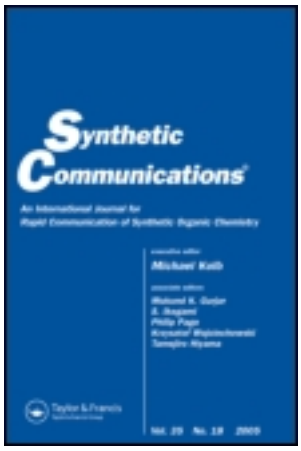


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Simple Synthesis of Pyridine Aminophosphinic Acids and Pyridine Aminophosphine Oxides. The Unusual Cleavage of Pyridylmethyl-(N-benzylamino)-phenylphosphinic Acids and Phosphine Oxides in Acidic Solutions

Bogdan Boduszek [a]

[a] Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology, Wroclaw, Poland

Version of record first published: 16 Aug 2006.

To cite this article: Bogdan Boduszek (2003): A Simple Synthesis of Pyridine Aminophosphinic Acids and Pyridine Aminophosphine Oxides. The Unusual Cleavage of Pyridylmethyl-(N-benzylamino)-phenylphosphinic Acids and Phosphine Oxides in Acidic Solutions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:23, 4087-4094

To link to this article: http://dx.doi.org/10.1081/SCC-120026350

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 23, pp. 4087–4094, 2003

A Simple Synthesis of Pyridine Aminophosphinic Acids and Pyridine Aminophosphine Oxides. The Unusual Cleavage of Pyridylmethyl-(*N*-benzylamino)-phenylphosphinic Acids and Phosphine Oxides in Acidic Solutions

Bogdan Boduszek*

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology, Wroclaw, Poland

ABSTRACT

Pyridine aminophosphinic acids were synthesized in reaction of *N*-(benzyl)-pyridylmethylimines with ethyl phenylphosphinate, in the presence of bromotrimethylsilane. Pyridine aminophosphine oxides were obtained in excellent yields by treatment of the corresponding imines with diphenylphosphine oxide. Among these compounds, the

*Correspondence: Bogdan Boduszek, Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology, 50-370 Wroclaw, Poland; E-mail: boduszek@kchf.ch.pwr.wroc.pl.

DOI: 10.1081/SCC-120026350 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

2-pyridyl and 4-pyridyl derivatives were subject to a simple cleavage in aqueous mineral acid solutions. Products of the cleavages were *N*-(pyridylmethyl)benzylamines and phenylphosphonic (or diphenylphosphinic) acid, respectively.

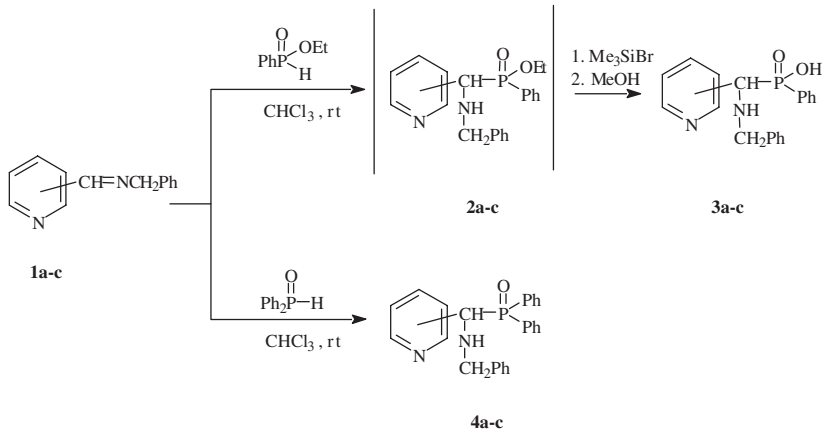
Aminophosphonic acids are an important class of compounds, because of their useful application in organic chemistry and biology.[1] Various pyridine derivatives of the aminophosphonic acids show properties that make them attractive in many areas; e.g., as chelating agents,[2] herbicides,[3a] fungicides,[3b] and neuroactive substances.[3c] Synthesis and reactions of pyridine aminophosphonic acids and esters were described in a few articles,[4a–d] but the corresponding pyridine aminophosphinic acids and aminophosphine oxides were not yet reported.

