Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Phosphinic Acid Analogues of Thiaproline and the Related Heterocyclic Aminophosphinic Acids

Mostafa Hatam [a] & Jürgen Martens [a]
[a] Fachbereich Chemie, Universität Oldenburg , P. O. Box 2503, D-26111, Oldenburg, Federal Republic of Germany
Published online: 23 Sep 2006.

To cite this article: Mostafa Hatam & Jürgen Martens (1995) Phosphinic Acid Analogues of Thiaproline and the Related Heterocyclic Aminophosphinic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:17, 2553-2559, DOI: 10.1080/00397919508011799

To link to this article: http://dx.doi.org/10.1080/00397919508011799

SYNTHETIC COMMUNICATIONS, 25(17), 2553-2559 (1995)

# PHOSPHINIC ACID ANALOGUES OF THIAPROLINE AND THE RELATED HETEROCYCLIC AMINOPHOSPHINIC ACIDS

Mostafa Hatam and Jürgen Martens*

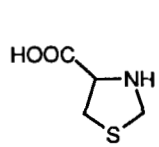
Fachbereich Chemie, Universität Oldenburg, P. O. Box 2503, D-26111 Oldenburg, Federal Republic of Germany



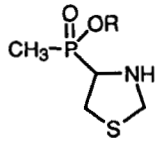
**Abstract:** Bis(trimethylsilyl) phosphonite adds in a 1,2 fashion to the C=N bond in 3-thiazolines **3a-d** to give after hydrolysis phosphinic acids **5a-d**. Starting from 3-oxazines, the corresponding **6a,b** phosphinic acids **7a,b** were obtained.

1-Aminoalkylphosphonic acids and 1-aminoalkylphosphinic acids, the isosters of 1-aminoalkylcarboxylic acids, have lately found increasing attention which reflects their applications in medicine and agriculture. The latter compounds are for example inhibitors of the angiotensine converting enzyme[1] HIV-protease[2] and glutamine synthease[3]. A number of phosphonic acid analogues of amino acids have been synthesized in the last years[4]. Because of the wide medical applications of derivatives of thiaproline[5] **1** and the interest for the synthesis of the related phosphinic acid analogues **5** we have earlier reported[6] on the synthesis of phosphinates **2** (R= alkyl), which was based on the addition of an alkyl phosphinate to the 1,3-thiazolines.

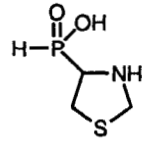
* To whom correspondence should be addressed.



1



2

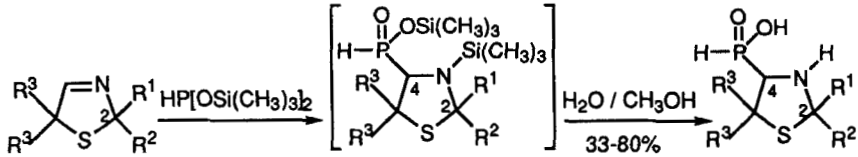


5

In the course of our investigations on the synthesis and chemistry of heterocyclic compounds with an reactive C=N-double bond (1,3-thiazolines[7], 1,3-oxazolines[8], and 1,3-oxazines[9]), we have used bis(trimethylsilyl) phosphonite for the addition to the imine compounds **3a-d** in order to prepare the new phosphinic acid analogues **5a-d** of thiaproline.

## Results and discussion

The reactivity of bis(trimethylsilyl) phosphonite[10] towards aldehydes, ketones[11] and the 1-diphenylmethylimines[12] is well estabilished. We have found that bis(trimethylsilyl) phosphonite reacts with 1,3-thiazolines **3a-d** under mild condition to

