 39.74 [ $-(\text{CH}_2)_5-$ ], 33.53 [ $\text{CH}(\text{CH}_3)_2$ ], 67.78 [C5], 71.09 [d,  $^1J = 55.2$  Hz, C4], 75.62 [d,  $^3J = 19.6$  Hz, C2];  $^{13}\text{C}$  NMR (minor diastereomer) ( $\text{CDCl}_3$ ):  $\delta = 19.72, 20.24$  [ $\text{CH}(\text{CH}_3)_2$ ], 21.76 [d,  $^1J = 54.1$  Hz,  $\text{CH}_3\text{PS}$ ], 22.03 [d,  $^1J = 54.5$  Hz,  $\text{CH}_3\text{PS}$ ], 23.73, 25.47, 27.55, 36.03, 39.28 [ $-(\text{CH}_2)_5-$ ], 35.44 [ $\text{CH}(\text{CH}_3)_2$ ], 68.55 [C5], 68.65 [d,  $^1J = 54.8$  Hz, C4], 73.85 [d,  $^3J = 17.6$  Hz, C2];  $^{31}\text{P}$  NMR (major diastereomer) ( $\text{CDCl}_3$ ):  $\delta = 37.36$  [P];  $^{31}\text{P}$  NMR (minor diastereomer) ( $\text{CDCl}_3$ ):  $\delta = 38.40$  [P]; MS (CI-isobutane):  $m/z$  (%) = 292 (100) [ $\text{MH}^+$ ], 198 (81) [ $\text{MH}^+ - (\text{CH}_3)_2\text{P}(\text{S})\text{H}$ ].  $\text{C}_{13}\text{H}_{26}\text{NPS}_2$  (291.4): calc. C 53.57, H 8.99, N 4.81; found C 53.31, H 8.88, N 4.46.

**(±)-7-Thia-13-aza-dispiro[5.1.4.2]tetradec-14-yl-dimethylphosphine sulfide  
3g**

mp.: 150–151 °C.; IR (KBr):  $\nu$  = 3270 cm<sup>-1</sup> (N-H). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.04 – 2.20 [m, 24H, 2 × CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-], 1.80 [d, <sup>2</sup>J = 12.6 Hz, 3H, CH<sub>3</sub>PS], 1.90 [d, <sup>2</sup>J = 12.8 Hz, 3H, CH<sub>3</sub>PS], 2.54–2.86 [br s, 1H, NH], 3.01 [d, <sup>2</sup>J = 7.3 Hz, 1H, C14-H]. <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 21.82 [d, <sup>1</sup>J = 53.9 Hz, CH<sub>3</sub>PS], 22.21 [d, <sup>1</sup>J = 56.1 Hz, CH<sub>3</sub>PS], 23.68, 23.73, 24.28, 25.53, 27.67, 36.44, 39.93, 40.90, 43.84 [-(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-], 69.20 [C6], 69.56 [d, <sup>1</sup>J = 54.3 Hz, C14], 81.34 [d, <sup>3</sup>J = 19.3 Hz, C12]. <sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta$  = 37.38 [P]. MS (CI-isobutane): *m/z* (%) = 304 (12) [MH<sup>+</sup>], 210 (100) [MH<sup>+</sup> – (CH<sub>3</sub>)<sub>2</sub>PHS]. C<sub>14</sub>H<sub>26</sub>NPS<sub>2</sub> (303.4): calc. C 55.41, H 8.64, N 4.62; found C 54.98, H 8.54, N 4.34.

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