Synthesis and examination of heterocyclic ferrocene derivatives

Theses of the PhD dissertation

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Preliminaries and aims of the work

Electrochemical properties and excellent stability of ferrocene still open up new areas of application even nowadays. Its derivatives are excellent ligands in homogeneous catalytic reactions, they can be used as redox active molecule or ion receptors, biosensors or redox switches. Ferrocene derivatives are also known to have antibacterial, anti-tumor or even anti-malarial effects, so they can also be of importance in medicine.

During my research, I aimed to prepare ferrocene derivatives bearing a heterocycle attached to the cyclopentadiene ring. According to literature data, similar compounds may have beneficial biological effects, for example antibacterial, antitumor, antileishmanian, antiamoebic or antioxidant activity. Many derivatives may have H-donor and H-acceptor groups capable of forming hydrogen bonds, so they are able to establish "host-guest" relationships. Considering the electrochemical properties of ferrocene, these compounds can serve as building blocks for molecular, anionic, cationic or DNA sensors.

In our group, it has already been shown that palladium-catalyzed aminocarbonylation reactions of iodoferrocene and secondary amines or amino acids lead to ferrocenylamide and ketoamide products. However, the carbonylative Sonogashira reaction of iodoferrocene and alkynes has not been described yet.

First, the coupling of a heterocyclic compound with ferrocene was attempted by the aminocarbonylation reaction of iodoferrocene and 2-aminopyrimidine derivatives. As another alternative, a two-step reaction pathway was studied that could lead to the target compounds by cyclization of alkynyl ketones obtained by carbonylative Sonogashira reaction of iodoferrocene. My goal was to determine the optimum conditions of carbonylative Sonogashira reaction, and then to examine the reactions of various acetylene derivatives. The cyclization of alkynyl ketones was accomplished by substituted hydrazine compounds and guanidine derivatives.

Some products containing a free amino group allowed the synthesis of urea derivatives capable of forming multiple hydrogen bonds. In case of one of the new compounds, the complexation of a suitably chosen guest molecule, 2,6-diaminopridine, was verified by NMR spectroscopy and cyclic voltammetric measurements.
Experimental methods applied

Shlenk technique and a stainless steel autoclave were used in carbonylation reactions. During the synthesis of urea derivatives inert Shlenk technique was applied.

The reactions were followed by gas chromatography and thin layer chromatography.

The products were purified by column chromatography.

The products were characterized by $^1$H-, $^{13}$C-NMR, 2D-NMR (NOESY), IR, MS measurements and elemental analysis. The structures of three compounds were proved by X-ray crystallography.

New scientific results

1. Two new ferrocene derivatives (6, 7) were synthesized in the palladium catalyzed carbonylation reaction of iodoferrocene (1) and 2-amino-4-hydroxy-6-methylpyrimidine.

![Reaction Scheme]

The main product was proved to be ester 7. The structure of the side chain of amide 6 is determined by hydrogen bonding between the amide C=O and pyrimidine NH. The structures of the compounds were confirmed by X-ray diffraction measurements.
2. During the carbonylation of iodoferrocene (1) in the presence of 2-amino-4-chloropyrimidine derivatives (4,5) multiple aminocarbonylation steps were found to take place. The amide product (8 or 9) reacted with the excess of the nucleophilic reagent (4 or 5) as the aryl-halide to result in compounds 10, 11.

3. Alkynyl-ferrocenyl-ketones were produced via a carbonylative Sonogashira reaction.

(a) The optimum conditions of the carbonylative Sonogashira coupling were determined in the reaction of iodoferrocene (1) and phenylacetylene (13a). Then the reaction of further acetylene derivatives (13b-h) was investigated. While most of the products were obtained in good yields, acetylene derivatives containing electron withdrawing groups either did not react (13g) or resulted in a very slow reaction. (13e). Furthermore, a copper catalyzed Glaser-type homo-coupling was also observed as a side reaction.
(b) The reaction of iodoferrocene (1) and phenylacetylene (13a) was also carried out with a heterogeneous palladium catalyst. The catalyst was found to produce the alkynyl ketone in nearly as high yield as the homogeneous system under the optimal conditions using a catalyst with a considerably lower palladium content and in the absence of the copper salt. In addition, the catalyst could be reused several times.

4. Substituted pyrazoles were prepared from the alkynyl ketones in the presence of hydrazine derivatives. One of the two regioisomeric products was formed with outstanding selectivity (96%) in all cases.

(a) During the reaction with methylhydrazine, 3-ferrocenyl compounds (17a-e) were obtained as the main products. Their structure was verified by NOESY. The alkynyl ketone (14e) with an electron withdrawing group was found to have outstanding reactivity even at room temperature.

