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Synthesis of New Ferrocene Derivatives with a 4,5-Dichloroisothiazole Fragment

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Abstract—Conjugates of ferrocene and 4,5-dichloroisothiazole were synthesized, where the ferrocene and isothiazole moieties are linked through various structural fragments. The acylation of ferrocene with 4,5-dichloroisothiazole-3-carbonyl chloride gave (4,5-dichloroisothiazol-3-yl) ferrocenyl ketone; the acylation of aminomethylferrocene furnished the corresponding amide. The esterification of ferrocene-1,1'-dicarboxylic acid with 4,5-dichloroisothiazol-3-yl-methanol resulted in the formation of the corresponding ester. The condensation of 1,1'-diacetylferrocene with 4,5-dichloroisothiazole-3-carbaldehyde afforded ferrocenophane containing 4,5-dichloroisothiazole moieties.

Keywords: ferrocene, ferrocenophane, isothiazole, ketones, aldehydes, amides, esters, acylation

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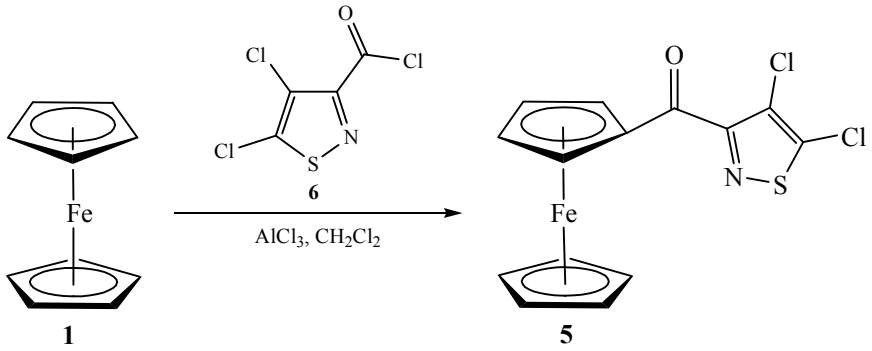
Ferrocene derivatives are of interest due to unusual chemical properties of these compounds and their various practical applications, including the use as bioactive substances. To date, ferrocene conjugates with amino acids, peptides, DNA, carbohydrates, steroids, hormones, various polyfunctional organic compounds have been obtained, a number of them showed high biological activity [1]. In particular, ferrocenylalkylazoles have antitumor activity comparable to the known cisplatin medication [2].

We have previously shown that functionally substituted 4,5-dichloroisothiazoles exhibit antitumor activity and are synergists of cytotoxic drugs used in chemotherapy and industrial insecticides [3–5]. In addition, it has been found that esters of ferrocene alcohols and 4,5-dichloroisothiazole-3-carboxylic acid also increase the effectiveness of insecticides of the pyrethroid and neonicotinoid series 1.3–1.8 times in 10% concentration [6]. In this regard, obtaining of new ferrocene derivatives with the 4,5-dichloroisothiazole fragment for subsequent screening as synergists of the known biologically active substances seems to be relevant.

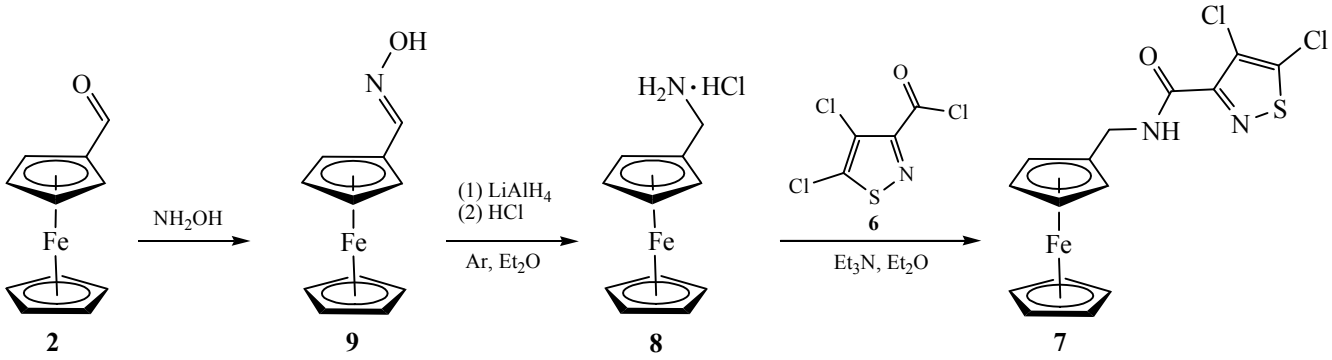
We aimed to synthesize ferrocene conjugates with 4,5-dichloroisothiazole, containing ferrocene and isothiazole moieties linked through various structural fragments. Ferrocene **1** and its mono- and disubstituted derivatives like formylferrocene **2**, ferrocene-1,1'-dicarboxylic acid **3** and 1,1'-diacetylferrocene **4** were used as the starting compounds. All these substances are available commercial products.

