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Diastereoselective Addition of Hypophosphorous Acid to *N*-(*R*)-α-Methylbenzyl-Substituted Schiff Bases

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ABSTRACT: *The addition of hypophosphorous acid to an azomethine bond of N-(R)-α-methylbenzyl Schiff bases of a variety of aldehydes led to the formation of N-(R)-α-methylbenzylamino-(S)-methanephosphonous acids in 100% diastereoselectivity. This fact allows us to suggest the probable mechanism of the Strecker-like reaction between hypophosphorous acid, an aldehyde, and (R)-α-methylbenzylamine.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:35–37, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20406

INTRODUCTION

Over 10 years ago, Hamilton et al. [1] written a very interesting paper, describing the modified Strecker reaction between an aldehyde, hypophosphorous acid, and the chiral α-methylbenzylamine, which led to the formation of 1-alkylaminophosphonous acids with 100% diastereoselectivity. This work gave an impulse to investigate more profoundly this reaction and thus, several reports concerning this conversion have been published until now [2–5]. We have contributed to this topic too, presenting a proof for different stereochemical behavior of ferrocenecarboxaldehyde in this reaction [4]. We have also made attempts to establish the mechanism of this conversion [4,5].

As we have mentioned in our previous works [4,5], there are two postulated mechanisms (Scheme 1). In one of them, it is suggested that the nucleophilic attack of an amine on the carbonyl bond of an aldehyde leads to the formation of a Schiff base, which is followed by the nucleophilic addition of hypophosphorous acid to its azomethine bond. The second possible mechanism includes the attack of hypophosphorous acid on an aldehyde leading to α-hydroxyphosphonous acid, which undergoes the nucleophilic substitution and it converts into the desired α-aminophosphonous acid. But it is not known which mechanism is operative; without knowing it, it is impossible to establish the reason for such a high diastereoselectivity of this conversion.

RESULTS AND DISCUSSION

In this communication, we report the addition of hypophosphorous acid to the azomethine bond of the previously isolated *N*-(*R*)-α-methylbenzyl Schiff bases is diastereoselective to 100%, leading exclusively to one diastereoisomeric form.

This work is dedicated to my mentor, Prof. Romuald Skowroński, University of Łódź, Łódź, Poland, on the occasion of his 80th birthday.

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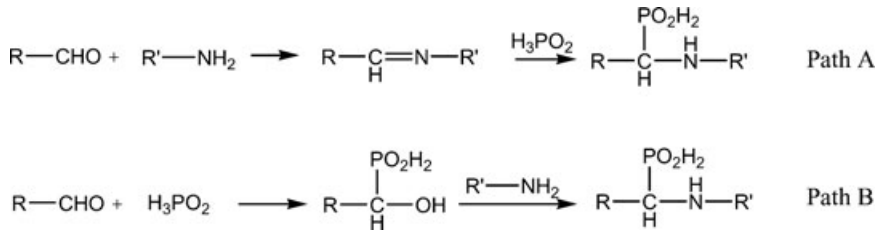


SCHEME 1

Simultaneously, we present here another approach to reveal the mechanism of this reaction.

We investigated the reactions of six model Schiff bases: *N*-furfurylidene (**1a**), *N*-benzylidene (**1b**), *N*-cyclohexylmethylidene (**1c**), *N*-*p*-nitrobenzylidene (**1d**), *N*-*o*-methoxybenzylidene (**1e**), and *N*-(3-phenylallylidene) ones (**1f**). This allowed us to study cases of Schiff bases of all types of aldehydes: heteroaromatic, aromatic, α,β-unsaturated, and aliphatic ones. ^{1}H and ^{31}P NMR spectroscopy revealed in all the cases the exclusive formation of the one diastereoisomer (Scheme 2).

