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Journal of Organometallic Chemistry 688 (2003) 138–143
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis and enantiomeric resolution of ferrocenyl(alkyl)azoles

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Received 23 June 2003; accepted 13 August 2003

Abstract

Ferrocenyl(alkyl)azoles were synthesized in high yields by interaction of α-ferrocenylcarbinoles with azoles in aqueous–organic in the presence of HBF_4 or by interaction of α-ferrocenylcarbinoles with *N*,*N*′-carbonyldiimidazole, *N*,*N*′-thionyldiimidazole, *N*,*N*′-thionyldibenzimidazole in boiling dichloromethane. The resulting enantiomers of ferrocenyl(alkyl)azoles and some carbinoles were separated using HPLC on silica bonded chiral stationary phases based on cyclodextrins and modified cellulose.

Keywords: Ferrocene derivatives; Enantiomeric resolution; HPLC; Ferrocenyl(alkyl)azoles; *N*,*N*′-Thionyldiimidazole

1. Introduction

Biologically active ferrocene compounds are of continuous interest in various current researches [1]. It was found that some of the ferrocenyl(alkyl)azoles obtained in racemic form displayed high antitumor activity and low toxicity [2]. Therefore ferrocenyl(alkyl)azoles are perspective potential ferrocene containing drugs. Earlier HPLC method was used for separation of enantiomers of ferrocene compounds [3].

We report here the synthesis of a number of new ferrocenyl(alkyl)azoles. The separation of synthesized enantiomers was carried out by HPLC on a chiral columns with silica gel bonded cyclodextrins, cyclic antibiotics and modified cellulose.

2. Results and discussion

2.1. Synthesis

Ferrocenyl(alkyl)azoles with nitrogen containing heterocycles (pK_a of the conjugate free acids less than 6) were synthesized according to known, well reproduced procedure [4], in aqueous–organic (H_2O–CH_2Cl_2) in the presence of the equimolar amount of 45% aqueous HBF_4 (**2a**–**g**). Benzotriazole, pyrazole and its derivatives were used as heterocycles (Scheme 1).

The reaction with strongly basic azoles is known to lead to protonated heterocycles only (H_2Az^+). Earlier we reported the method for introducing ferrocenylalkyl groups into the molecules of imidazole (HIm, pK_a = 7.00) based on the reaction of α-ferrocenylcarbinoles with *N*,*N*′-carbonyldiimidazole (CDI) [5]. Some trends of the reaction were found. A reasonable scheme is suggested (Scheme 2).

The carbamate group ImOCO– at α-position to the ferrocene fragment is a labile, good-leaving group open for nucleophilic attack by imidazole eliminated in the second stage. The similar derivatives of imidazole (**5a**, **b**) were obtained from the reaction between CDI and ω-ferrocenyl alcohols (2-ferrocenylethanol, 4-ferrocenylbutanol). Structures of compounds **5a** and **5b** were further supported by a strong IR-absorption (KBr) at 1760–1770 cm^{-1} (C=O stretch vibration). This speaks in favor of species **3** to actually serve as an intermediate in the reaction. Moreover, (*N*-alcoxy-carbonyl)- and (*N*-aryloxy-carbonyl)-imidazoles (carbamates) were found to form under the same conditions [6] (Scheme 3).

If the approach to a hydroxyl group is sterically hindered (R = *t*-Bu), the reaction does not proceed, and the lone product is the source carbinol **1**. However, if in