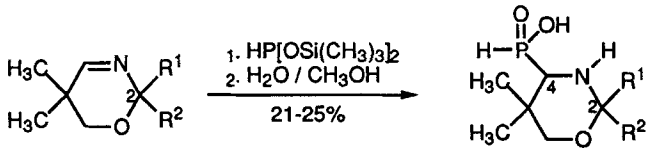


**3a-d** **4a-d** **5a-d**

| 3,4,5 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | *t*-C4H9 | H | CH3 |
| b | *i*-C3H7 | H | CH3 |
| c | —(CH2)5— | | CH3 |
| d | CH3 | CH3 | H |

give the corresponding *N,O*-bis(trimethylsilyl) phosphinates **4a-d**. These were then converted easily without previous isolation by simple hydrolysis into the free 1-amino phosphinic acids **5a-c** in 20-80% yield (Scheme 1). In the case of **5d**, a mixture of P-C-N and P-N-C isomers was observed with the overall yield of 80%.

The extension of this reaction to the chemistry of 1,3-oxazines **6a** and **6b** afforded the corresponding α-amino phosphinic acids **7a** and **7b** in 21 and 25% yield respectively. Table 1 shows the yields, melting points, IR and mass spectroscopy data of the obtained products.




**6a-b** **7a-b**

| 6,7 | $R^1$ | $R^2$ |
|---|---|---|
| a | —$(CH_2)_5$— | |
| b | H | *i*-$C_3H_7$ |

**Table 1**

| Product | Yield[%][a] | m.p(°C)[c] | IR($cm^{-1}$)[d] | MS[e] |
|---|---|---|---|---|
| **5a** | 33[b] | 185 | 3405, 2300 | 238(100)[f] |
| **5b** | 20[b] | 182 | 3399, 2900 | 127(100)[g] |
| **5c** | 20 | 203 | 3420, 2900 | 250(100)[f] |
| **5d** | 80 | oil | 3410, 2910 | 182(25)[f] |
| **7a** | 25 | 199 | 3400, 2910 | 248(5)[f] |
| **7b** | 21[b] | 191 | 3390, 2920 | 141(100)[g] |

[a] overall yield based on the amount of **3a-d** and **6a-b** respectively; [b] diastereomeric ratio :≥ 95%; [c] uncorrected; [d] $\nu_{max}$ , the OH and PH characteristic bands respectively, **5a-c** and **7a-b** in KBr cell, **5d**: neat; [e] CI, Isobutane, *m/e* (%); [f] $[MH^+]$; [g] $[MH^+-H_2PO_2-2CH_3]$.

The structures of the products **5a-d** and **7a-b** were confirmed by mass spectroscopy, NMR and elemental analysis. The starting materials **3a**, **3b**, and **6b** have a stereogenic center at C-2 which released an 1,3-distereoselectivity induction at C-4 through the addition of bis(trimethylsilyl) phosphonite. The analysis of NMR data of the related products **5a**, **5b** and **7b** have demonstrated a diastereoselectivity ≥

95:5. Taking into account the well-known fact that the orientation of the addition of other reagents to the C=N double bond of 1,3-thiazolines[13], 1,3-oxazolines[14] and 1,3-oxazines[9] was strongly induced with a stereogenic center at C-2, this observation for the 1,3-induction is not far-off the expected.

## Experimental

Melting points were determined in an open capillary tube on a Dr. Linström instrument and were uncorrected. The elemental analyses were carried out on a Carlo Erba Stumentalione (MOD 1104) and the results were in agreement within satisfactory microanalysis ± 0.4. The IR spectra were recorded on a Beckman spectrophotometer(IR 4220). The $^{1}H$-, $^{13}C$- and $^{31}P$-NMR spectra were recorded on a Bruker-Karlsruhe AM 300 spectrometer and chemical shifts were presented in ppm from the internal standards tetramethylsilane for $^{1}H$ and $^{13}C$ and phosphoric acid 85% for $^{31}P$ measurements( in NaOD/$D_2O$). The 1,3-thiazolines[6] and 1,3 oxazines[9,15] were prepared according to the literature. The mass spectroscopy data were recorded on a Finnigan-MAT 212(data system SS 300) spectrometer.

