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Synthesis and properties of 5-ferrocenyl-1*H*-pyrazole-3-carbaldehydes

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ABSTRACT

New ferrocene derivatives – ethyl esters of 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acids were synthesized. The corresponding aldehydes were obtained from acid esters in two steps. The reductive amination reaction of 5-ferrocenyl-1-phenyl-1*H*-pyrazole-3-carbaldehyde was studied. Several of these compounds were investigated by cyclic voltammetry. All of them exhibited a reversible one-electron oxidation–reduction wave owing to the ferrocene–ferricinium redox couple with a positive shift (0.51–0.69 V) compared with that of ferrocene (0.46 V). The X-ray crystal structure of the ethyl ether 1-(3-chloro-2-fluorophenyl)-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acid is also presented.

1. Introduction

Ferrocene-heterocyclic compounds are of great interest both as exhibiting biological activity and as ligands for asymmetric catalysis. Earlier, heterocyclic ferrocene-containing compounds were shown to exhibit a wide range of biological activities such as antianemic, antibacterial, antitumor, and fungicidal ones [1–4]. Besides, ligands having ferrocenylheterocyclic moieties are suitable for the reactions of hydration, allylation, silylation, cyanation and many others [5,6].

The including of pyrazoles as key motifs in biologically active compounds has grown rapidly in the past decade. Both the pharmaceutical and agrochemical industries employ them as the central building blocks for the synthesis of compound libraries. At present, commercial drugs on the base of pyrazole are widely used in the clinical practice, e.g., sildenaphyl (Viagra™), phenybutasole (an antiphlogistic drug), or herbicidal diphenzoquat.

Recently, it was shown that the derivatives of 3-ferrocenyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (FPCA), i.e. the products of reductive amination by different amines (especially *tret*-butilamine and cyclohexylamine) exhibited antimicrobial activity comparable with amikacin and tetracycline [2] in tests on a wide range of microorganisms, whereas 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo [1,5-a]pyrazin-4(5*H*)-one derivatives demonstrated antitumor activity [3]. Besides, Vukićević et al. showed that FPCA derivatives of the amino acids (especially those containing heteroaromatic rings such as histidine and tryptophan) appeared to be the most active against myelogenous leukemia K562 cell lines with a better cytotoxic potential than the starting FPCA precursor [4].

Therefore, the purpose of this study was the development of the method for synthesis of isomeric ferrocenylpyrazolecarbaldehydes and investigation of their reactivity in the reaction of direct reductive amination. In the present paper we report the obtainment of *N*-substituted 5-ferrocenyl-1-aryl-1*H*-pyrazole-3-aldehydes and the corresponding ethyl carboxylates, the cyclic voltammetry study of several compounds synthesized and X-ray determination of the molecular structure of ethyl ether 1-(3-chloro-2-fluorophenyl)-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acid.

2. Results and discussion

2.1. Synthesis of ethyl esters of 5-ferrocenyl-1H-azole-3-carboxylic acids

The condensation of 1,3-dicarbonyl compounds and hydrazine or monosubstituted hydrazines is known to be the most suitable method for the synthesis of pyrazole ring. Ethyl ester of ferrocenoylpyruvic acid was used as the starting materials. The Claisen condensation of acetylferrocene (**1**) and diethyl oxalate in the

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presence of NaOEt was reported to furnish ethyl 2,4-dioxo-4-ferrocenylbutanoate (**2**) (52%) [7]. To choose a base – solvent system providing the best results we have tested several reaction systems (Scheme 1). In general, it turned out that the reactions produced the corresponding product in good yields in almost all tested base systems.

The use of potassium *tert*-butoxide in benzene allows a facile isolation and purification of the intermediate potassium salt of ethyl 2,4-dioxo-4-ferrocenylbutanoate. Addition of an equimolar amount of acetic acid to the suspension of salt in CH_2Cl_2 eliminated the free ester (89% overall yield). The presence of a broad singlet at 15 ppm (OH proton) and a singlet (1H) at 6.54 ppm in the ^{1}H NMR spectrum recorded in $CDCl_3$ solution at room temperature proves that the ester **2** exists entirely in enol form.

Esters of 5-ferrocenyl-1-aryl-1*H*-pyrazole-3-carboxylic acids were synthesized in high to quantitative yields by the condensation between ethyl 2,4-dioxo-4-ferrocenylbutanoate **2** (enol form) and monosubstituted arylhydrazines. Noteworthy, the reaction with catalytic amounts of acetic acid in boiling ethanol affords one isomer only (Scheme 2). The structures of compounds were assigned on the basis of ^{1}H and ^{13}C NMR spectra, ^{1}H/^{13}C heteronuclear correlations, and NOE-experiments. The coupling of ethyl esters of acetyl- or benzoylpyruvic acid with monoarylhydrazine yields pyrazoles with the same arrangement of substituents in the heterocyclic fragment [8–10].