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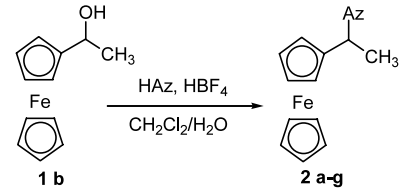
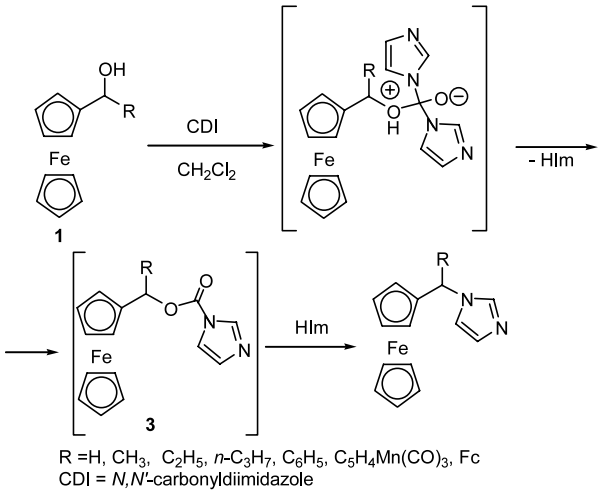
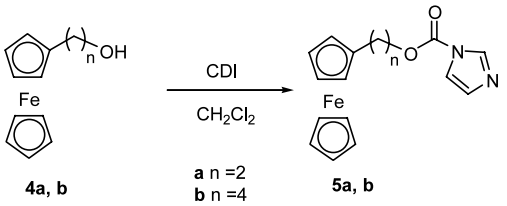
doi:10.1016/j.jorganchem.2003.08.039



Scheme 1.

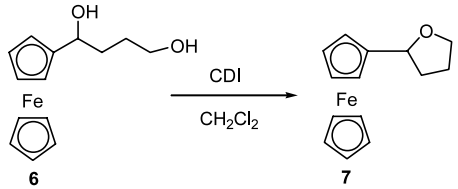


Scheme 2.



Scheme 3.

source alcohol R = Fc, $C_5H_4Mn(CO)_3$, the interaction with CDI results to ferrocenyl(alkyl)imidazoles (yields 81 and 83% accordingly). We ascribe these results to the major mobility of a hydroxyl group located between two elementoorganic substitutes. If the initial carbinol has nucleophilic group (OH, NR_2, etc.) the intramolecular nucleophilic substitution takes place (Scheme 4). Thus, the reaction between 1-ferrocenyl-1,4-butandiol **6** and *N*,*N*′-carbonyldiimidazole leads to 2-ferrocenyltetrahydrofuran **7** as the single product.



Scheme 4.

It is known that thionyl containing analogs of CDI have similar reactivity [7]. We synthesized *N*,*N*′-thionyldiimidazole (TDI) by the procedure described [8]. The thionyl containing derivatives obtained were used in the reaction with ferrocenyl alcohols. The yields of ferrocenylalkylated imidazoles are similar to those for the reaction with CDI (Table 1, Scheme 5).

The results obtained moved us to prepare *N*,*N*′-thionyldibenzimidazole (TDBI) from thionyl chloride and benzimidazole in chloroform. Analogously, ferrocenylalkylated benzimidazoles were obtained in high yields from the reaction between α-ferrocenylcarbinoles and TDBI in boiling dichloromethane (Scheme 6, Table 2).

It is worthy of note that these simple procedures allow us to realize the ferrocenylalkylation reactions of imidazole and benzimidazole selectively. Actually 1*N*-ferrocenyl(alkyl)imidazole or benzimidazole were the single products formed.

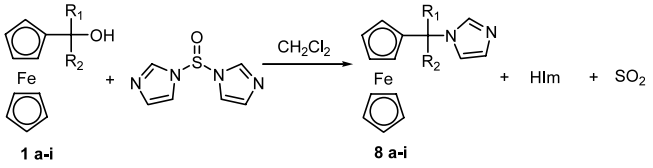
2.2. Enantiomeric separation

Ferrocenyl(alkyl)azoles were prepared from racemic carbinols and thus contain one chiral carbon center in their structure and give racemic mixtures of two enantiomers. In order to separate mixtures of enantiomeric ferrocene derivatives, for example—ferrocenylethanol, Armstrong et al. [3] used HPLC on columns with bonded β-cyclodextrin. In our work, we used HPLC columns based on β- and γ-cyclodextrins and modified cellulose (Chiralcel OD and Chiralcel OD-H). The enantiomeric separation data are summarized in Table 3.

