Synthesis of ferrocene-substituted- and condensed heterocycles as well as chiral salen complexes with promising therapeutic potential

THESIS

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1. Aims of the research

As the main purpose of my research I envisaged the synthesis of different types of ferrocene derivatives having potential interest from point of view. It was a pronounced aspect that the ferrocene unit would be incorporated into the target molecules by using easily available reagents under relatively simple reaction conditions. Taking these circumstances into account formylferrocene seemed to be the choice as an easily accessible and easy-to-handle precursor for the planned Biginelli reactions and the synthesis of novel chiral salen complexes. Ferrocene was also used as a precursor for the multistep-synthesis of ferroceno[*g*]indazoles, a further class of my targeted compounds of potential biological relevance, proceeding *via* a racemic mixture of ferrocenocyclohexenone. In the frame of an ongoing cooperation, the biological evaluation of the compunds prepared int he course of my research is in progress. Besides the biological activity their native forms, some of our targeted compounds contain such functional groups which are suitable to conjugation to biomolecules including peptides and saccharides. On the other hand, on the basis of a number of examples found in the literature, the combination of heterocycles with ferrocene may have beneficial to the pharmacological properties including the enhanced tendency to cross the cell membrane.

2. The methods employed in the course of the research

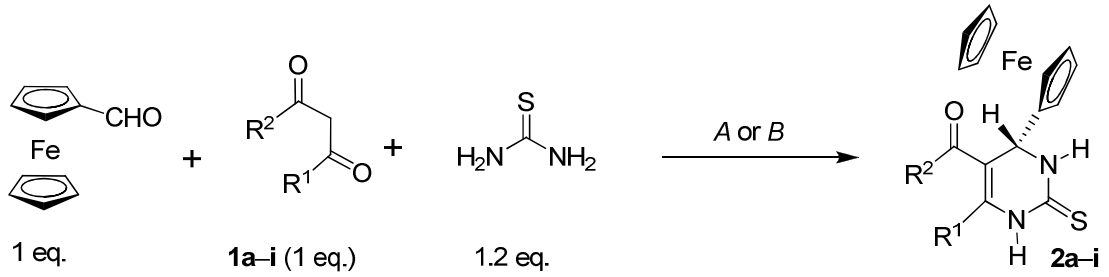
The syntheses were performed under inert (Ar) atmosphere. The reactions were monitored by TLC. The same simple method was used to check the purity of the isolated compounds. The separation of the isomer products formed int he reactions was performed by flash column chromatography. The structures of the novel compounds were determined by spectroscopic methods (IR, 1D- and 2D versions of ^{1}H-, ^{13}C- and ^{15}N-NMR) and single crystal x-ray diffraction. On the basis of the results of quantumchemical calculations we proposed mechanisms for some reactions. The reactivities of the characteristic representatives of certain ferrocene derivatives were also interpreted by theoretical modelling. All calculations were carried out at B3LYP/6-31 G(d) level of density functional theory (DFT) using Gaussian 03 suite of programs.

3. The results of the research discussed in the thesis

3.1 Reactions targeting the synthesis of ferrocene-containing dihydropyrimidine-2-thions and quinoxalines [1]

The first part of my work was devoted to the extension of the group of ferrocene-containing dihydropyrimidine-2-thions of versatile biological interst, which are also suitable to further transformations involving the sulfur centre. Consequently, thiourea, 1,3-dioxo reagents and formylferrocene were used for the construction of the pyrimidine ring. Besides the evaluation of two catalytic systems (Scheme 1), the pathways of the expected and unexpected reactions were also disclosed in the course of this segment of research.

I established that the catalytic system composed of boric acid and acetic acid (Method „*A*"), producing higher yields, is superior to the system represented by ytterbium-*tris*-(trifluormethanesulfonate) dissolved in acetonitrile (Method „*B*"). The reactions of acyclic 1,3-dioxo components (**1a–i**) afforded the expected products (**2a–i**) (Scheme 1).