Some pyridine aminophosphonic acids[4c] are succumbed to a cleavage in the presence of strong mineral acids.[4a] For example, heating of the 2-pyridylmethyl(*N*-alkylamino)phosphonic acids or esters, in aqueous sulphuric acid solutions causes a splitting of these phosphonic acids and formation of the secondary pyridyl-benzyl amines and phosphoric acid.[4b] The mechanism of such cleavage was given and discussed.[4d]

In search of other compounds showing a prospective behavior in acidic conditions, we elaborated a synthetic route leading to some new pyridine aminophosphinic acids and phosphine oxides.

For synthetic work, we exploited some commercially available phosphinic esters and phosphines, which were known as good nucleophiles in reactions with imines.[5] In this case, the ethyl phenylphosphinate and diphenylphosphine oxide were proved to be effective nucleophilic reagents, suitable for addition to a C=N double bond of imines. Thus, when pyridylmethyl(*N*-benzyl)imines **1** were mixed in situ with ethyl phenylphosphinate (or diphenylphosphine oxide) in an inert solvent, the pyridine amino(phenyl)phosphinates **2** (or the pyridine amino(diphenyl)phosphine oxides **4**) were formed in high yields (Sch. 1). Such hydrophosphinylation reaction proceeded easily and cleanly, at room temperature.

Formed pyridyl amino(phenyl)phosphinates **2** were not isolated, but converted to the aminophosphinic acids **3** by means of bromotrimethylsilane (used as dealkylating agent),[6] which was added to a reaction mixture (Sch. 1). Use of bromotrimethylsilane was allowed to obtain aminophosphinic acids **3** in a one-pot procedure,[7] without a need of a hydrolysis of the formed phosphonic esters, in the first stage.



a: 2-pyridyl, **b**: 3-pyridyl, **c**: 4-pyridyl

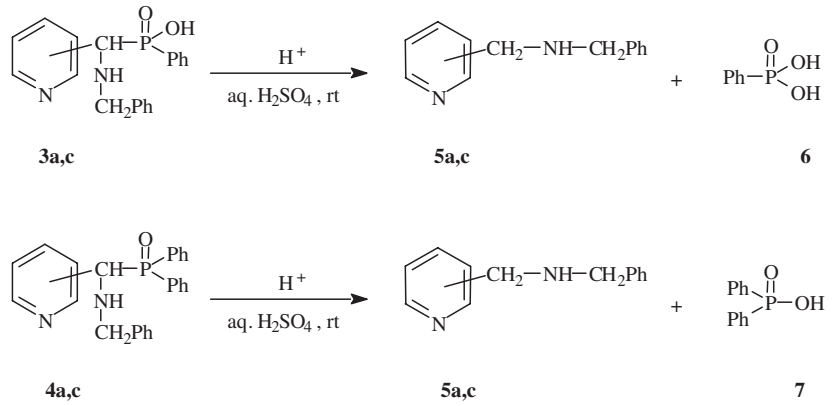
Scheme 1. Synthesis of pyridine aminophosphinic acids and pyridine phosphine oxides.

As a result of this procedure, was an effective preparation of the desired pyridine aminophosphinic acids **3** and phosphine oxides **4**, in high yields and purity.

The aim of this work was to demonstrate that, despite of the reported pyridine aminophosphonic acids,[4a–d] other pyridine phosphorus compounds (as for example, these ones presented here), are also susceptible for a cleavage. Indeed, pyridine aminophosphinic acids **3a**,**c** and phosphine oxides **4a**,**c** proved to be exceptionally easily cleaved in aqueous mineral acid solutions, at ambient temperature. Thus, the 2-pyridylmethyl(*N*-benzylamino)phenylphosphinic acid (**3a**) in aq. 10% H_2SO_4 (or HCl) was split to form the *N*-(2-pyridylmethyl)-benzylamine (**5a**) and phenylphosphonic acid (**6**) (Sch. 2).

Cleavage of the **3a** proceeded in a few hours at 20°C and it therefore could be monitored by means of ^{31}P NMR and ^{1}H spectroscopy, in deuterated solvents. Likewise, the 4-pyridylmethyl(*N*-benzylamino)-phenylphosphinic acid (**3c**) was cleaved in aq. 10% H_2SO_4, however, rate of the cleavage was considerably slower. A complete decomposition of the **3c** at 20°C required about 70 h, as it was estimated from the NMR spectra.

A detailed inspection of these cleavages revealed, that pyridyl benzylamines (**5a**,**c**) and phenylphosphonic acid (**6**) (Sch. 2) were only products in these processes.



Scheme 2. Cleavage of pyridine aminophosphinic acids **3** and pyridine phosphine oxides **4**.