(b) In the reaction of phenylhydrazine, the 5-ferrocenyl derivative (20a) was obtained with 96% selectivity. Its structure was also verified by NOESY. Due to the lower reactivity of phenylhydrazine, this reaction took place only at a higher temperature.
5. Ferrocenyl pyrimidines were obtained from alkynyl ketones (14a-c, f) in the presence of guanidine.

(a) The reaction was studied in the presence of both guanidine hydrochloride and guanidine carbonate. The best yields were achieved by the use of the second reagent, although by-products formed in the addition reaction of ethanol and the alkynyl ketone also appeared in the reaction mixture.

(b) From ketones 14a, b, further pyrimidine derivatives were prepared using N-benzoyl-L-arginine ethyl ester.HCl as reagent. The products were obtained with a lower yield than with simple guanidine.

6. In the reaction of 2-amino-4-ferrocenyl pyrimidine derivatives and isocyanates 16 new 2-ureido-4-ferrocenilpyrimidine compounds were prepared.

When optimizing the reaction conditions, the best yield was obtained in solvent-free conditions with an excess of isocyanate. Both the R₁ group of the pyrimidine (21) and R₂ group of the isocyanate group had a significant influence on the reactivity. In the pyrimidine ring electron-donating, while in the isocyanate electron withdrawing groups favor the formation of substituted urea. tBu isocyanate did not react at all under the conditions used.
7. The structure of 2-ureido-4-ferrocenyl pyrimidines was confirmed by several spectroscopic methods.

![Diagram of 2-ureido-4-ferrocenyl pyrimidine]

The $^1$H-NMR and IR measurements showed that, among several possible tautomeric conformers, conformers A and B are present in solution. Quantum chemical calculations show that stability of conformer A is higher. In the solid phase only the presence of conformer A could be confirmed by X-ray diffraction.

8. Electrochemical and $^1$H-NMR methods were used for the determination of the host-guest relationship of 2-ureido-4-ferrocenylpyrimidine 28c and 2,6-diaminopyridine.

![Diagram of the complex formation]

(a) Electrochemical measurements revealed that the complex is formed only in an apolar solvent. The anodic shift of the $E_{pa}$ value indicates that the formation of H-bonds between host and guest hinders oxidation of ferrocene to a ferrocenium cation.

(b) Formation of the complex was also proved by $^1$H-NMR measurements, furthermore the association of 2,6-diaminopyridine was found to increase the stability difference between the two conformers of the host molecule.
Scientific publications and presentations related to the dissertation

Publications:
1. **C. Fehér**, A. Kuik, L. Márk, L. Kollár, R. Skoda-Földes
   A two-step synthesis of ferrocenyl pyrazole and pyrimidine derivatives based on carbonylative Sonogashira coupling of iodoferrocene

2. **C. Fehér**, I. Habus, J. Wouters, R. Skoda-Földes
   Synthesis of ferrocene-labelled 2-aminopyrimidine derivatives via homogeneous catalytic carbonylation

   Synthesis of 2-ureido-4-ferrocenyl Pyrimidine Guests. Investigation of Complementary Molecular Recognition of 2,6-Diaminopyridine
   *Organometallics, 2016, 35 (24), 4023–4032.* IF: 4.186

Presentations:
1. **Kuik, Á., Fehér, C.,** Kollár, L., Skoda-Földes, R.
   A new method for the synthesis of ferrocene-based alkynyl ketones (P638)
   XXIII International Conference on Organometallic Chemistry, (poszter)

2. **Fehér, Cs.,** Skoda-Földes, R.
   Synthesis of ferrocene labelled heterocyclic derivatives via palladium catalysed carbonylation (P177C)
   20th EuCheMS Conference on Organometallic Chemistry, (poster)
3. Fehér, Cs., Skoda-Földes, R.
Jódférfocén aminokarbonilezési reakciójának vizsgálata 2-aminopirimidin-származékokkal
19. Nemzetközi Vegyészkonferencia, (oral presentation)

4. Fehér, Cs., Wouters, J., Skoda-Földes, R.
Synthesis of ferrocene labelled 2-amino-pyrimidine derivatives via homogeneous catalytic
carbonylation (3P133)
XXVI International Conference on Organometallic Chemistry, (poster)

5. Fehér, Cs., Wouters, J., Skoda-Földes, R.
Synthesis of 2-ureido-4-ferrocenyl-pyrimidines and examination of their electrochemical
properties (P12)
International Symposium on Synthesis and Catalysis 2015, (poster)