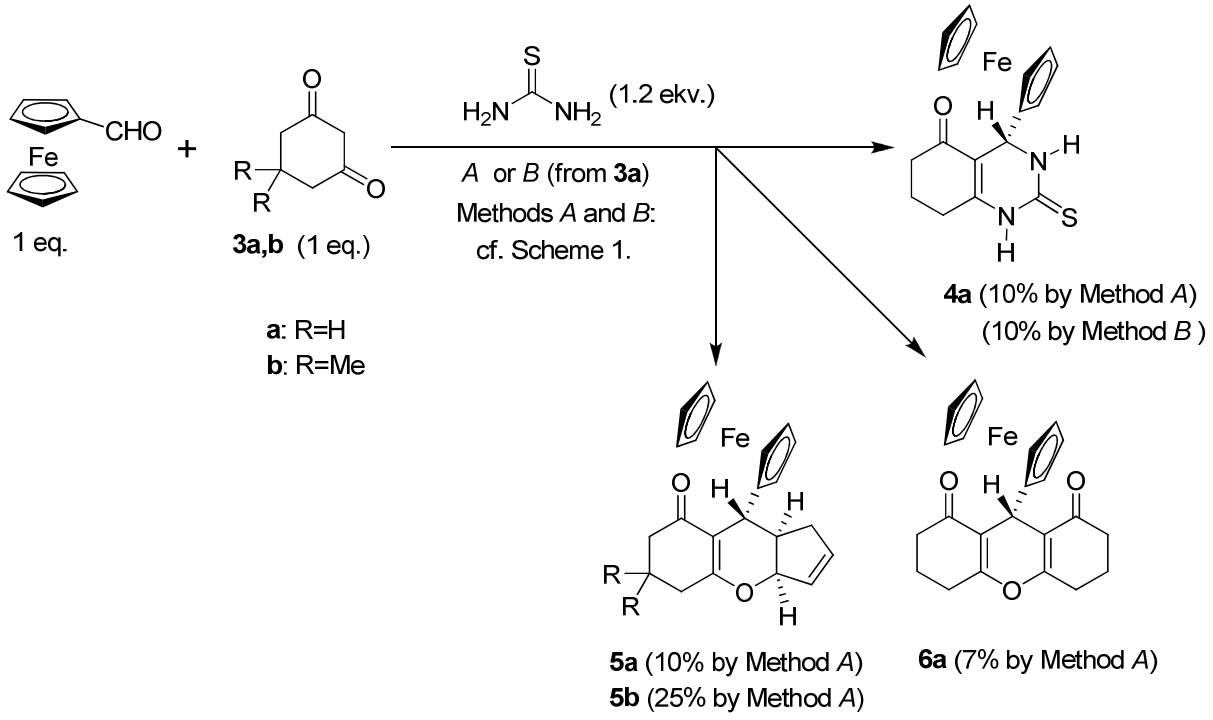
1, 2	R^1	R^2	Isolated yields of compounds type **2** (%) *A*	*B*
a	Me	Me	46	31
b	Me	OMe	55	53
c	Me	OEt	37	30
d	Me	O^{t}Bu	36	25
e	Me	NEt_2	50	40
f	Me	Ph	53	4
g	Ph	OEt	36	10
h	CH_2CO_2Me	OMe	21	3
i	CH_2CO_2Me	OEt	21	7

Method *A*: H_3BO_3 (0.2 eq.), AcOH, 100 °C, 5 h, Ar

Method *B*: $Yb(OTf)_3$ (0.05 eq.) , MeCN, reflux, 6 h, Ar

Scheme 1.

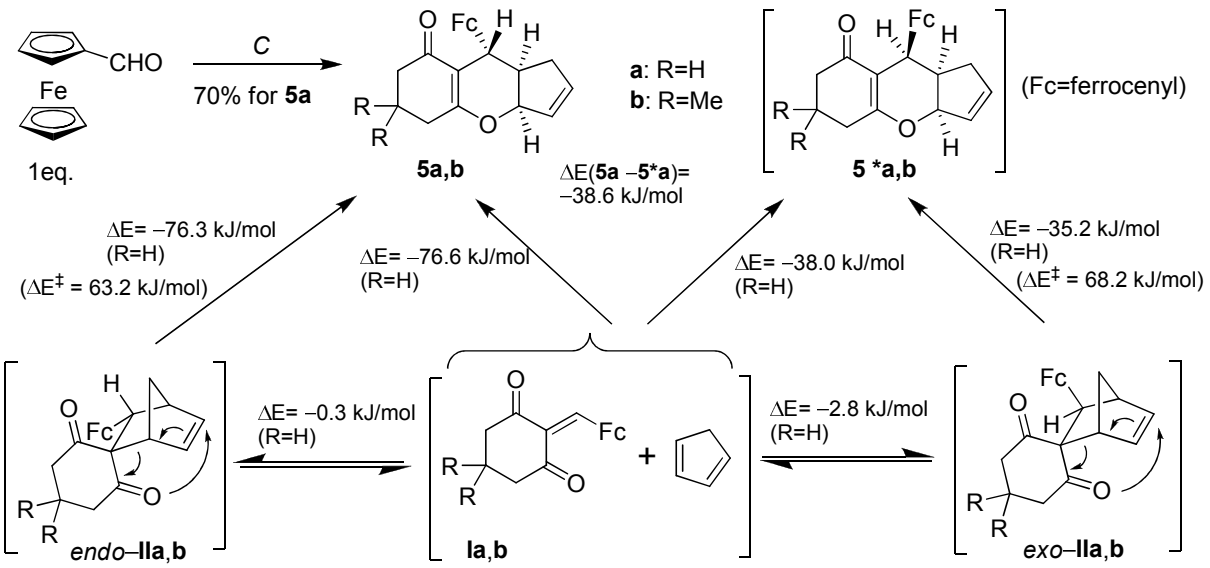
I observed that besides the expected ferrocenylquinoxaline (**4a**) a symmetric xantene derivative (**6a**) and (3aR*,9S*,9aR*)-9-ferrocenyl-3a,5,6,7,9,9a-hexahydrocyclopenta[*b*]chromen-8(1*H*)-ones (**5a,b**) were also formed in the reactions carried out with cyclic 1,3-dioxo components **3a,b** (Scheme 2).



