Synthesis and properties of optically active ferrocenylethylindazoles

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The stereochemistry of two processes, *viz.*, α-ferrocenylalkylation of indazole with optically active *S*-(+)-1-ferrocenylethanol and the thermal rearrangement of *S*-(+)-2-*N*-(ferrocenylethyl)indazole into *S*-(+)-1-*N*-(ferrocenylethyl)indazole, was studied. Both reactions proceed stereoselectively.

Key words: ferrocenes, ferrocenylalkylation, enantiomeric resolution, high-performance liquid chromatography.

Acid-catalyzed ferrocenylalkylation of nitrogen-containing heterocycles with ferrocenylcarbinols and ferrocenyl(alkyl)amines provides a convenient procedure for the introduction of the ferrocenylalkyl group into nucleophiles. For example, refluxing of (*R,S*)-dimethyl{1-[2-(diphenylphosphino)ferrocenyl]ethyl}amine with pyrazoles in acetic acid afforded pyrazole-containing *P,N*-bidentate ligands in 30—70% yields (*ee* 95%).[1] A very convenient method for ferrocenylalkylation is based on reactions of N-heterocycles with ferrocenylcarbinols under conditions of acid phase-transfer catalysis, which allows one to prepare products in high yields (60—95%).[2] After the introduction of the ferrocene fragment into molecules of organic compounds, the latter often exhibit biological activity due to their ability to penetrate through lipid cell membranes and abnormal metabolism.[3,4] Earlier,[5] we have demonstrated that compounds of the ferrocenyl(alkyl)azole series possess pronounced antitumor activity in combination with low toxicity.

The present study was aimed at investigating the stereochemistry of α-ferrocenylalkylation of indazole with optically active *S*-(+)-1-ferrocenylethanol (**1**) as well as of the thermal rearrangement of positional isomers, *viz.*, of *S*-(+)-(indazol-2-yl)ethylferrocene (**2**) into *S*-(+)-(indazol-1-yl)ethylferrocene (**3**).

It is known[6] that the single-phase nucleophilic substitution in α-derivatives of ferrocene proceeds with retention of the configurations of the starting reagents, which is associated with the structural features of α-ferrocenyl carbocations.

Analytical resolution of enantiomers was carried out and the enantiomeric excess was determined by HPLC on chiral columns.[7] To estimate the efficiency of the method, all the compounds used were initially synthesized as racemates. The reaction of racemic 1-ferrocenylethanol **1** with indazole in the two-phase CH_2Cl_2—H_2O system afforded two isomeric ferrocenylethylindazoles **2** and **3** in 29 and 60% yields, respectively.[8]

Racemates **1—3** were resolved into enantiomers by HPLC on columns with carbamate-modified cellulose (Chiralcel OD) and 4-(3,5-dinitrobenzamido)tetrahydrophenanthrene ((*R,R*)-Whelk-01) grafted on silica gel. The results of the study are given in Table 1. The chromatogram of resolution of α-(indazol-2-yl)ethylferrocene enantiomers (**2**) is shown in Fig. 1.

To study the stereochemistry of ferrocenylalkylation of indazole, wy prepared alcohol *S*-**1** from *N,N*-dimethylaminoethylferrocene.[6] This alcohol was resolved into enantiomers with the use of (+)-tartaric acid according to a procedure described earlier.[9] According to the HPLC data, the enantiomeric excess (*ee*) was 97%. The reaction

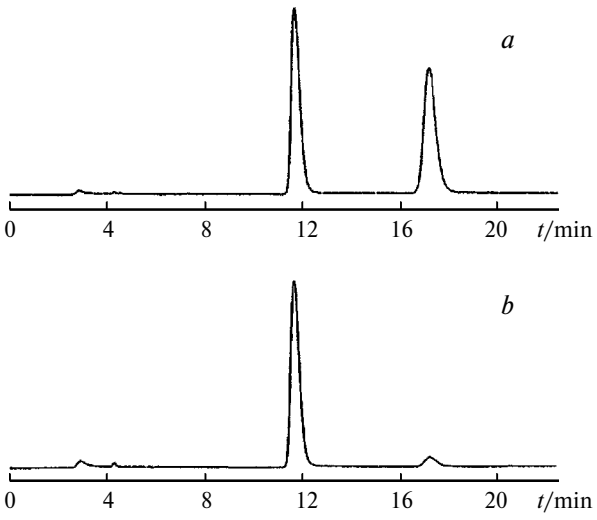
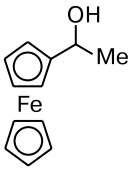
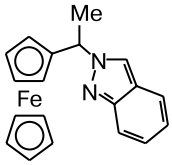
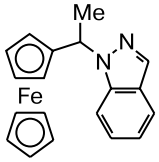


Fig. 1. Chromatographic resolution of α-(indazol-2-yl)ethylferrocene enantiomers: (*a*) racemic mixture of **2**, (*b*) enantiomerically enriched product **2a** (a Chiracel OD column).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 901—903, April, 2004.