**1-Aminoalkylphosphinic Acids 5a-d and 7a-b; General Procedure:**

In a 3-neck round-bottomed flask equipped with septum and condenser were heated ammonium phosphite[16] (20 mmol, 1.67 g) and hexamethydisilazane (20 mmol, 4.3 mL), together under argon at 100-110°C for 1-2 h. The *in situ* prepared bis(trimethylsily)phosphonite, BTSP, was cooled to 0°C and absolute dichloromethane was injected(10 mL), followed by the imine compound (20 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight. In the cases of **5a-c** and **7a-b**, a mixture of water (5 mL) and methanol (15 mL) was added and stirred for 5h. The solvent was evaporated under reduced pressure, methanol (10 mL) was added to the crude product and a certain time was given until the precipitation was completed. The white crystals were filtered and dried in *vaco*. In the case of **5d** the product was first filtered off from the white solid materials of the reaction mixture and then hydrolyzed as explained above followed by complete removing of the solvent under reduced pressure. The product was obtained as a colorless oil.

***rac*-2-tert-butyl-5,5-dimethyl-4-thiazolidinyl phosphinic acid; 5a:**

$^1$H-NMR(NaOD-$D_2O$/δ): 0.60[s, 9H, $C(CH_3)_3$]; 1.03, 1.22(2s, 6H, C5-$CH_3$); 2.38(d, $J$= 9.33 Hz, 1H, C4-H); 4.10(s, 1H, C2-H); 5.83-7.57(2d, $J_{PH}$=521 Hz, 1H, PH).

$^{13}$C-NMR(NaOD-$D_2O$/δ): 26.64[C($\underline{C}H_3)_3$]; 28.65, 29.05(C5-$CH_3$); 33.70(C5); 57.53 [$\underline{C}(CH_3)_3$]; 72.34(C4); 81.19(C2).

$^{31}$P-NMR(NaOD-$D_2O$/δ): 20.61.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_9H_{20}NO_2PS$(237.1) | Calc. | C | 45.55 | H | 8.50 | N 5.91 |
| | found | C | 45.23 | H | 8.19 | N 5.91 |

***rac*-2-isopropyl-5,5-dimethyl-4-thiazolidinyl phosphinic acid; 5b:**

$^1$H-NMR(NaOD-$D_2O$/δ): 0.77-0.84[2d, J= 6.56 Hz, 6H, $CH(C\underline{H}_3)_2$]; 1.29, 1.45(2s, 6H, C5-$CH_3$); 1.67-1.80[m, 1H, $C\underline{H}(CH_3)_2$]; 2.61(d, $J$=10.30 Hz, C4-H); 4.21(d, J=7.02 Hz, C2-H); 5.96-7.79(2d, $J_{PH}$=519.6 Hz, $^3J$=31.9 Hz, 1H, PH).

$^{13}$C-NMR(NaOD-$D_2O$/δ): 19.64, 20.25[$CH(\underline{C}H_3)_2$]; 28.87, 29.29(C5-$\underline{C}H_3$); 33.60 [$\underline{C}H(CH_3)_2$]; 58.18(C5); 72.42(C4); 77.36(C2).

$^{31}$P-NMR(NaOD-$D_2O$/δ): 20.80.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_8H_{18}NO_2PS$(223.1) | Calc. | C | 43.03 | H | 8.13 | N 6.28 |
| | found | C | 42.91 | H | 8.29 | N 6.10 |

***rac*-1-thia-4-aza-spiro[4.5]dec-3-yl phosphinic acid; 5c:**

$^1$H-NMR(NaOD-$D_2O$/δ):0.99, 1.11(2s, 6H, 2×$CH_3$); 0.82-2.00(m, 10H, cyclohexy -$CH_2$); 2.59(d, $J$=10.71Hz, C3-H); 5.76-7.49(d, $J_{PH}$=518.8 Hz, 1H, PH).