The use of the columns with bonded modified cellulose gave better results in comparison with those with bonded cyclodextrins. The size of the ferrocenyl moiety present in the molecule obviously permits formation of an inclusion complex with β-cyclodextrin which offers a relatively hydrophobic conical cavity with approximate diameter 7.8 A to the 'guest'. The chiral recognition of the 'guest' enantiomers results from enantioselective steric or polar interactions of the ferrocene substituent with hydroxyl groups sticking out on the surface of the cone of the cyclodextrin molecule. In our cases, such interaction cannot be realized for all compounds. It is connected first with rather bulk substituents at the α-carbon atom (Ph, $C_5H_4Mn(CO)_3$, BIm etc.), and secondly, in case of compound **8h**—ferrocenophane fragment simply cannot be included in the cone of cyclodextrine. On the other hand, recognition mechanism on cellulose is connected apparently, with formation of specific hydrogen bonds between the nitrogen atom of azole fragments or the hydroxyl group of carbinols and carbamate units of the modified cellulose. It was proved by the introduction of electron accepting substituents (CF_3, COOH **2b**, **2c**, **2f**

Table 1
Yields of ferrocenyl(alkyl)imidazoles from the reactions of with CDI, TDI

Number	Number	R_1	R_2	Yield, % (CDI)	Yield, %(TDI)
1a	**8a**	H	H	80	75
1b	**8b**	H	Me	85	86
1c	**8c**	H	Et	81	87
1d	**8d**	H	*n*-Pr	78	83
1e	**8e**	H	Ph	82	80
1f	**8f**	Me	Me	80	84
1g	**8g**	H	$C_5H_4Mn(CO)_3$	83	81
1h	**8h**	[3]-Ferrocenophanol-1		89	88
1i	**8i**	H	Fc	81	80



Scheme 5.

Table 2
Yields of ferrocenyl(alkyl)benzimidazoles in the reaction with TDBI

Number	Number	R_1	R_2	Yield, %
1a	**9a**	H	H	85
1b	**9b**	H	Me	82
1c	**9c**	H	Et	85
1d	**9d**	H	*n*-Pr	87
1e	**9e**	H	Ph	75
1f	**9f**	Me	Me	76

and **2g**) in pyrazole. In ferrocenyl(ethyl)-1*N*-(3-carboxy-5-methyl)pyrazole **2c**, the formation of dimers due to an intermolecular hydrogen bond is possible. In these cases, the separation of enantiomers was not achieved both in normal, and in reversed-phase modes on all columns used. The difficulties in separation of enantiomers of imidazole **8h** may result from the impossibility recognize two enantiomers of the ferrocenophane fragment.

3. Experimental

^{1}H-NMR spectra were obtained on a "Bruker-200-WP" instrument. EI mass spectra were taken on a "Kratos MS-890" spectrometer at 70 eV, and IR spectra were recorded with a IR-20 spectrometer (Karl Zeiss).

Dichloromethane was dried over $CaCl_2$, CDI was purchased from Lancaster and used without purification. TDI was prepared by interaction between thionylchloride and imidazole. Carbinols **1b**–**f**,**g**, **6** were synthesized by acylation of ferrocene by corresponding acid chlorides or acid anhydride [9] with the subsequent reduction by lithium aluminium hydride in Et_2O [10]. 2-Ferrocenyl-2-hydroxypropane **1e** was obtained by the reaction of ferrocene with acetone in sulfuric acid [11]. Carbinols **4a**,**b** were synthesized by reduction of corresponding acids by lithium aluminium hydride in Et_2O [12].