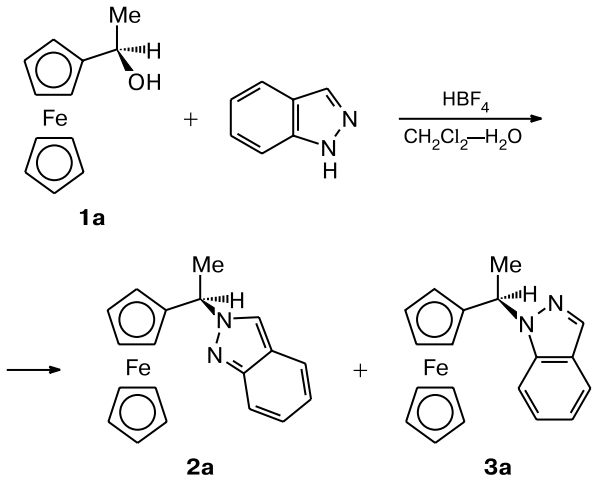
1066-5285/04/5304-0939

Table 1. Chromatographic resolution of racemic compounds into enantiomers

Compound	HPLC data					
	Chiral stationary phase	k'_1	k'_2	α	R_s	Eluent
 (**1**)	(R,R)-Whelk-01	7.06	7.93	1.12	1.02	C_6H_{14}—Pr^iOH (99 : 1)
 (**2**)	Chiralcel OD	7.46	11.52	1.54	4.0	C_6H_{14}—Pr^iOH (99 : 1)
 (**3**)	Chiralcel OD	7.08	9.59	1.35	1.33	C_6H_{14}—Pr^iOH (100 : 4)

of **1a** with indazole in the two-phase CH_2Cl_2—H_2O medium in the presence of HBF_4 afforded two ferrocenylalkylation products **3a** and **2a** (Scheme 1); *ee* was 91 and 90%, respectively.

Scheme 1



Based on the data on conformational stability of α-ferrocenyl carbocations, the (*S*) configuration can be assigned to the compounds synthesized. In particular, the structure and absolute configuration of *S*-(+)-α-(3,5-dimethylpyrazolyl)ethylferrocene, which was prepared by ferrocenylalkylation of 3,5-dimethylpyrazole with *S*-(+)-1-ferrocenylethanol, were established by X-ray diffraction analysis.* A decrease in the enantiomeric excess in the reaction products prepared under conditions of heterophase catalysis compared to the enantiomeric excess achieved in the reaction in AcOH [1] is apparently associated with the fact that the carbocation that formed is less stabilized by solvent molecules in a nonpolar phase and has a lower energy barrier to rotation about the C—C bond.

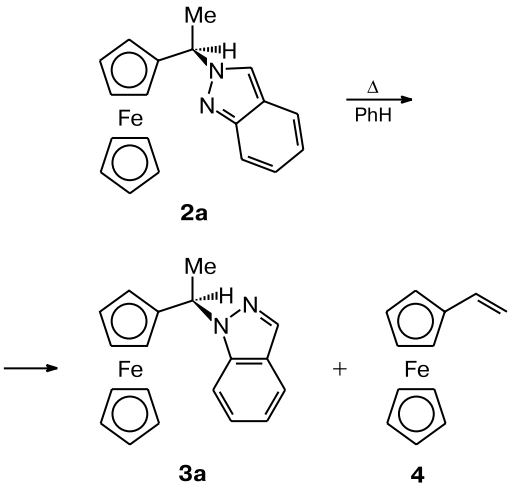
It is known[10] that thermal stability of 2-*N*-substituted indazoles is much lower than that of the corresponding 1-*N* isomers, which was exemplified by ferrocenylalkylindazoles.[8] Thermal treatment leads to isomerization of their 2-*N* isomers into the corresponding 1-*N* derivatives. To elucidate the stereochemistry of this reaction, we carried out the rearrangement of optically active *S*-(+)-**2a** into *S*-(+)-**3a**.

As a result, we isolated two products, *viz.*, **3a** and vinylferrocene (**4**) (Scheme 2). Study of compound **3a** by HPLC demonstrated that the thermal rearrangement proceeds with retention of the configuration (*ee* 90%). Hence, this transformation can be assigned to 1,2-sigmatropic rearrangements.

To summarize, our investigation of the stereochemistry of two processes, *viz.*, α-ferrocenylalkylation of indazole with optically active *S*(+)-1-ferrocenylethanol (**1**) and the thermal rearrangement of *S*-(+)-(indazol-2-yl)ethylferrocene into *S*-(+)-(indazol-1-yl)ethylferrocene, showed that both reactions proceed stereoselectively.