The acylation of ferrocene **1** with 4,5-dichloroisothiazole-3-carbonyl chloride **6** under the Friedel–Crafts reaction conditions resulted in the formation of (4,5-dichloroisothiazol-3-yl)ferrocenyl ketone **5** (Scheme 1). The process proceeds slowly, with incomplete conversion and is accompanied by tarring. The optimum conditions are boiling the reagents in methylene chloride for 480 hours using aluminum chloride as a catalyst. Under these conditions, the conversion was 50%, the yield of the target ketone **5** did not exceed 30% or 60% relative to the reacted ferrocene. Reduction of the process duration led to a decrease in the yield of ketone **5** (for example, up to 15% when the reaction time was 200 h). An increase in the process duration led to intensification of tar formation and reduction of the ketone yield. Replacement of the solvent with higher boiling dichloroethane or chloroform and the catalyst with aluminum bromide resulted in a complete tarring of the reaction mixture.

Scheme 1.



Scheme 2.



The formation of the ketone **5** was confirmed by the presence of a strong characteristic bands at 1644 (C=O) and 1454–1644 cm^{-1} (C=C, C=N) in the IR spectrum. The ^{13}C NMR spectrum contained the signal of carbonyl group at 189.86 ppm; the signals at 129.90, 149.47 and 162.33 ppm corresponded to the three carbon atoms of the heterocycle. In the ^{1}H NMR spectrum the unsubstituted cyclopentadienyl moiety was characterized by a singlet at 4.25 ppm; four CH groups of the second cyclopentadienyl ring appeared as two multiplets at 4.67 and 5.07 ppm.

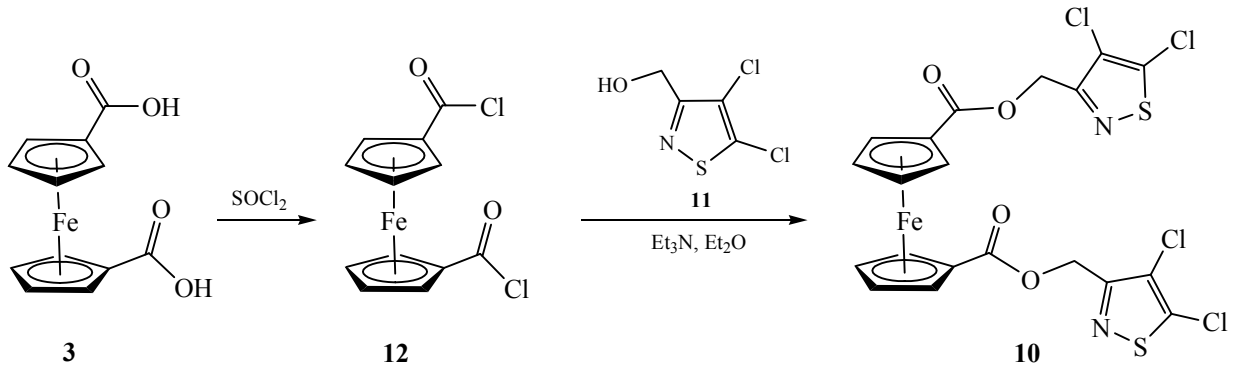
The resulting ketone **5** is a metallocene analog of (4,5-dichloroisothiazol-3-yl)*p*-tolyl ketone, exhibited synergistic activity being combined with insecticides [7].

In order to synthesize the conjugate of ferrocene and 4,5-dichloroisothiazole with the amide linker, (4,5-dichloroisothiazol-3-yl)-*N*-[(ferrocenyl)methyl]carboxamide **7**, we acylated ferrocenylmethanamine hydrochloride **8** with chloride **6** (Scheme 2). Amine hydrochloride **8** was prepared from formylferrocene **2** by reaction with hydroxylamine and subsequent reduction of the oxime **9** with lithium aluminum hydride in an inert atmosphere and treating the resulting amine with dry HCl [8].