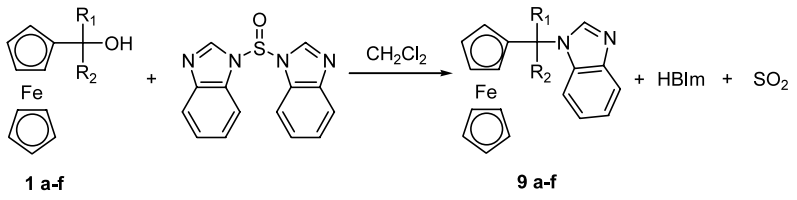
3.1. Synthesis of ferrocenyl(alkyl)azoles

3.1.1. General procedure 1 [4]

To a mixture of 1.0 mmol of ferrocenylcarbinol and 1.0 mmol of the corresponding azoles in 1.0 ml of methylene dichloride, 0.18 ml of 45% aqueous solution of fluoroboric acid was added under vigorous stirring. The agitation was continued for 5 min then 15 ml of Et_2O, the same amount of cold water, and 5–10 mg of ascorbic acid were added to the reaction flask. After vigorous shaking of the mixture the organic solution was separated, washed with cold water (5×15 ml), the solvent was removed and the residue was dried over $CaCl_2$.

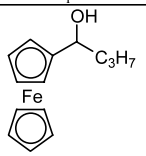
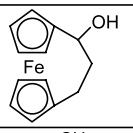
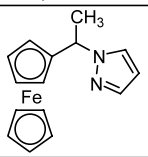
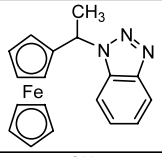
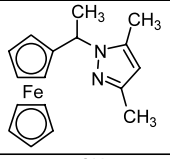
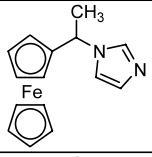
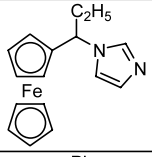
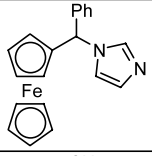
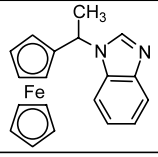
3.1.2. Ferrocenyl(ethyl)pyrazole (**2a**)

Yield 86%. Orange crystals, m.p. 52–54 °C, Anal.: C, 64.38; H, 5.91; N, 9.79%. Calc. for $C_{15}H_{16}FeN_2$: C, 64.31; H, 5.76; N, 10.00%. MS *m*/*z* (relative intensity,



Scheme 6.

Table 3
Enantiomeric separation of racemic mixtures

№	Compound	Chiral stationary phase	k'$_1$, k'$_2$	α	Eluent
1-c		γ-Cyclodextrin	8.96 9.43	1.05	C_6H_{14}/i-PrOH 9/1
1-h		Chiralcel OD	5.90 6.45	1.09	C_6H_{14}/i-PrOH 9/1
2-a		Chiralcel OD-H	7.46 11.52	1.54	C_6H_{14}/i-PrOH 99/1
2-d		OD-H Chiralcel OD	7.08 9.59	1.35	C_6H_{14}/i-PrOH 100/4
2-e		Chiralcel OD-H	3.16 3.64	1.15	C_6H_{14}/i-PrOH 99/1
8-b		Chiralcel OD	9.09 10.37	1.14	C_6H_{14}/i-PrOH 100/4
8-c		Chiralcel OD	5.44 7.47	1.37	C_6H_{14}/i-PrOH 100/4
8-e		Chiralcel OD	9.09 10.37	1.18	C_6H_{14}/i-PrOH 100/4
9-b		Chiralcel OD	8.18 9.17	1.12	C_6H_{14}/i-PrOH 100/4

%): 280 (95) $[M]^+$. IR (KBr) ν, cm^{-1}: 3115, 2965, 1525, 1411, 1293, 1120, 1045, 968, 853, 720, 665, 538, 498. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.53 (d, 3H, CH_3); 4.01–4.15 (m, 9H, Fc); 5.19 (q, 1H, CH); 6.00 (s, 1H, CH); 7.22 (s, 1H, CH); 7.49 (s, 1H, CH).

3.1.3. Ferrocenyl(ethyl)-1N-(3-trifluoromethyl-5-(2)-thiophene)pyrazole (**2b**)

Yield 84%. Yellow–orange oil, MS *m/z* (%): 430 (88) $[M]^+$. IR (KBr) ν, cm^{-1}: 3115, 3005, 2950, 1520, 1423, 1345,1223, 1191, 1154, 998, 834, 726, 498. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.65 (d, 3H, CH_3); 3.85–4.00 (m, 9H, Fc); 5.45 (q, 1H, CH); 6.87 (s, 1H, CH); 7.10 (s, 1H, CH); 7.35 (s, 1H, CH), 7.63 (s, 1H, CH).