* A. A. Simenel, Yu. V. Kuzmenko, and Z. A. Starikova, unpublished results.

Scheme 2



Experimental

The ^{1}H NMR spectra were recorded on a Bruker-200-WP spectrometer in $CDCl_3$ with Me_4Si as the internal standard. The mass spectra were obtained on a Kratos MS-890 spectrometer (the energy of ionizing electrons was 70 eV; the temperature of the ionization chamber was 200 °C). The IR spectra were measured on a UR-20 spectrometer (Karl Zeiss) in KBr pellets. Chromatographic resolution was carried out with the use of Chiracel OD (Daicel Chemicel Industries, Ltd) and Whelk-01 (Regis Technologies, Inc) (250×4.6 mm, 5 μm) chiral columns and a Bruker LC 31 instrument equipped with a UV detector (254 nm); the flow rate was 1.0 mL min^{-1} at a constant temperature. The specific rotation was determined on a Perkin—Elmer 141 polarimeter. The TLC control was performed on plates with SiO_2 (Silufol). 1-Ferrocenylethanol (**1**) was prepared by reduction of acetylferrocene with $LiAlH_4$.[11]

Synthesis of *S*-(+)-α-(indazol-1-yl)ethylferrocene (3a) and *S*-(+)-α-(indazol-2-yl)ethylferrocene (2a). A 48% aqueous solution of HBF_4 (0.18 mL, 1 mmol) was added with intense stirring to a suspension of *S*-(+)-1-ferrocenylethanol (0.23 g, 1 mmol) and indazole (0.118 g, 1 mmol) in CH_2Cl_2 (1 mL). After 5 min, water (10 mL) and Et_2O (10 mL) were added. The organic layer was separated, washed with water (2×20 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* using a rotary evaporator. The products were separated on a column (4×25 mm, silica gel); the dark-yellow band was eluted with benzene and compound **3a** was obtained in a yield of 0.24 g (73%), $[\alpha]^{20}_D$ +10.0 (*c* 0.3; benzene), as a yellow crystalline compound, m.p. 92—94 °C, R_f 0.54 (benzene). MS, *m/z* (I_{rel} (%)): 330 $[M]^+$ (38). ^{1}H NMR, δ: 1.89 (d, 3 H, Me, J = 7.8 Hz); 4.03—4.23 (m, 9 H, Fc); 5.65 (m, 1 H, CH); 7.04—7.48 (m, 4 H, ABCD system, indazole); 7.98 (s, 1 H, C(3)H, indazole). IR, ν/cm^{-1}: 3117, 2921, 1654, 1476, 1453, 1155, 1112, 1011—1000, 914, 823, 722, 615, 597, 438.

The yellow band was eluted with chloroform and compound **2a** was obtained in a yield of 0.04 g (15%), $[\alpha]^{20}_D$ +14.0 (*c* 0.3; benzene), as a yellow-orange crystalline compound, m.p. 116—118 °C, R_f 0.46 (benzene). MS, *m/z* (I_{rel} (%)): 330 $[M]^+$ (62). ^{1}H NMR, δ: 1.99 (d, 3 H, Me, J = 12.0 Hz); 4.13—4.43 (m, 9 H, Fc); 5.67 (m, 1 H, CH); 6.99—7.47 (m, 4 H, ABCD system, indazole); 7.68 (s, 1 H, C(3)H, indazole). IR, ν/cm^{-1}: 3110, 2919, 1653, 1481, 1459, 1160, 1110, 1014—1000, 920, 824, 618, 587, 436.

Rearrangement of *S*-(+)-α-(indazol-2-yl)ethylferrocene (2a) into *S*-(+)-α-(indazol-1-yl)ethylferrocene (3a). Benzene (5 mL) was added to compound **2a** (0.02 g). The reaction mixture was refluxed for 15 h, cooled, and chromatographed on Al_2O_3 (Brockmann II neutral). Elution with hexane afforded vinylferrocene **4** in a yield of 0.002 g (15%). MS, *m/z* (I_{rel} (%)): 212 $[M]^+$ (100). Elution with Et_2O gave *S*-(+)-α-(indazol-1-yl)ethylferrocene (**3a**) in a yield of 0.015 g (75%) as a yellow-orange crystalline compound, $[\alpha]^{20}_D$ +10.0 (*c* 0.3; benzene) (*ee* 90%), m.p. 92—94 °C.

This study was in part financially supported by the Presidium of the Russian Academy of Sciences (Program for Support of Young Scientists, 2003).

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Received January 23, 2004;
in revised form March 12, 2004