The ^{1}H NMR spectra of compounds shows several sets of signals assigned, respectively, to the protons of substituted and unsubstituted cyclopentadienyl rings (3.90–4.44 ppm), the CH-pyrazole proton (6.54–7.13 ppm), and the protons of the ethyl and aryl substitutes. The assignments of the signals in the ^{13}C NMR spectra of ferrocenyl-compounds were based on the HSQC spectra. In NOE-experiments, the interaction between protons of the aryl substituent and those of the substituted cyclopentadienyl ring revealed that counted in favor the assigned structures of ethyl esters of 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acids. Moreover, for ethyl 1-(2-fluoro-3-chlorophenyl)-5-ferrocenyl-3-pyrazolecarboxylate **3j**, the molecular structure was determined by means of X-ray analysis (Fig. 1). It can be mentioned that pyrazole and one of Cp moieties are almost coplanar (the magnitude of the respective interplanar angle is 4.8°). At the same time, the phenyl group is perpendicular to the plane of the pyrazole moiety. The reason of these structural peculiarities is the presence of Cl and F atoms which increase the steric hindrance in 3-ethylcarboxypyrazole fragment.

The reaction of **2** with hydroxylamine hydrochloride leads to the single product, ethyl ester 5-ferrocenyl-3-isoxazole carboxylic acid **3l** (Scheme 5). At the same time, the condensation of **2** and methyl hydrazine in boiling ethanol with catalytic amounts of acetic acid yielded a mixture of two possible isomers with a ratio 60:40 (based on ^{1}H NMR-data), with ethyl ester 5-ferrocenyl-1-methyl-3-pyrazole carboxylic acid **3k** being the major one (Scheme 3). Crystallization from ethanol-chloroform mixture (50/1) repeated twice allowed us to separate **3k** in analytically pure form. The reaction of **2** and methyl hydrazine in glacial acetic acid leads to the formation of ethyl ester 5-ferrocenyl-1-methyl-3-pyrazole carboxylic acid **3k** in 85% yield; its structure was assigned on the basis of ^{1}H and ^{13}C NMR spectra, and ^{1}H/^{13}C (HSQC and HMBC) heteronuclear correlations.

2.2. Synthesis of aldehydes

The corresponding alcohols were obtained in 90–95% yields by reduction of esters **3a**–**k** with $LiAlH_4$ in a THF-1,4-dioxane mixture.

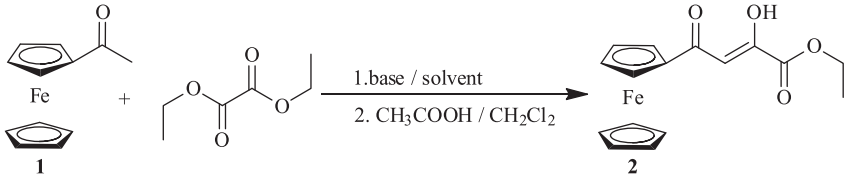
(5-Ferrocenyl-1-phenyl-1*H*-pyrazol-3-yl)methanol **4a** was chosen as a model compound for carrying out the oxidation reaction (Scheme 4). The use of the Corey's reagent (pyridinium chlorochromate) in dichloromethane at room temperature in argon atmosphere allows preparation of the target aldehyde in 12% yield [11]. The Pfitzner–Moffatt oxidation (DMSO-DCC) [12] and oxidation with MnO_2 in CH_2Cl_2 at room temperature [13] lead to the formation of aldehyde in similar yields (85 and 87%, respectively), the former mode requiring an additional purification of the product. The purification was carried out either *via* the bisulphite derivative or by means of column chromatography (SiO_2, eluent – chloroform).

Other aldehydes, i.e. 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-aldehydes, 5-ferrocenyl-1-methyl-1*H*-pyrazole-3-aldehyde and 5-ferrocenylisoxazole-3-aldehyde were obtained similarly. The overall yields of the products from reduction and oxidation reactions were 82–94% (Scheme 5).

2.3. Reductive amination of *5a*

The reactions of aldehydes or ketones with ammonia, primary or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively, known as reductive aminations (of the carbonyl compounds) or reductive alkylations (of the amines) are among the most useful and important tools in the synthesis of different kinds of amines. The reductive amination reaction described as a direct reaction without prior formation of the intermediate imine or iminium salt when a carbonyl compound and an amine are mixed with the proper reducing agent. The stepwise or indirect reaction involves the formation of the intermediate imine followed by reduction in a separate step.

The obtainment of amino derivatives of 3-ferrocenyl-1-phenyl-4-formylpyrazole that exhibited antimicrobial activity was reported in a recently published paper [2]. These amino derivatives were



Entry	Base	Solvent	Time	Yield[a]
1[b]	NaH	THF	3 h	62
2[b]	*t*-BuOK	Benzene	2 h	89
3[b]	*t*-BuOK	THF	1 h	74

[a] Isolated yields. [b] Reaction conditions: acetylferrocene (10 mmol), base (10 mmol), diethyl oxalate (10 mmol), solvent (25 mL), Ar atmosphere, reflux

Scheme 1. Formation of ethyl 2,4-dioxo-4-ferrocenylbutanoate **2**.