3.1.4. Ferrocenyl(ethyl)-1N-(3-carboxy-5-methyl)pyrazole (**2c**)

Yield 62%. Yellow–brawn crystals, m.p. 162–164 °C (dec.), MS *m/z* (%): 338 (38) $[M]^+$. IR (KBr) ν, cm^{-1}: 3160, 2931,1715–1680, 1421, 1265, 1132, 1063, 974, 853, 713, 665, 517, 498. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.49 (d, 3H, CH_3); 2.10 (s, 3H), 3.97–4.15 (m, 9H, Fc); 5.15 (q, 1H, CH); 7.80 (s, 1H, CH); 7.10 (s, 1H, CH); 7.35 (s, 1H, CH), 10.85 (s, 1H, OH).

3.1.5. Ferrocenyl(ethyl)benzotriazole (**2d**)

Yield 97%. Orange crystals, m.p. 82 °C, Anal.: C, 64.38; H, 5.14; N, 12.54%. Calc. for $C_{18}H_{17}FeN_3$: C, 65.28; H, 5.17; N, 12.69%. MS *m/z* (%): 331 (43) $[M]^+$. IR (KBr) ν, cm^{-1}: 3125, 2943, 1640, 1567, 1490, 1402, 1220, 1100, 891, 470. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.05 (d, 3H, CH_3); 4.05–4.27 (m, 9H, Fc); 4.32 (q, 1H, CH); 6.00 (s, 1H, CH); 7.22 (s, 1H, CH); 7.49 (s, 1H, CH).

3.1.6. Ferrocenyl(ethyl)-1N-(3,5-dimethyl)pyrazole (**2e**)

Yield 92%. Orange crystals, m.p. 74–76 °C, Anal.: C, 66.80; H, 6.56; N, 8.38%. Calc. for $C_{17}H_{20}FeN_2$: C, 66.25; H, 6.54; N, 9.09%. MS *m/z* (%): 308 (97) $[M]^+$. IR (KBr) ν, cm^{-1}: 3010, 2890, 1560, 1470, 1009, 840, 778, 539, 472. ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.24 (d, 3H, CH_3); 1.78 (s, 3H), 2.17 (s, 3H), 4.05–4.25 (m, 9H, Fc); 5.25 (q, 1H, CH); 5.72 (s, 1H, CH).

3.1.7. Ferrocenyl(ethyl)-1N-(3-trifluoromethyl-5-methyl)pyrazole (**2f**)

Yield 88%. Yellow crystals, m.p. 47 °C, MS *m/z* (%): 362 (91) $[M]^+$. IR (KBr) ν, cm^{-1}: 3029, 2898, 1564, 1456, 1265, 1011, 844, 776, 547, 472. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.52 (d, 3H, CH_3); 2.43 (s, 3H), 4.01–4.08 (m, 9H, Fc); 5.34 (q, 1H, CH); 7.32 (s, 1H, CH).

3.1.8. Ferrocenyl(ethyl)-1N-(3,5-ditrifluoromethyl)pyrazole (**2g**)

Yield 87%. Dark brown oil, MS *m/z* (%): 416 (100) $[M]^+$. IR (KBr) ν, cm^{-1}: 3010, 2964, 1575, 1510, 1462, 1415, 1396, 1163, 1040, 987, 840, 715, 498. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.63 (d, 3H, CH_3); 4.01–4.10 (m, 9H, Fc); 5.26 (q, 1H, CH); 7.27 (s, 1H, CH).

3.1.9. General procedure 2 [5]

A mixture 1 mmole of ferrocenylcarbinol and 1.3 mmole CDI (or *N*,*N*′-thionyldiimidazole, *N*,*N*′-thionyldibenzimidazole) in anhydrous CH_2Cl_2 was refluxed for 1 h. The resulting mass was cooled, 50 ml ether was added and then washed by 20% solution of phosphoric acid (2 × 50 ml). The aqueous phase was alkalized up to pH 5 and then extracted by CH_2Cl_2 (2 × 50 ml). The organic layer was dried over anhydrous Na_2SO_4. Solvents were removed in vacuo. The resulting product was dried over $CaCl_2$.