Cleavages of the aminophosphinic acids **3** were considerably accelerated at elevated temperatures. For instance, boiling solutions of the **3a**, or **3c**, in aq. 10% H_2SO_4 were completely cleaved in a few minutes, giving the corresponding pyridyl benzylamines (**5a**,**c**) and phenylphosphonic acid (**6**).

The pyridine phosphine oxides **4a**,**c** were also easily cleaved. Thus, the 2-pyridylmethyl(*N*-benzylamino)diphenylphosphine oxide (**4a**) in aq. 10% H_2SO_4, was cleaved to form the *N*-(2-pyridylmethyl)benzylamine (**5a**) and diphenylphosphinic acid (**7**), (Sch. 2). Cleavage of the **4a** proceeded in a few hours at room temperature, but this cleavage might be completed in a few minutes at 90–95°C. Also, the 4-pyridylmethyl- (*N*-benzylamino)diphenylphosphine oxide (**4c**) was split to form the amine **5c** and diphenylphosphinic acid (**7**), at the same conditions (Sch. 2).

Chemistry and character of cleavages of the pyridine aminophosphinic acids and phosphine oxides resemble the cleavages of pyridine aminophosphonic acids, reported a few years ago.[4b,d] It is worthy to point out, that the pyridine aminophosphinic acids **3** and phosphine oxides **4** are split much faster than related aminophosphonic acids.[4d] Estimated rates (calculated from NMR spectra) of cleavage of the **3** and **4** are about 10^2 times larger, than the rates of cleavage of the corresponding pyridine aminophosphonic acids.[4d]

Mechanistic aspects of the C=P bond splitting, observed on pyridyl aminophosphinic acids and pyridyl phosphine oxides, are now under a detailed investigation in our laboratory. According to preliminary results, the considered cleavages bear an electrophilic character, being a kind of substitution of a phosphinic group by an electrophile. The stability of pyridine aminophosphinic acids **3** and aminophosphine oxides **4** in neutral, or basic solutions might confirm the above assertion. Studies on chemistry of these compounds and the results will be given in a separate publication.

EXPERIMENTAL

NMR spectra were taken on a Bruker Avance TM DRX spectrometer in D_2O or $CDCl_3$, at 300 MHz for ^1H, and 121.5 MHz for ^{31}P nucleus, respectively. Melting points were measured on a Electrothermal 9200 apparatus. Elemental analyses were done in the Laboratory of Instrumental Analysis, in the Institute. All commercially available reagents were used as received from the Aldrich Company.

A Typical Procedure for Preparation of Pyridine Aminophosphinic Acids 3

A mixture of 2-. 3-, or 4-pyridinecarboxaldehyde (1.07 g, 10 mmol) and benzylamine (1.07 g, 10 mmol) in $CHCl_3$ (25 mL) was prepared. The mixture was left for 24 h, then anh. Na_2SO_4 added (4–5 g), filtered and the filtrate (containing the imine **1a–c**), was used directly in a next step. To a stirred solution of the imine, ethyl phenylphosphinate (1.7 g, 10 mmol) was added followed by bromotrimethylsilane (4.6 g, 30 mmol). After 24 h, reaction mixture was evaporated and a resulting oily product was dissolved in methanol (10 mL), diethyl ether added (20 mL) and a mixture was refrigerated. Phosphinic acid **3** has been separated as a crystalline solid. The product was collected by filtration, washed with diethyl ether and dried.

2-Pyridylmethyl(*N*-benzylamino)phenylphosphinic acid (3a). Yield 81%. M.p.: 185–187°C. ^1H NMR (D_2O): δ 8.41–8.37 (m, 2H, pyr), 7.85–7.79 (m, 2H, pyr.), 7.41–7.15 (m, 10H, Ph's), 4.78–4.74 (d, 1H, $J = 11.8$ Hz, CH-P), 4.40–4.20 (m, 2H, CH_2N). ^{31}P NMR: δ 20.03 (s). Anal. calcd. for $C_{19}H_{19}N_2O_2P$, requires N, 8.28; P, 9.15. Found: N, 8.21; P, 9.11%.