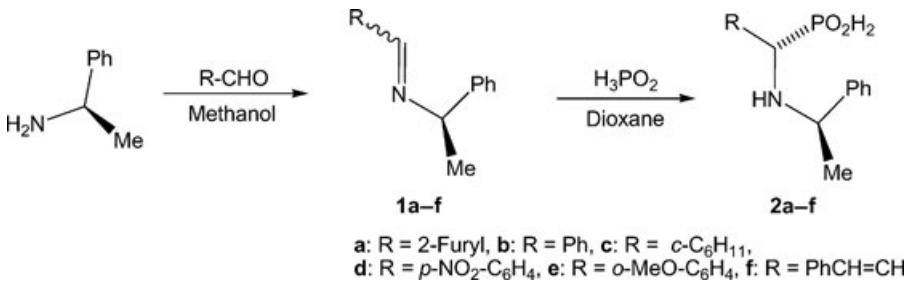
Reactions were carried out in acetonitrile, and all obtained products were analyzed by means of ^{1}H and ^{31}P NMR spectroscopy as well as melting point and specific optical rotation measurements. All new compounds **2d–f** gave satisfactory values of elemental analysis.

The comparison of the ^{1}H NMR data and specific optical rotation values with experimental literature data for three first cases **2a–c** [1,3] demonstrated that they are consistent. This allowed us to state that the exclusively formed diastereoisomer adopted the *S* configuration around the newly formed center of chirality in these three cases. Melting points of acids **2b–c** differ from the literature data, but it may result from different apparatuses used by us and Hamilton et al. [1] Aminophosphonous acids **2d–f** have never been described in the literature, but their *S* configuration may also be considered analogously to previous cases.

The fact that the Strecker-like reaction reported by Hamilton et al. gave the same results as the addition of hypophosphorous acid to chiral Schiff bases **1a–f** allowed us to suggest that the reaction of hypophosphorous acid, an aldehyde, and *N*-(*R*)-α-methylbenzylamine proceeded through the mechanism following the pathway (a), that is, the formation of a Schiff base followed by the addition of hypophosphorous acid (Scheme 1). This is consistent with our suggestions presented in our two previous works [4,5].

EXPERIMENTAL

All used solvents were routinely distilled and dried prior to use. Aldehydes and (*R*)-α-methylbenzylamine Aldrich (Poznań, Poland) were used as received. Hypophosphorous acid was obtained from its commercial 50% aqueous solution (Aldrich) using the published procedure [6]. Schiff bases **1a–f** were synthesized following the published procedure [7]. Melting points were measured on a MelTemp II apparatus and were not corrected. Optical rotation was measured on a Perkin–Elmer 241MC polarimeter. NMR spectra were recorded on a Bruker Gemini 200BB spectrometer, operating at 200 MHz (^{1}H NMR) and 81 MHz (^{31}P NMR). Elemental analyses were performed at the Center of Molecular and Macromolecular Studies, the Polish Academy of Science in Łódź, Poland.



SCHEME 2

Preparation of N-(R)-α-methylbenzylaminomethanephosphonous Acids **2a–f**

Schiff base **1a–f** (5 mmol) was dissolved in acetonitrile and H_3PO_2 (5 mmol), and the mixture was refluxed for 5 h, then stirred at room temperature for 24 h. The formed precipitate was collected by filtration, which was then dissolved in 0.1 M NaOH. The solution was filtrated and acidified to precipitate the product, which was collected by filtration.

(2-Furyl)-N-(R)-α-methylbenzylaminomethanephosphonous Acid **2a**

Yield 39%; mp 216–218°C; lit [3] 216–218°C; +28.8° (*c* 0.2, MeOH); lit [3] +30.0° (*c* 0.2, MeOH).

^{1}H NMR (CD_3OD, 200 MHz): δ 7.64 (m, $H^5{}_{fur}$, 1H); 7.50 (m, PhH, 5H); 7.25 (d, $^2J_{PH}$ = 549.6 Hz, PH, 1H); 6.57 (m, $H^3{}_{fur}$, 1H); 6.52 (m, $H^4{}_{fur}$, 1H); 4.64 (q, J = 6.8 Hz, C<u>H</u>CH_3, 1H); 4.17 (d, $^3J_{PH}$ = 15.8 Hz, CHP, 1H); 1.70 (d, J = 6.8 Hz, CHC<u>H</u>$_3$, 3H). ^{31}P NMR (CD_3OD, 81 MHz): δ 15.37.

(Phenyl)-N-(R)-α-methylbenzylaminomethanephosphonous Acid **2b**

Yield 44%; mp 227–230°C; lit [1] 241.5–242.5; +37.6° (*c* 1.2 M NaOH); lit [1] +40.0° (*c* 1.2 M NaOH).