*3.1.10. (2-Ferrocenylethyloxy)-(carbonyl)-1-imidazole (**5a**)*

Yield 98%. Orange crystals, m.p. 94–96 °C, MS *m*/*z* (%): 324 (80) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3245, 3090, 1764, 1487, 1430, 1383, 1335, 1261, 1192, 1117, 1019, 980, 850, 824, 778, 487. ^{1}H-NMR (DMSO-d_6, *δ*, ppm): 1.87 (t, 2H, CH_2), 2.60 (t, 2H, CH_2), 3.94–4.05 (m, 9H, Fc); 6.93 (s, 1H, CH); 7.40 (s, 1H, CH); 8.10 (s, 1H, CH).

*3.1.11. (4-Ferrocenylbutyloxy)-(carbonyl)-1-imidazole (**5b**)*

Yield 97%. Orange crystals, m.p. 74–75 °C, MS *m*/*z* (%): 352 (100) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3250, 3065, 1762, 1486, 1419, 1397, 1336, 1281, 1192, 1109, 1022, 851, 824, 773, 489. ^{1}H-NMR (DMSO-d_6, *δ*, ppm): 1.40 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 2.24 (m, 2H, CH_2), 3.92–4.01 (m, 9H, Fc); 4.23 (t, 2H CH_2); 6.88 (s, 1H, CH); 7.41 (s, 1H, CH); 8.08 (s, 1H, CH).

*3.1.12. Ferrocenyl(methyl)imidazole (**8a**)*

Yield 80% (CDI) (75% (TDI)). Yellow crystals, m.p. 65 °C, MS *m*/*z* (%): 266 (100) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3150–2970, 1690–1520, 1450, 1220–1100, 1110–1000, 830, 491. ^{1}H-NMR ($CDCl_3$, *δ*, ppm): 4.15–4.12 (m, 9H, Fc); 4.83 (s, 2H, CH_2); 6.87 (s, 1H, CH); 6.98 (s, 1H, CH); 7.44 (s, 1H, CH).

*3.1.13. Ferrocenyl(ethyl)imidazole (**8b**)*

Yield 85% (86%). Red–orange crystals, m.p. 75–76 °C, MS *m*/*z* (%): 280 (38) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3118, 2992, 2940, 2868, 1671, 1510, 1415–1390, 1240, 1115, 1090, 1010, 923, 840, 754, 641. ^{1}H-NMR ($CDCl_3$, *δ*, ppm): 1.73–1.77 (d, 3H, CH_3); 4.10–4.16 (m, 9H, Fc); 5.07–5.17 (q, 1H, CH); 6.86 (s, 1H, CH); 6.96 (s, 1H, CH); 7.44 (s, 1H, CH).

*3.1.14. Ferrocenyl(propyl)imidazole (**8c**)*

Yield 81% (87%). Yellow oil, MS *m*/*z* (%): 294 (65) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3204, 3011, 2972, 1650, 1522, 1426, 1113, 1028, 844, 452. ^{1}H-NMR (DMSO-d_6, *δ*, ppm): 0.55 (t, 3H, CH_3) 1.92 (m, 2H, CH_2); 3.90–4.11 (m, 9H, Fc); 4.73 (t, 1H, CH); 6.69 (s, 1H, CH); 7.02 (s, 1H, CH); 7.56 (s, 1H, CH).

*3.1.15. Ferrocenyl(butyl)imidazole (**8d**)*

Yield 78% (83%). Dark brown oil, MS *m*/*z* (%): 308 (100) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3109, 2972, 2885, 1692, 1511, 1425, 1292, 1174, 1118, 1090, 1040–1020, 923, 835, 754. ^{1}H-NMR ($CDCl_3$, *δ*, ppm): 0.93 (m, 3H, CH_3); 1.15 (m, 2H, CH_2); 2.00 (m, 2H, CH_2); 4.05–4.15 (m, 9H, Fc); 4.92 (t, 1H, CH); 6.89 (s, 1H, CH); 7.01 (s, 1H, CH); 7.52 (s, 1H, CH).