3-Pyridylmethyl(*N*-benzylamino)phenylphosphinic acid (3b). Yield 84%. M.p.: 225–227°C. ^{1}H NMR(D_2O): δ 8.56 (d, 1 H, $J = 5.7$ Hz, pyr-6), 8.29 (s, 1H, pyr-2), 8.18 (d, 1 H, pyr-4), 7.42 (m, 1H, pyr-5), 7.32–7.10 (m, 10H, Ph's), 4.59–4.55 (d, 1H, $J = 11.1$ Hz, CH-P), 4.20 (bs, 2H, CH_2N). ^{31}P NMR: δ 21.18 (s). Anal. calcd. for $C_{19}H_{19}N_2O_2P$, requires N, 8.28; P, 9.15. Found: N, 8.19; P, 9.10%.

4-Pyridylmethyl(*N*-benzylamino)phenylphosphinic acid (3c). Yield 80%. M.p.: 171–173°C. ^{1}H NMR(D_2O): δ 8.44 (d, 2H, $J = 6.5$ Hz, pyr-2,6), 7.53 (d, 2H, $J = 5.7$ Hz, pyr-3,5), 7.45–7.12 (m, 10H, Ph's), 4.69–4.65 (d, 1H, $J = 11.2$ Hz, CH-P), 4.24 (d, 2H, $J = 3.1$ Hz, CH_2N). ^{31}P NMR: δ 20.52 (s). Anal. calcd. for $C_{19}H_{19}N_2O_2P$, requires N, 8.28; P, 9.15. Found: N, 8.17; P, 9.14%.

A typical procedure for preparation of pyridine aminophosphine oxides 4. To a solution of imine **1a–c** (3 mmol), in $CHCl_3$ (25 mL), prepared as described above, diphenylphosphine oxide (0.61 g, 3 mmol) in $CHCl_3$ (10 mL) was added. A mixture was left for 24 h and evaporated to dryness. A resulting oily product was dissolved in diethyl ether (10 mL), then hexane added (10 mL) and refrigerated. Product (**4a–c**) separated as a crystalline solid, which was filtered, washed with hexane and dried.

2-Pyridylmethyl(*N*-benzylamino)diphenylphosphine oxide (4a). Yield 88%. M.p.: 102–104°C. ^{1}H NMR($CDCl_3$): δ 8.41 (d, 1H, $J = 3.9$ Hz, pyr-6), 7.77–7.14 (m, 18H, arom), 4.69–4.65 (d, 1H, $J = 13.5$ Hz, CH-P), 3.81–3.77 (d, 1H, $J = 13.0$ Hz, CH_2N), 3.56–3.51 (d, 1H, $J = 13.0$ Hz, CH_2N). ^{31}P NMR: δ 31.49 (s). Anal. calcd. for $C_{25}H_{23}N_2OP$, requires C, 75.36; H, 5.82; N, 7.03; P, 7.77. Found: C, 75.11; H, 5.92; N, 6.82; P, 8.01%.

3-Pyridylmethyl(*N*-benzylamino)diphenylphosphine oxide (4b). Yield 94%. M.p.: 134–6°C. ^{1}H NMR($CDCl_3$): δ 8.46 (d, 1H, $J = 3.9$ Hz, pyr-6), 8.16 (s, 1H, pyr-2), 7.82–7.08 (m, 17 H, arom), 4.41–4.38 (d, 1H, $J = 10.2$ Hz, CH-P), 3.86–3.82 (d, 1H, $J = 13.2$ Hz, CH_2N), 3.48–3.44 (d, 1H, $J = 13.3$ Hz, CH_2N). ^{31}P NMR: δ 32.80 (s). Anal. calcd. for $C_{25}H_{23}N_2OP$, requires C, 75.36; H, 5.82; N, 7.03; P, 7.77. Found: C, 75.23; H, 5.85; N, 6.98; P, 7.72%.

4-Pyridylmethyl(*N*-benzylamino)diphenylphosphine oxide (4c). Yield 91%. M.p.: 148–149°C. ^{1}H NMR($CDCl_3$): δ 8.42 (d, 2H, $J = 5.5$ Hz, pyr-2,6), 7.76 (m, 2H. py-3,5), 7.49–7.08 (m, 15H, Ph's), 4.39–4.34 (d, 1H, $J = 11.4$ Hz, CH-P), 3.86–3.82 (d, 1H, $J = 13.3$ Hz, CH_2N), 3.48–3.44 (d, 1H, $J = 13.3$ Hz). ^{31}P NMR: δ 32.40 (s). Anal. calcd. for $C_{25}H_{23}N_2OP$, requires C, 75.36; H, 5.82; N, 7.03; P, 7.77. Found: C, 75.09; H, 5.75; N, 6.91; P, 7.99%.

