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Synthesis of chiral shiff base: Ferrocene-conjugates of amino acid esters

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ABSTRACT

Two novel chiral ferrocene-conjugates of amino acid esters were designed and prepared by condensation with formylFerrocene and enantiomerically pure amino acid esters. The products were characterized by melting point determination, rotation determination, IR, element analysis and ^{1}H-NMR. Esterification of amino acids using thionyl chloride results enantiomerically pure amino acid esters(L-Phenylalanine methyl ester and L-Leucine methylester).

KEYWORDS

Ferrocene;
Shiff base;
Amino acid methyl ester hydrochloride;
Chiral;
Synthesis.

INTRODUCTION

Schiff base and its complexes are widely used in the fields of biology, catalysis and material etc. Thus, studies on the synthesis of novel Schiff base complexes and their properties and application are significant development of coordination chemistry. Study of amino acids and their derivatives is an important direction of development, with advantage such as anti-cancer drugs with low toxicity and resistance, therefore there arrives a significant work interest for the study of amino acids. Chiral ferrocene Schiff bases compounds are very important molecules in many scientific areas. They have been employed in various fields, such as asymmetric catalysis[1], biological activity including antifungal, antiviral and anticancer activities[2-4]. Considerable effort has been directed at the design of ferrocene-conjugates amino acids with potential applications in drug delivery and biomedical engineering. α-aminoacids can be produced by the reductiom of imine. Its wide applicability provide synthetically useful intermediates for preparing nitrogen-containing natural and bioactive compounds including amino sugar, β-amino acids, γ-amino acids and β-lactams[5–6].

In this paper, two novel chiral ferrocene-conjugates of amino acid esters were designed and prepared, condensation with formylFerrocene and enantiomerically pure amino acid esters. Application of the compounds are under way.

RESULTS AND DISCUSSION

Synthesis, IR and NMR spectroscopy

Two optically active ferrocene Schiff bases were synthesized by the reactions of formylferrocene with and enantiomerically pure amino acid esters. The products were characterized by melting point determination, rotation determination, IR, element analysis and ^{1}H-NMR. The spectral and analytical data for all the imines were in good agreement with their structure. Imine function

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of the compounds was registered as strong signals at about 1620cm^{-1} in IR-spectra, as well as at about 8.01 and 8.34ppm in ^{1}H NMR. Signals at 3.96-4.46ppm in ^{1}H NMR spectra of compound 4 belonged to ferrocene protons.

We applied the modified general procedure to synthesize compound 4[7]. In order to remove the water in regents and improve reaction yield, we mixed with 4A° molecular sieve in water separator. L-phenylalanine methyl ester hydrochloride and L- Leucine methylester hydrochloride were synthesized by reacting with amino acids in amethanol solution of thionyl chloride. Neutralization with $NaHCO_3$ solution affords L-phenylalanine methyl ester and L- Leucine methylester.

EXPERIMENTAL

General procedure

All reactions were carried out under argon and monitored by thin-layer chromatograph (TLC). Melting point (uncorrected) was measured with a XT4 melting point apparatus. ^{1}H NMR spectra were recorded on a Varian EM-300 spectrometer, using $CDCl_3$ as solvent and TMS as the internal standard. Optical rotations were measured on a WZZ-3 polarimeter. Formylferrocene was prepared by literature methods[8], mp. 122-124°C.

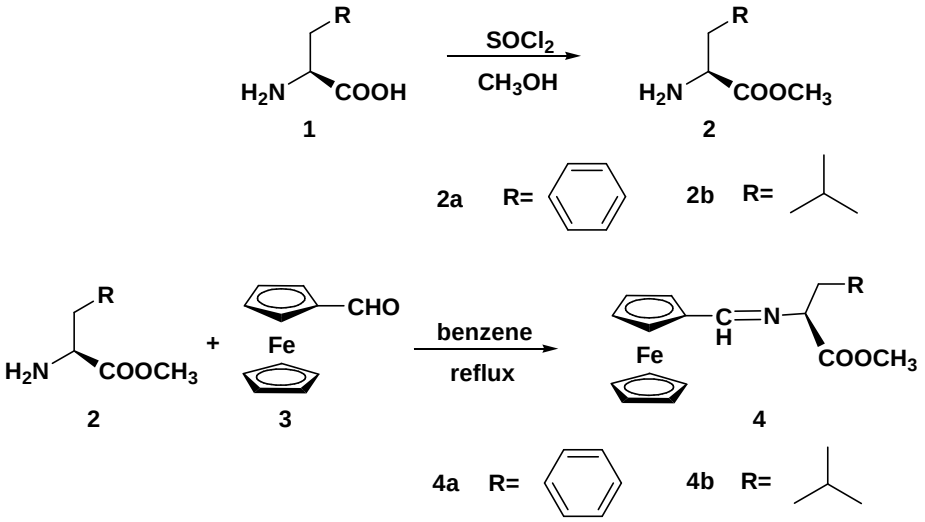
Synthesisi of chiral α-amino acid esters

