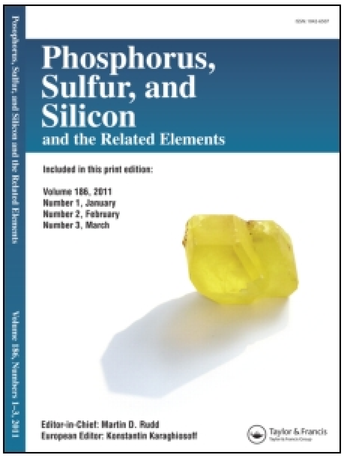

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First Synthesis of Ferrocenyl-*N*-Alkylaminophosphonic Acids

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First Synthesis of Ferrocenyl-*N*-Alkylaminophosphonic Acids

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*The first synthesis of novel ferrocenyl-*N*-alkylaminomethanephosphonic acids* ***3a–c*** *via their trimethylsilyl esters is presented.*

Keywords Aminophosphonic acids; bis(trimethylsilyl) phosphate; ferrocenecarboxaldehyde; Schiff bases

INTRODUCTION

The importance of aminophosphonic acids and esters is commonly known. After the first preparation[1,2] of various phosphono-analogs of natural amino acids, one could notice the great development of their chemistry in the aspect of the synthesis,[3–5] the stereochemistry,[6–8] biochemical properties,[9] and their applications in various fields of agriculture and medicine.[10,11]

Since the last decade, ferrocene-derived compounds have been widely employed in molecular recognition because they are able to make metal-centered redox systems to generate oxidized or reduced form of different properties.[12] Therefore, various molecular switches containing a ferrocene moiety have been synthesized.[12–14] The syntheses of ferrocenylalanine[15,16] and 1,1-ferrocenyl-bis-(alanine)[17] were also reported.

Regarding all the above, we wanted to synthesize aminophosphonic acids bearing a ferrocenyl moiety. Previously we published the synthesis of *N*-substituted ferrocenylaminomethane phosphonates;[18] in this

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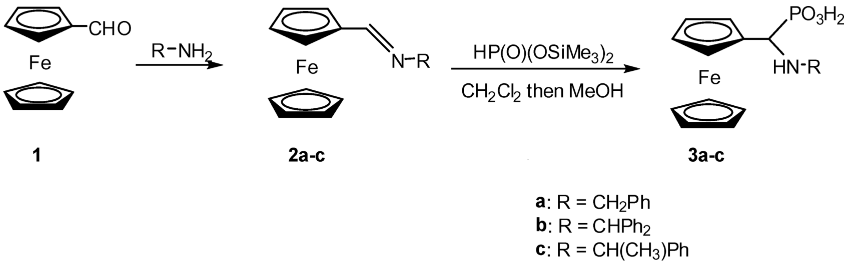
communication, we present the first synthesis of *N*-substituted ferrocenylaminomethane phosphonic acids using the modified Boduszek's methodology.[19] These compounds may eventually show potential properties as plant-protection agents or antitumor drugs.

RESULTS AND DISCUSSION

Three model ferrocenecarboxaldehyde Schiff bases **2a–c** (*N*-benzyl, *N*-furfuryl, and *N*-(*R*)-(*α*)-methylbenzyl derivatives, respectively) were synthesized following the published procedure[18] and were characterized by the ^{1}H NMR as well as by melting point measurements and compared to authentic samples (Scheme 1).



SCHEME 1

Acids **3a–c** have been synthesized based on the methodology described by Boduszek and Luboch.[19] Diethyl phosphite was converted into its bis(trimethylsilyl) ester by reaction of diethyl phosphite with trimethylsilyl bromide, and the so formed bis(trimethylsilyl) phosphite was added to Schiff bases **2a–c**. The reaction was carried out in methylene chloride and afforded aminophosphonic acids **3a–c** in moderate yields (Scheme 1). The acids **3a–c** are new compounds, which have never been described in the chemical literature. They were characterized by means of ^{1}H and ^{31}P NMR spectroscopy and elemental analysis.

According to the NMR spectra, the precipitated *N*-(*R*)-(*α*)-methylbenzylamine(ferrocenyl)-methanephosphonic acid **3c** consisted of only one diastereomer: it gave one set of signals in the ^{1}H NMR spectrum and one signal in the ^{31}P NMR spectrum. ^{1}H and ^{31}P NMR investigation of the mixture after precipitation of the product **3c** showed small amount of the second isomer of the product **3c** as well as of unreacted starting material (Schiff base, silyl compounds). This means that the addition of bis(trimethylsilyl) phosphite to the chiral *N*-ferrocenylidene (*R*)-(*α*)-methylbenzylamine is highly diastereoselective (de = 80%), yielding the acid **3c** as a mixture of two diastereomers in a 9:1 ratio.

Most important, the predominant diastereoisomer precipitated from the reaction mixture in pure form, not contaminated by the second isomer.

Certainly, the described matter requires much more profound study, especially determination of absolute configuration of the predominant diastereoisomer of **3c**, and that is why the problem is still investigated.