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 6.81 (m, PhH, 5H); 6.53 (m, PhH, 5H); 6.49 (d, $^2J_{PH}$ = 520.1 Hz, PH, 1H); 3.71 (d, $^3J_{PH}$ = 15.8 Hz, CHP, 1H); 3.14 (q, J = 6.2 Hz, C<u>H</u>CH_3, 1H); 1.70 (d, J = 6.2 Hz, CHC<u>H</u>$_3$, 3H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 26.00.

(Cyclohexyl)-N-(R)-α-methylbenzylaminomethanephosphonous Acid **2c**

Yield 39%; mp 217–219°C; lit [1] 228–230; +49.0° (*c* 1.2 M NaOH); lit [1] +48.7° (*c* 1.2 M NaOH).

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.13 (m, PhH, 5H); 6.76 (d, $^2J_{PH}$ = 500.1 Hz, PH, 1H); 3.83 (q, J = 6.6 Hz, C<u>H</u>CH_3, 1H); 1.93 (dd, $^3J_{PH}$ = 9.1 Hz and $^3J_{HH}$ = 3.2 Hz, CHP, 1H); 1.34 (m, $H_{cyclohexyl}$, 5H); 1.10 (d, J = 6.6 Hz, CHC<u>H</u>$_3$, 3H); 0.89 (m, $H_{cyclohexyl}$, 6H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 28.30.

(p-Nitrophenyl)-N-(R)-α-methylbenzylaminomethanephosphonous Acid **2d**

Yield 65%; mp 204–205°C; +167.2° (*c* 0.2, MeOH).

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.87 (m, PhH, 2H); 7.07 (m, PhH, 3H); 6.88 and 6.74 (2d, J = 7.1 Hz, p-C_6H_4, 4H); 6.85 (d, $^2J_{PH}$ = 522.1 Hz, PH, 1H); 3.28 (d, $^3J_{PH}$ = 17.4 Hz, CHP, 1H); 3.18 (q, J = 6.3 Hz, C<u>H</u>CH_3, 1H); 1.01 (d, J = 6.3 Hz, CHC<u>H</u>$_3$, 3H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 24.33.

Calcd for $C_{15}H_{17}N_2O_4P$: C, 56.25; H, 5.36; N, 8.75. Found: C, 56.43; H, 5.40; N, 8.69.

(o-Methoxyphenyl)-N-(R)-α-methylbenzylaminomethanephosphonous Acid **2e**

Yield 54%; mp 228–230°C; +24.8° (*c* 1.2 M NaOH).

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.17–7.07 (m, PhH, 8H); 6.85 (m, PhH, 1H); 6.79 (d, $^2J_{PH}$ = 521.2 Hz, PH, 1H); 4.05 (d, $^3J_{PH}$ = 15.4 Hz, CHP, 1H); 3.78 (q, J = 6.4 Hz, C<u>H</u>CH_3, 1H); 1.21 (d, J = 6.4 Hz, CHC<u>H</u>$_3$, 3H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 26.55.

Calcd for $C_{16}H_{20}N_3O_3P$: C, 62.94; H, 6.60; N, 4.59. Found: C, 63.07; H, 6.49; N, 4.37.

(1-(2-Phenylethenyl))-N-(R)-α-methylbenzylaminomethanephosphonous Acid **2f**

Yield 49%; mp 205–207°C; −28.0° (*c* 1.2 M NaOH).

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.54–7.29 (m, PhH, 10H); 7.05 (d, $^2J_{PH}$ = 539.9 Hz, PH, 1H); 6.68 (dd, $^3J_{HH}$ = 15.5 Hz and $^4J_{HH}$ = 2.5 Hz, Ph<u>CH</u>=CH, 1H); 6.12 (ddd, $^3J_{HH}$ = 15.5 Hz and $^3J_{HH}$ = 8.5 Hz and $^3J_{PH}$ = 11.9 Hz, CH=<u>CH</u>–CHP, 1H); 4.70 (q, J = 6.5 Hz, C<u>H</u>CH_3, 1H); 3.74 (d, $^3J_{HH}$ = 8.5 Hz and $^3J_{PH}$ = 11.9 Hz, CHP, 1H); 1.70 (d, J = 6.5 Hz, CHC<u>H</u>$_3$, 3H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 16.95.

Calcd for $C_{17}H_{20}NO_2P$: C, 67.76; H, 6.69; N, 4.65. Found: C, 67.57; H, 6.87; N, 4.47.

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