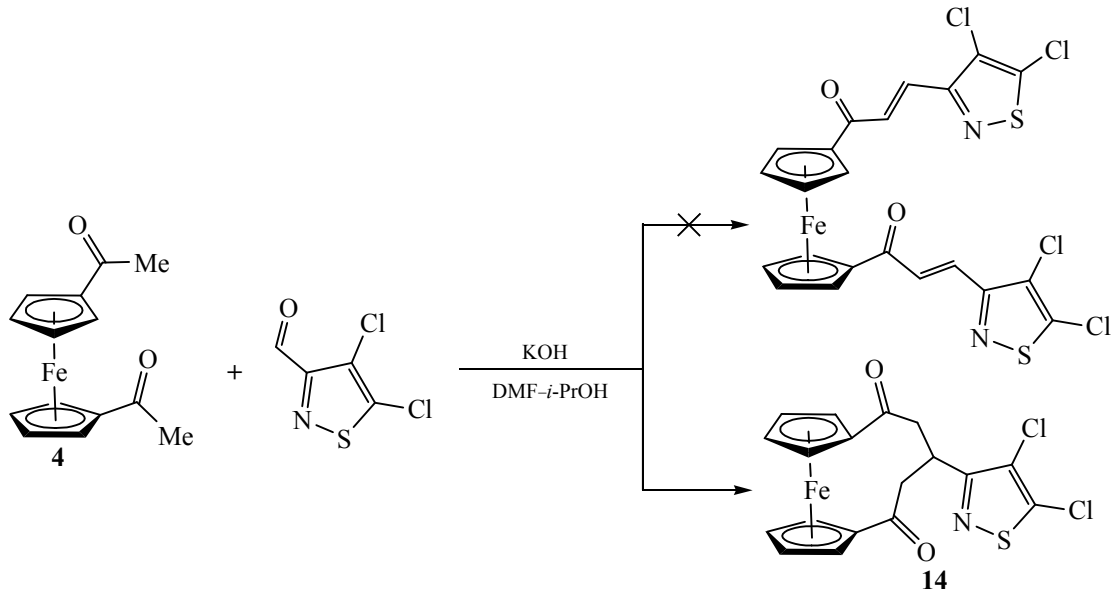
The synthesized amide **7** was identified by IR, ^{1}H, ^{13}C NMR spectroscopy and elemental analysis data. In the IR spectrum, the amide fragment was characterized by absorption of stretching vibrations of C=O (1663 cm^{-1}) and N–H (3371 cm^{-1}) bonds.

In addition to monosubstituted ferrocene derivatives **5** and **7**, a conjugate with two dichloroisothiazole fragments in the molecule bound to ferrocene through ester linker, namely, bis[(4,5-dichloroisothiazol-3-yl)methyl]ferrocene-1,1'-dicarboxylate **10** was obtained (Scheme 3). The synthesis of diester **10** was carried out starting from ferrocene-1,1'-dicarboxylic acid **3** and (4,5-dichloroisothiazol-3-yl)methanol **11**, whose synthesis was described earlier [9]. Various experimental approaches were tested. Thus, direct acylation of alcohol **11** with ferrocenedicarboxylic acid **3** in dimethylformamide in the presence of dimethylaminopyridine (DMAP), as well as an attempt to transesterify dimethyl ferrocene-1,1'-dicarboxylate using *p*-toluenesulfonic acid did not lead to the formation of the desired product **10**: the

Scheme 3.



Scheme 4.



reactions did not proceed. Diester **10** was synthesized by acylation of dichloroisothiazolylmethanol **11** with ferrocene-1,1'-dicarbonyl chloride **12**. The mentioned product yield was 80%. Acid chloride **12** was prepared quantitatively yield by reacting ferrocene-1,1'-dicarboxylic acid **3** with thionyl chloride as described in [10].

The presence of the ester group in compound **10** was confirmed by the absorption bands at 1759 and 1719 cm^{-1} in the IR spectrum due to stretching vibrations of C=O bonds. In the ^{13}C NMR spectrum, both carboxyl fragments appeared as one signal at 169.97 ppm.

We also investigated the possibility of isotiazole-containing ferrocene-1,1'-dipropenyl ketone obtaining by condensation of diacetylferrocene **4** with 4,5-dichloroisothiazole-3-carbaldehyde **13** synthesized from alcohol **11** [11]. Surprisingly, the reaction led to the formation of 3-(4,5-dichloroisothiazol-3-yl)[5]ferrocenophane-1,5-dione **14** [12] both in ethanol medium and in a mixture of isopropanol and dimethylformamide (Scheme 4).