*3.1.16. Ferrocenyl(benzyl)imidazole (**8e**)*

Yield 82% (80%). Yellow crystals, m.p. 91–92 °C, MS *m*/*z* (%): 342 (75) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3111, 2944, 2872, 1518, 1472, 1140, 1123, 1015, 927, 840, 740–710. ^{1}H-NMR ($CDCl_3$, *δ*, ppm): 4.10–4.25 (m, 9H, Fc); 6.15 (s, 1H, CH); 6.82 (s, 1H, CH); 7.05 (s, 1H, CH); 7.14–7.30 (m, 5H, Ph); 7.45 (s, 1H, CH).

*3.1.17. Ferrocenyl(iso-propyl)imidazole (**8f**)*

Yield 80% (84%). Yellow crystals, m.p. 104–105 °C, MS *m*/*z* (%): 294 (23) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3118, 3090, 3011, 1510, 1482, 1398, 1380, 1281, 1215, 1116, 1087, 1010, 910, 850, 830–815, 724, 510, 482. ^{1}H-NMR ($CDCl_3$, *δ*, ppm): 1.45 (s, 6H, CH_3), 4.10–4.19 (m, 9H, Fc); 6.89 (s, 1H, CH); 6.93 (s, 1H, CH); 7.38 (s, 1H, CH).

*3.1.18. N-Imidazolyl-ferrocenyl-cyclopentadienylmanganesetricarbonyl-methane (**8g**)*

Yield 83% (81%). Dark red crystals, m.p. 98–100 °C, MS *m*/*z* (%): 468 (19) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3109, 3011, 2031, 1943 1513, 1381, 1215, 1115, 1083, 1011, 910, 850, 724, 482. ^{1}H-NMR (DMSO-d_6, *δ*, ppm): 4.10–4.19 (m, 9H, Fc); 4.88 (s, 1H, CH); 5.18–5.24 (m, 4H) 7.59 (s, 1H, CH); 7.93 (s, 1H, CH); 8.38 (s, 1H, CH).

*3.1.19. [3]-Ferrocenophan-1-N-imidazole (**8h**)*

Yield 89% (88%). Yellow crystals, m.p. 151 °C, MS *m*/*z* (%): 292 (60) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3118, 3090, 3011, 1510, 1482, 1398, 1380, 1281, 1215, 1116, 1087, 1010, 910, 850, 830–815, 724, 510, 482. ^{1}H-NMR (DMSO-d_6, *δ*, ppm): 1.96 (m, 2H, CH_2), 4.05–4.19 (m, 8H, 2Cp); 4.45 (t, 2H, CH_2); 4.63 (t, 1H, CH); 6.64 (s, 1H, CH); 7.08 (s, 1H, CH); 7.51 (s, 1H, CH).

*3.1.20. Diferrocenylimidazolylmethane (**8i**)*

Yield 81% (80%). Yellow–brown oil, MS *m*/*z* (%): 450 (25) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3107, 2885, 1693, 1509, 1464, 1412, 1281, 1226, 1110, 1088, 1051, 1009, 824, 759, 483. ^{1}H-NMR (DMSO-d_6, *δ*, ppm): 3.95–4.13 (m, 9H, Fc); 5.88 (s, 1H, CH); 6.89 (s, 1H, CH); 6.93 (s, 1H, CH); 7.38 (s, 1H, CH).

*3.1.21. Ferrocenyl(methyl)benzimidazole (**9a**)*

Yield 85%. Yellow crystals, m.p. 123–125 °C, MS *m*/*z* (%): 316 (93) $[M]^+$. IR (KBr) *ν*, cm^{-1}: 3150–2970, 1690–1520, 1450, 1220–1100, 1110–1000, 830, 491. ^{1}H-

NMR ($CDCl_3$, δ, ppm): 4.02–4.20 (m, 9H, Fc); 5.01 (s, 2H, CH_2); 6.96–7.12 (m, 2H); 7.45–7.52 (m, 2H) 8.10 (s, 1H, CH).