$^{13}$C-NMR(NaOD-$D_2O$/δ):28.73, 30.92(2×$CH_3$); 23.26, 25.88, 40.33, 40.60, 58.73 (cyclohexy-$CH_2$); 34.74(C5); 69.10(C6); 80.40(C2)

$^{31}$P-NMR(NaOD-$D_2O$/δ): 21.11.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{10}H_{20}NO_2PS$(249.3) | Calc. | C | 48.18 | H | 8.09 | N 5.62 |
| | found | C | 47.82 | H | 8.25 | N 5.31 |

***rac*-2,2-dimethyl-4-thiazolidinyl phosphinic acid; 5d:**

$^1$H-NMR(NaOD-$D_2O$/δ):1.59, 1.64(2s, 6H, 2×$CH_3$); 2.87-2.94(m, 1H, C4-H); 3.23-3.41(m, 2H, $CH_2S$); 5.85-7.89(d, $J_{PH}$=612.4 Hz, 1H, PH).

$^{13}$C-NMR(NaOD-$D_2O$/δ):22.06, 22.26(2×$CH_3$); 30.79(C5); 59.87(C4); 74.21(C2).

$^{31}$P-NMR(NaOD-$D_2O$/δ): 20.22.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_5H_{12}NO_2PS$(181.0) | Calc. | C | 33.14 | H | 6.68 | N 7.74 |
| | found | C | 32.89 | H | 6.21 | N 8.04 |

**rac-3,3-dimethyl-1-oxa-5-aza-spiro[5.5]undec-4-yl phosphinic acid; 7a:**

$^1$H-NMR(NaOD-$D_2O$/δ):0.97, 1.15(2s, 6H, 2×$CH_3$); 0.82-2.00(m, 10H, cyclohexy -$CH_2$); 2.59(d, $J$=13.24 Hz, C4-H); 3.29-3.38(m, 2H, $CH_2O$); 6.08-7.87(d, $J_{PH}$=538.19 Hz, 1H, PH).

$^{13}$C-NMR(NaOD-$D_2O$/δ):28.43, 30.28(2×$CH_3$); 23.42, 24.53, 40.60, 40.33, 58.73 (cyclohexy-$CH_2$); 35.43(C5); 58.60(C6); 70.44(C2).

$^{31}$P-NMR(NaOD/δ): 19.40.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{11}H_{22}NO_3P$(247.1) | Calc. | C | 53.41 | H | 8.97 | N 5.67 |
| | found | C | 53.21 | H | 8.62 | N 5.39 |

***rac*-2-isopropyl-5,5-dimethyl-4-oxazinanyl phosphinic acid;7b:**

$^1$H-NMR(NaOD-$D_2O$/δ):0.69-0.79, 0.83-0.91(m, 12H, 4×$CH_3$); 1.59-1.70[m, 1H, C<u>H</u>($CH_3$ )$_2$]; 2.63(d, $J$=10.11 Hz, C4-H); 3.15, 3.39(2×d, $J$=10.92 Hz, 2H, $CH_2O$); 4.30(m, 1H, C2-H); 5.99-7.18(d, $J_{PH}$=521.23 Hz, 1H, PH).

$^{13}$C-NMR(NaOD-$D_2O$/δ):17.18, 17.25, 21.30, 21.65(4×<u>C</u>$H_3$); 17.54[<u>C</u>H($CH_3$)$_2$]; 32.62(C5); 72.03(C6), 81.28(C2).

$^{31}$P-NMR(NaOD-$D_2O$/δ): 19.91.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_9H_{20}NO_3P$(221.2) | Calc. | C | 48.86 | H | 9.11 | N 6.33 |
| | found | C | 48.49 | H | 8.87 | N 6.48 |

***Acknowledgement:*** This research was supported, in part, by the *Fonds der Chemischen Industrie*, *Deutsche Forschungsgemeinschaft* and *Degussa AG*.

## References and note:

(1) Wyvratt, M. J.; Patchett, A. A. *Medical Research Reviews* **1985**, *5*, 483.

(2) Peyman, A.; Budt, K.-H. ; Spanig, J. ; Stowasser, B.; Rupert, D. *Tetrahedron Lett.* **1992**, *33*, 4549.