Cleavage of Aminophosphinic Acids 3 and Isolation of the Products 5, 6

A sample of pyridine aminophosphonic acid (**3a** or **3c**) (0.34 g, 1 mmol) was dissolved in 10% aq. H_2SO_4 (10 mL) and the solution was kept at room temperature for 12 h (**3a**) and for 72 h (**3c**), respectively. The reaction mixture was then alkalized with sodium carbonate (1.6 g, 15 mmol) and extracted with chloroform (25 mL), and the extract was evaporated to give the amine, as an oily product (**5a** or **5c**, 0.18 g, ~90%). The amines **5a**,**c** were characterized as oxalate salts.[4b] Aqueous layer remained was acidified with aq. 10% H_2SO_4 (5 mL) and evaporated to dryness. A residue was treated with absolute ethanol (25 mL), filtered and the filtrate evaporated to give phenylphosphonic acid **6** (0.15 g), as a white solid.

Cleavage of the **3** at elevated temperature: a sample of pyridine aminophosphinic acid (**3a** or **3c**) (0.34 g, 1 mmol) was dissolved in 10% aq. H_2SO_4 (10 mL) and refluxed for 15 min. Work-up and isolation of the products (**5**,**6**) was carried out as described above.

Cleavage of Aminophosphine Oxides 4 and Isolation of the Products 5, 7

A sample of pyridine aminodiphenylphosphine oxide (**4a** or **4c**) (0.20 g, 0.5 mmol) was dissolved in 10% aq. H_2SO_4 (3 mL) and solution was left for 48 h. After several hours, diphenylphosphinic acid (**7**) began to separate as a crystalline solid. The crystalline product was (after 48 h) collected by filtration and dried (0.10 g). The filtrate remained, was alkalized with sodium carbonate (0.5 g) and extracted with chloroform (10 mL). Evaporation of the extract gave the crude amines (**5a**,**c**) (0.10 g), which were characterized as oxalate salts.[4b]

A cleavage of aminophosphine oxides (**4a**,**c**) at elevated temperature was done as follows: A sample of the **4a** or **4c** (0.20 g, 0.5 mmol) was dissolved in aq. 10% H_2SO_4 and refluxed for 15 min. Isolation of the products was carried out as described above.

The products of the cleavages: *N*-(pyridylmethyl)benzylamines are known compounds and their physico-chemical data are given in the Lit.[4b] Likewise, phenylphosphonic acid and diphenylphosphinic acid are known, commercial compounds and their data are given elsewhere.

ACKNOWLEDGMENT

This work was supported by the Faculty of Chemistry, Wroclaw University of Technology.

REFERENCES

1. Kukhar, V.P.; Hudson, H.R. *Aminophosphonic and aminophosphinic acids*; *Chemistry and Biological Activity*; John Wiley & Sons, Ltd.: Chichester, 2000; Chapter 2, 13–18.
2. Lipinski, R.; Chruscinski, L.; Mlynarz, P.; Boduszek, B.; Kozlowski, H. Inorg. Chim. Acta **2001**, *322*, 157–161.
3. (a) Suzuki, F.; Fujikawa, Y.; Yamamoto, S.; Mizutani, H.; Ohya, T.; Ikai, T.; Oguchi, T. Ger. Offen. **1979**, *2*, 831,578; Chem. Abstr. **1979**, *90*, 187124a; (b) Maier, L.; Diel, P. J. Phosphorus, Sulfur, and Silicon **1991**, *62*, 15–25; (c) Ortwine, D.J.; Malone, T.C.; Bigge, C.F.; Drummond, J.T.; Humblet, C.; Johnson, G.; Pinter, G.W. J. Med. Chem. **1992**, *35*, 1345–1358.
4. (a) Boduszek, B. Phosphorus, Sulfur, and Silicon **1996**, *113*, 209–218; (b) Boduszek, B. Tetrahedron **1996**, *52*, 12483–12494; (c) Boduszek, B. Phosphorus, Sulfur, and Silicon **1997**, *122*, 27–32; (d) Boduszek, B.; Latajka, R.; Lesniak, W. Phosphorus, Sulfur, and Silicon **2000**, *165*, 53–75.
5. Baylis, K.; Campbell, C.D.; Dingwall, J.G. J. Chem. Soc. Perkin Trans. I **1984**, 2845–2853.
6. Wozniak, L.; Chojnowski, J. Tetrahedron **1989**, *45*, 2465–2472.
7. Boduszek, B. Polish J. Chem. **2001**, *75*, 663–672.

Received in Poland April 18, 2003