EXPERIMENTAL

All solvents (POCh, Poland) were routinely distilled and dried prior to use. Ferrocenecarboxaldehyde, amines, trimethylsilyl bromide, and dimethyl phosphite (Aldrich, Poland) were used as received. NMR spectra were recorded with a Bruker DPX-250 Avance spectrometer operating at 250 MHz (^{1}H) and 101 MHz (^{31}P). Elemental analyses were performed in the Center for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź, Poland. Schiff bases **2a–c** were synthesized following the known procedures.[18]

Synthesis of Acids 2*a*–*c*: General Procedure

Dimethyl phosphite (2.5 mmol, 0.28 g) was dissolved in dry CH_2Cl_2 and Me_3SiBr (6.8 mmol, 0.9 mL) was added dropwise during a period of 10 min. The mixture was then stirred for 1 h at room temperature, and a solution of the appropriate Schiff base **2a–c** (2.5 mmol) in dry CH_2Cl_2 was added. The mixture was refluxed for 4 h, then CH_2Cl_2 was removed in vacuo, the residue was dissolved in methanol, and the mixture was stirred for 45 min at room temperature until a solid precipitate formed. If the solid did not form, 10 mL of propylene oxide was added, and the mixture was stored in a refrigerator for 3 days. The formed solid was collected by filtration and washed with methanol.

N-Benzylamino-ferrocenemethanephosphonic Acid (*3a*)

Yield: 0.56 g (58%); mp 205–207 °C. ^{1}H NMR (NaOD/D_2O): δ 7.33–7.13 (m, 5H, Ph); 4.15 (m, 2H, $(CH)_2^{fer}$); 4.02 (m, 2H, $(CH)_2^{fer}$); 3.97 (d, $J = 9.4$ Hz, 1H, CH_2Ph), 3.93 (d, $J = 9.4$ Hz, 1H, CH_2Ph); 3.87 (s, 5H, $C_5H_5^{fer}$); 3.33 (d, $^{2}J_{PH} = 15.8$ Hz, 1H, CHP). ^{31}P NMR (D_2O): δ 16.1. Calcd for $C_{18}H_{20}FeNO_3P$: C, 56.13; H, 5.23; N, 3.64. Found: C, 56.16; H, 5.08; N, 3.76%.

N-Benzhydrylamino-ferrocenemethanephosphonic Acid (*3b*)

Yield: 0.46 g (46%); mp 185–187°C. ^{1}H NMR (NaOD/D$_2$O): δ 7.48 (m, 2H, Ph); 7.38–7.16 (m, 8H, Ph); 5.89 (s, 1H, C$\underline{H}$Ph$_2$); 4.25 (m, 2H, $(CH)_2^{fer}$); 3.98 (m, 2H, $(CH)_2^{fer}$); 3.92 (s, 5H, $C_5H_5^{fer}$); 3.58 (d, $^2J_{PH} = 17.5$ Hz, 1H, CHP). ^{31}P NMR (NaOD/D$_2$O): δ 16.3. Calcd for $C_{24}H_{24}FeNO_3P$: C, 62.49; H, 5.24; N, 3.04. Found: C, 62.12; H, 5.14; N, 3.13%.

N-(R)-α-Methylbenzylamino-ferrocenemethanephosphonic Acid (*3c*)

Major Diastereoisomer

Yield: 0.60 g (52%); mp 200–201°C. ^{1}H NMR (NaOD/D$_2$O): δ 7.43 (d, $J = 6.8$ Hz, 2H, Ph); 7.31 (t, $J = 6.8$ Hz, 2H, Ph); 7.17 (d, $J = 6.8$ Hz, 1H, Ph); 4.15 (m, 2H, $(CH)_2^{fer}$); 3.96 (m, 3H, C$\underline{H}$Ph, $(CH)_2^{fer}$); 3.89 (s, 5H, $C_5H_5^{fer}$); 3.45 (d, $^2J_{PH} = 15.0$ Hz, 1H, CHP); 1.35 (d, $J = 5{,}9$ Hz, CH$_3$). ^{31}P NMR (NaOD/D$_2$O): δ 15.6. Calcd for $C_{19}H_{22}FeNO_3P$: C, 57.16; H, 5.55; N, 3.51. Found: C, 57.08; H, 5.50; 3.50%.

Minor Diastereoisomer

(5% estimated by NMR): ^{1}H NMR (NaOD/D$_2$O): δ 7.43 (d, $J = 6.8$ Hz, 2H, Ph); 7.31 (t, $J = 6.8$ Hz, 2H, Ph); 7.17 (d, $J = 6.8$ Hz, 1H, Ph); 4.15 (m, 2H, $(CH)_2^{fer}$); 3.86 (m, 3H, C$\underline{H}$Ph, $(CH)_2^{fer}$); 3.89 (s, 5H, $C_5H_5^{fer}$); 3.14 (d, $^2J_{PH} = 14.9$ Hz, 1H, CHP); 1.15 (d, $J = 5{,}9$ Hz, CH$_3$). ^{31}P NMR (NaOD/D$_2$O): δ 15.3.

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