(3) Bayer, E.; Gugel, K. H.; Hägele, K.; Hagenmaier, H.; Jessipow, S.; König, W. A.; Zähner, A. *Helv. Chim. Acta* **1972**, 55, 224.

(4) (a) Tam, C. C.; Mattoks, K. L.; Tishler, M. *Synthesis* **1982**, 188; (b) Oleksyszyn, J.; Gruszecka, E.; Kafarski, P.; Mastalerz, P. *Monatsh. Chem.* **1982**, *113*, 59; (c): Vasella, A.; Veoffray, R. *Helv. Chim. Acta* **1982**, *65*, 1953; (d) Subotkowski, W.; Kowalik, J.; Tyka, R.; Mastalerz, P. *Pol. J. Chem.* **1981**, *55*, 853; (e) Zygmunt, J.; Mastalerz, P. *Pol. J. Chem.*

**1981**, *55*, 411; (f) Issleib, K.; Döpfer, K.-P., Balzuweit, A. *Z. Chem.* **1982**, *22*, 215; (g) Kowalik, J.; Zygmunt, J.; Mastalerz, P. *Pol. J. Chem.* **1981**, *55*, 713 ; (h) Jiao, X.-Y.; Borloo, M.; Verbruggen, C.; Haemers, A., *Tetrahedron Lett.* **1994**, *35*, 1103.

(5) (a) Jaffe, J. A. *Arthritis Rheum.* **1970**, *13*, 436; (b) Sternlieb, I.; Scheinberg, I. H. *J. Am. Med. Assoc.* **1946**, *189*, 748; (c) Crawhall, J. C.; Scowen, E. F.; Watts, R. W. E., *Brit. Med. J.* **1963**, *1*, 588; (d) Henkin, R. J.; Keiser, H. R.; Jaffe, J. A.; Sternlieb, I.; Scheinberg, I. H. *Lancet* **1967**, 1268.

(6) Drauz, K.; Koban, H. G.; Martens, J.; Schwarze, W. *Liebigs Ann. Chem.* **1985**, 448.

(7) (a) Martens, J.; Kintscher, J.; Arnold, W. *Tetrahedron* **1991**, *47*, 7029; (b) Wagner, B.; Martens, J.; Beck, W. *Z. Naturforsch.* **1992**, *47b*, 1343; (c) Martens, J.; Janknecht, H.-H. *Sulfur Lett.* **1990**, *11*, 263; (d) Martens, J.; Lindner, K.; Kintscher, J. *Sulfur Lett.* **1992**, *14*, 1; (e) Kintscher, J.; Martens, J. *Synthesis* **1992**, 837; (f) Köpper, S.; Lindner, K.; Martens, J. *Tetrahedron* **1992**, *48*, 10277; (g) Martens, J.; Kintscher, J.; Lindner, K; Pohl, S; Saak, W.; Haase, D. *Liebigs Ann. Chem.* **1991**, 305.

(8) Weber, M.; Jakob, J.; Martens, J. *Liebigs Ann. Chem.* **1992**, 1.

(9) Hatam, M.; Gröger, H; Martens, J., to be submitted.

(10) Issleib, K.; Mogelin, W.; Balszuweit, A. *Z. Anorg. Chem.* **1985**, *530*, 16.

(11) Pidovic, A. N.; Konowalowa, I. W.; Romanov, G. W.; Nasmutdinov, R. J. *Phosphorus* **1975**, *5*, 105.

(12) Grobelny, D. *Synthesis* **1987**, 942.

(13) See Ref. 8(a).

(14) Weber, M., *Ph. D.* Dissertation, University of Oldenburg, Germany, **1992**, 58.

(15) Dömling, A.; Ugi, I. K. *Tetrahedron*, **1993**, *49*, *42*, 9495.

(16) Ammonium phosphite was prepared simply by carefully adding an equimolar amount of commercially available aqueous phosphinic acid(50 %) to the ammonia solution(25%) followed by evaporation of the water under reduced pressure and rigorous drying over $P_2O_5$ in vaco.

(Received in the UK 22 December 1994)