2a: Anhydrous methanol 65mL contained in a 250mL three-neck flask, stirring and cooled to -10°C with ice-salt bath, 7.2mL (0.099 mol) $SOCl_2$ was slowly added drop by drop(cannot exceed 0°C), when the addition was complete, the whole was cooled under -5-0°C about 1 hours. Then 8.0g (0.076 mol) L- Phenylalanine was added, continue to stir 3 hours at room temperature then reflux 2 hours. After cooling, under Vacuum distillation removal a large number of liquids gave white crude solide. The crude material was recrystallized from ethanol- ether giving white needle crystal (11.3g, 83.2%). m.p.157°C-159°C, $[\alpha]_D^{20}$+ 37.5° (C 2.0, C_2H_5OH). (lit. $[\alpha]_D^{27}$+38.1° (C=2.0, C_2H_5OH))[9]. Calc. for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Anal. Found: C, 55.48; H, 6.39; N, 6.23; IR ν/cm^{-1}: 3001.85; 2963.72; 2625.84; 1754.61; 1583.69; 1491.30; 1237.23. The crystal was dissolved in water, added saturated $NaHCO_3$ solution until pH=8, the reaction mixture was extracted with methylene chloride, the organic layer was washed with water and dried over anhydrous magnesium sulfate, and evaporated to afford L-Phenylalanine methylester **2a** (colorless oil). IR data are list in TABLE 1.

2b: It was prepared in similar manner to that for the preparation of **2a**, staring with L-Leucine. The crude material was recrystallized from ethanol-ether giving white needle crystal (9.9g, 72.1%). mp 150-152°C, ($[\alpha]_D^{20}$+13.2 (c 2.0, H_2O). (lit. $[\alpha]_D^{26}$+13.4°(C=2.0,

TABLE 1 : IR data of Amino acids ester compounds

Entry	Compounds	IR ν/cm^{-1}			
		-NH_2	C=O	CH_3	C-O-C
1	L-pheynylalanine methyl ester	3391.6	1741.2	1391.2	1236.2
2	L-Leucine methyl ester	3398.8	1738.9	1371.4	1220.3



Scheme 1 : Synthesis of ferrocene-conjugates of amino acid esters

H_2O))[10]. Calc. for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88; N, 7.71, Anal. Found: C, 46.09; H, 8.25; N, 7.73; IR ν/cm^{-1}: 2960.27; 2627.68; 1736.13; 1583.68; 1223.37. IR data are list in TABLE 1.

Synthesisi of ferrocene- Conjugates Amino acids ester compounds

The title compound was prepared according to Scheme 1, Formylferrocene 3 (5 mmol) was reacted in benzene at 80°C with L-Phenylalanine methyl ester(L-Leucine methyl ester)(5 mmol) through modification of reported procedures giving imines 4a and 4b respectively. After evaporation of the solvent, both imines were recrystallized from dichloromethane/petroleum ether giving orange crystals.

4a: 82.6%. mp 118-120°C. The IR spectrum indicated the presence of the unsubstituted cyclopentadienyl ring (1103.9 and 996.6cm^{-1}), 1022.0 ~1147.6cm^{-1} (single substituted cyclopentadienyl), 486.1cm^{-1} and 509.9cm^{-1}(ν_{Fe-C}), 1621cm^{-1}(N=CH); ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 8.01 (s, 1H, N=CH), 7.25-7.14 (m, 5H, Ar-H), 4.46-4.30 (m, 4H, Cp-H), 4.17 (s, 5H, Cp-H), 4.15-4.10 (m, 1H, N-CH), 3.72 (s, 3H, OCH_3)), 3.38-3.10 (m, 2H, Ar-CH_2).

4b: 75.1% mp 106-108°C. The IR spectrum indicated the presence of the unsubstituted cyclopentadienyl ring (1100.1 and 996.0cm^{-1}), 1021.0 ~1145.6cm^{-1} (single substituted cyclopentadienyl), 486.5cm^{-1} and 509.7cm^{-1}(ν_{Fe-C}), 1620cm^{-1}(N=CH); ^{1}H NMR (300MHz, $CDCl_3$, ppm): δ 8.34 (s, 1H, N=CH), 4.45-4.31 (m, 4H, Cp-H), 3.96 (s, 5H, Cp-H), 3.72 (s, 3H, OCH_3), 3.63-3.60 (d, 1H, N-CH), 2.41-2.30 (m, 2H, $(CH_3)_2$CH-CH_2), 1.01-0.85 (t, 6H, CH_3).

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