The obtained ferrocenofane structure was confirmed by IR, ^1H and ^{13}C NMR spectral and elemental analysis data. There were no vinyl proton signals in the ^1H NMR spectrum, and the signals of CH_2 group were registered at 2.59 and 2.98 ppm. The protons of CH group and cyclopentadienyl ring appeared as a multiplet in the range of 4.45–4.71 ppm. The ^{13}C NMR spectrum also contained CH_2-groups signals at 69.44 and 71.96 ppm, as well as the signal of CH fragment at 42.60 ppm. In the IR spectrum of compound **14** there were absorption bands of carbonyl groups (1663, 1651 cm^{-1}) and no bands corresponding to vibrations of hydroxy group that could be attributed to β-

hydroxyketone, formed as an intermediate in the Kleisen–Schmidt addition of 4,5-dichloroisothiazole-3-cabaldehyde to diacetylferrocene **4**.

It should be noted that ferrocenophanes with isothiazole fragments are unknown [12, 13], and ferrocene-isothiazole conjugates have been described only by several esters examples in our recent publications [6, 14, 15].

The synthesized conjugates of ferrocene and 4,5-dichloroisothiazole are of interest for screening as as cytostatics and insecticides synergists, and also for studying the influence of the linker between the ferrocene and isothiazole moieties nature on the biological activity of these compounds.

EXPERIMENTAL

IR spectra were recorded on an IR Protégé-460 Nicolet Fourier spectrophotometer from KBr pellets. ^{1}H and ^{13}C NMR spectra were registered on an Avance-500 Bruker spectrometer in $CDCl_3$ (**5**, **12**) or $(CD_3)_2CO$ (**7**, **14**); the chemical shifts were measured with respect to the residual solvent signals.

The reactants of the 4,5-dichloroisothiazole series (acid chloride **6**, alcohol **11**, and aldehyde **13**) were prepared as described in [9, 10]. Ferrocenylmethanamine hydrochloride was synthesized from formylferrocene oxime **9** by the known method [8]. Ferrocene-1,1'-dricarboxyl chloride **12** was prepared by the procedure reported in [12].

(4,5-Dichloroisothiazol-3-yl) ferrocenyl ketone (5). A mixture of 0.216 g (1 mmol) of acid chloride **6**, 0.241 g (1.3 mmol) of ferrocene **1**, and 0.173 g (1.3 mmol) of aluminum chloride in 30 mL of methylene chloride was boiled for 480 h, then poured into 200 mL of 3% hydrochloric acid solution and stirred for 1.5 h. The organic phase was separated, washed with water, $NaHCO_3$ solution, and dried over sodium sulfate. The solvent was distilled off in a vacuum, and the residue was purified by chromatography on a silica gel column, eluting with hexane–ethyl acetate, 8 : 1. Yield 30% (0.11 g), mp 98–100°C. IR spectrum, ν, cm^{-1}: 3420, 3265, 3091, 2956, 2923, 2853, 1726, 1644, 1454, 1401, 1387, 1348, 1257, 1112, 1105, 1029, 829, 749, 665, 498, 486, 474. ^{1}H NMR spectrum, δ, ppm: 4.25 c ($5H_{Cp}$), 4.65–4.69 m ($2H_{Cp}$), 5.05–5.09 m ($2H_{Cp}$). ^{13}C NMR spectrum, δ_C, ppm: 70.50 ($5CH_{Cp}$), 71.66 ($2CH_{Cp}$), 73.98 ($2CH_{Cp}$), 76.81 (C_{Cp}), 129.90, 149.47, 162.33 ($3C_{tert}$), 189.86 (C=O). Found, %: C 45.79; H 2.71; Cl 19.48; Fe 15.34; N 3.79; S 8.87. $C_{14}H_9Cl_2FeNOS$. Calculated, %: C 45.94; H 2.48; Cl 19.37; Fe 15.26; N 3.83; S 8.76. *M* 366.04.

(4,5-Dichloroisothiazol-3-yl)-*N*-[(ferrocenyl)-methyl]carboxamide (7). To a solution of 1.46 g (6.75 mmol) of 4,5-dichloroisothiazolyl-3-carbonyl chloride **6** in 80 mL of anhydrous diethyl ether was added 1.70 g (6.43 mmol) of aminomethylferrocene hydrochloride **9**, followed by the addition of 1.3 g (12.9 mmol) of triethylamine. The reaction mixture was stirred for 18 h at 23°C. The precipitate was filtered off, and the filtrate was washed with $NaHCO_3$ solution, water, a saturated NaCl solution, and dried over sodium sulfate. The solvent was removed in a vacuum, and the residue was dried in a vacuum. Yield 92% (2.34 g), mp 114–116°C. IR spectrum, ν, cm^{-1}: 3371, 3096, 2958, 2923, 2854, 1663, 1532, 1480, 1431, 1354, 1341, 1263, 1240, 1199, 1103, 1024, 995, 932, 816, 638, 521, 481, 444. ^{1}H NMR spectrum, δ, ppm: 4.10–4.14 m ($2H_{Cp}$), 4.26–4.32 m (4H, $2H_{Cp}$ + CH_2), 4.22 s ($5CH_{Cp}$), 8.09 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 39.14 (CH_2), 68.83 ($2CH_{Cp}$), 69.28 ($2CH_{Cp}$), 69.56 ($5CH_{Cp}$), 86.75, 125.00, 150.99, 159.26, 159.63 ($5C_{tert}$). Found, %: C 45.82; H 3.15; Cl 18.11; Fe 14.27; N 7.12; S 8.21. $C_{15}H_{12}Cl_2FeN_2OS$. Calculated, %: C 45.60; H 3.06; Cl 17.95; Fe 14.14; N 7.09; S 8.11. *M* 395.08.