*3.1.22. Ferrocenyl(ethyl)benzimidazole (**9b**)*

Yield 82%. Yellow crystals, m.p. 91–93 °C, MS *m/z* (%): 330 (87) $[M]^+$. IR (KBr) ν, cm^{-1}: 3110, 2952, 1621, 1490, 1290, 1113, 1010, 925, 843, 759, 490. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.72 (d, 3H, CH_3); 4.00–4.25 (m, 9H, Fc); 5.57 (q, 1H, CH); 7.00 (m, 2H); 7.40 (m, 2H); 8.05 (s, 1H, CH).

*3.1.23. Ferrocenyl(propyl)benzimidazole (**9c**)*

Yield 85%. Yellow oil, MS *m/z* (%): 344 (45) $[M]^+$. IR (KBr) ν, cm^{-1}: 3113, 2965, 1710, 1622, 1490, 1409, 1291, 1230, 1109, 836, 485. ^{1}H-NMR (DMSO-d_6, δ, ppm): 0.57 (t, 3H, CH_3) 2.18 (m, 2H, CH_2); 3.93–4.33 (m, 9H, Fc); 5.22 (t, 1H, CH); 7.02 (m, 2H); 7.40 (m, 1H); 8.21 (s, 1H, CH).

*3.1.24. Ferrocenyl(butyl)benzimidazole (**9d**)*

Yield 87%. Dark brown oil, MS *m/z* (%): 358 (22) $[M]^+$. IR (KBr) ν, cm^{-1}: 3102, 2882, 1720, 1623, 1501, 1465, 1376, 1114, 1061, 1040, 832, 759. ^{1}H-NMR (DMSO-d_6, δ, ppm): 0.93 (m, 3H, CH_3); 1.15 (m, 2H, CH_2); 2.00 (m, 2H, CH_2); 4.05–4.15 (m, 9H, Fc); 4.92 (t, 1H, CH); 6.89 (s, 1H, CH); 7.01 (s, 1H, CH); 7.52 (s, 1H, CH).

*3.1.25. Ferrocenyl(benzyl)benzimidazole (**9e**)*

Yield 75%. Dark brown oil, MS *m/z* (%): 392 (36) $[M]^+$. IR (KBr) ν, cm^{-1}: 3111, 2952, 1624, 1493, 1410, 1293, 1231, 1110, 1009, 924, 852, 761, 498. ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.88–4.18 (m, 9H, Fc); 6.65 (s, 1H, CH); 7.01 (m, 2H, CH); 7.10–7.25 (m, 5H, Ph); 7.42 (m, 2H, CH); 8.08 (s, 1H, CH).

*3.1.26. Ferrocenyl(iso-propyl)benzimidazole (**9f**)*

Yield 76%. Yellow crystals, m.p. 140–143 °C, MS *m/z* (%): 344 (10) $[M]^+$. IR (KBr) ν, cm^{-1}: 3110, 2872, 1629, 1495, 1400, 1291, 1230, 1110, 1020, 840, 760, 489. ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.14 (s, 6H, CH_3), 4.18–4.31 (m, 9H, Fc); 7.39 (s, 1H, CH); 7.52 (m, 2H, CH); 7.71 (m, 2H, CH).

3.2. Chromatographic separation of enantiomers

Following chiral columns (250 × 4.6 mm, 5 μm) were used: Chiracel OD, Chiracel OD-H, (R, R) Whelk-01 (Pirkle covalent), Chirobiotic T, Cyclobond I 2000. The HPLC system, Bruker LC 31 with a UV 254 detector was operated at a flow rate of 1.0 ml^{-1} and ambient temperature.

Acknowledgements

We thank Maya Karadzhaeva for performing some experiments. This work has been partially supported by The Scientific Training Center of Biomedical Chemistry (Grant No A0078, the Federal Target Program "Integration").

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