Bis[(4,5-dichloroisothiazol-3-yl)methyl]ferrocene-1,1'-dicarboxylate (10). To a mixture of 0.31 g (1.00 mmol) of ferrocene-1,1'-dicarbonyl chloride **12** and 0.38 g (2.06 mmol) of (4,5-dichloroisothiazol-3-yl)methanol **11** in 50 mL of diethyl ether was added 0.11 g (2.08 mmol) of triethylamine. The mixture was stirred at 20–23°C for 24 h. The precipitate of triethylamine hydrochloride was filtered off; the filtrate was washed with 5% aqueous $NaHCO_3$ solution, 10% aqueous NaCl solution, and dried over sodium sulfate. The solvent was removed in vacuum, and the residue was recrystallized from acetone–hexane, 1 : 4. Yield 80% (0.49 g), mp 112–113°C. IR spectrum, ν, cm^{-1}: 3428, 2924, 1759, 1719, 1462, 1445, 1378, 1272, 1136, 1107, 1027, 981, 969, 847, 839, 808, 774, 523, 493, 472. ^{1}H NMR spectrum, δ, ppm: 4.45 s ($4H_{Cp}$), 4.89 s ($4H_{Cp}$), 5.32 s (4H, $2CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 61.25 ($2CH_2$), 72.10 ($4CH_{Cp}$), 73.64 ($4CH_{Cp}$), 74.62 ($2C_{Cp}$), 122.92, 148.85, 161.61 ($6C_{tert}$), 169.97 (2C=O). Found, %: C 39.72; H 2.20; Cl 23.54; Fe 9.29; N 4.69; S 10.69.

$C_{20}H_{12}Cl_4FeN_2O_4S_2$. Calculated, %: C 39.63; H 2.00; Cl 23.40; Fe 9.21; N 4.62; S 10.58. *M* 606.09.

3-(4,5-Dichloroisothiazol-3-yl)[5]ferrocenophane-1,5-dione (14). A dispersion of 0.2 g (0.74 mmol) of diacetylferrocene **4** and 0.01 g (0.22 mmol) of KOH in a mixture of 30 mL of isopropanol and 20 mL of DMF was stirred for 5 min, then 0.14 g (0.76 mmol) of dichloroisothiazolcarbaldehyde **13** was added. The mixture was stirred for an additional 12 h, after which 4 drops of acetic acid were added and the reaction mixture was poured into water. The precipitate was filtered off and dried over calcium chloride. Yield 65% (0.21 g), mp 207°C (decomp.). IR spectrum, ν, cm^{-1}: 3110, 3086, 2921, 2853, 1663, 1651, 1509, 1466, 1435, 1398, 1380, 1342, 1284, 1239, 1105, 1092, 1062, 1039, 996, 912, 831, 547, 503. ^1H NMR spectrum, δ, ppm: 2.59 br.s (2H, CH_2), 2.98 t (2H, CH_2, J = 11.6 Hz), 4.45–4.71 m ($4H_{Cp}$ + CH), 4.84 br.s ($2H_{Cp}$), 4.87 br.s ($2H_{Cp}$). ^{13}C NMR spectrum, δ_C, ppm: 42.60 (CH), 69.44 (CH_2), 71.96 (CH_2), 73.98 ($4CH_{Cp}$), 74.66 ($4CH_{Cp}$), 82.00 ($2C_{Cp}$), 122.17, 148.10, 168.60 ($3C_{tert}$), 197.61 (2C=O). Found, %: C 49.51; H 3.18; Cl 16.60; Fe 12.68; N 3.32; S 7.47. $C_{18}H_{13}Cl_2FeNO_2S$. Calculated, %: C 49.80; H 3.02; Cl 16.33; Fe 12.86; N 3.23; S 7.39. *M* 434.11.

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