Scheme 2.

The symmetric xantene **6a** was obviously resulted from the simple condensation of formylferrocene with two equivalents of cyclohexane-1,3-dione, while the highly diastereoselective formation of **5a,b** can be reasoned by more complex processes (Scheme 3).

By means of preparative experiments carried out by Method „*C*" (Scheme 3) I proved that the cyclopentadiene incorporated in the tricyclic skeleton is originated from the acid-catalysed decomposition of formylferrocene. On the basis of the observed diastereoselectivity and the results of theoretical calculations depicted on Scheme 3. we proposed the one-step mechanism for the cycloaddition, ruling out the alternative pathway proceeding *via* diastereomer spirocyclic intermediates type **I** of wich *oxa*-Cope rearrangement would give the final products as mixture of diastereomers types **5** and **5***. The different reactivities of the acyclic- and cyclic 1,3-dioxo components were also interpreted by theoretical modelling.



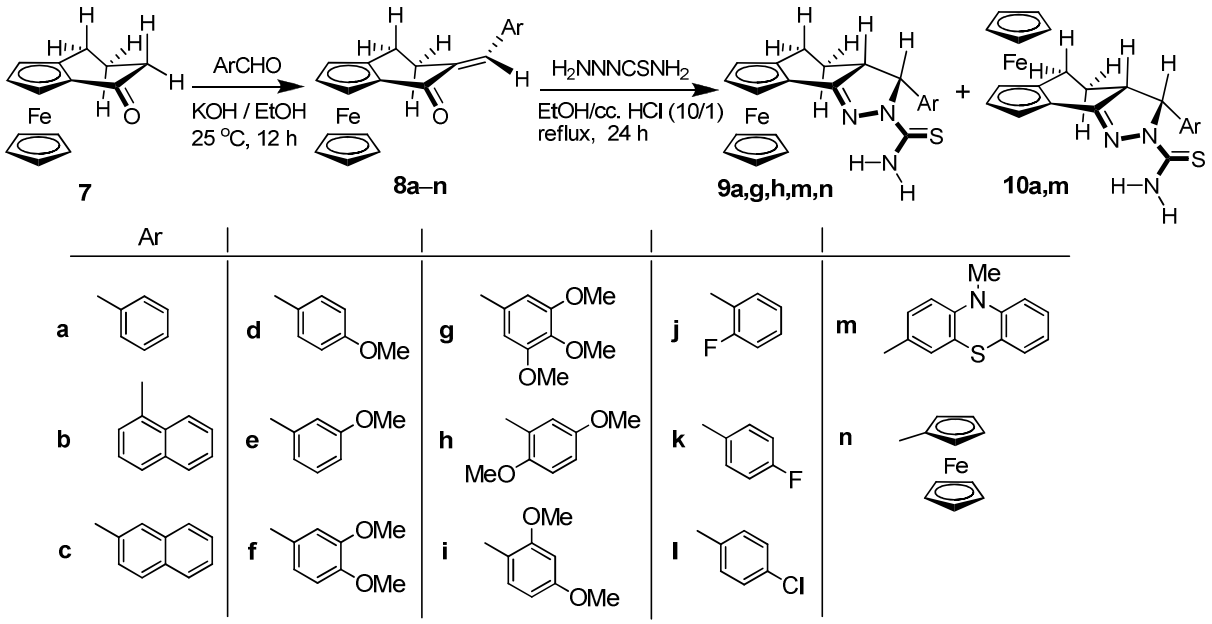
Method *C*: **3a** (1,5 eq.), H_3BO_3 (0,2 eq.), AcOH, 100 ^oC, 1 h, then + cyclopentadiene (2 eq.) 7 h, Ar

Scheme 3.

3.2 Synthesis, structure determination and theoretical modelling of novel condensed chalcone derivatives and related ferroceno[*g*]indazoles [2]

In the course of the second part of my research, following a three-step protocol (Friedel-Crafts acylation, Clemmensen reduction and acid-catalysed cyclisation), described in the literature, from ferrocene and succinic anhydride I prepared ferrocenocyclohexanone **7** in racemic form. Using this ketone and aryl aldehydes as precursors I performed the synthetis of ferrocene-fused chalcones **8a**–**n** (Scheme 4.). I subjected five representatives of this novel class of building blocks to cyclisation reactions with thiosemicarbazide conducted in the mixture of ethanol and concentrated hydrochloric acid to afford diastereomer ferroceno[*g*]indazoles **9a**,**g**,**h,m,n** and **10a,m** carrying thiocarbamoyl group suitable to further transformations (eg. Hantsch thiazole synthesis).

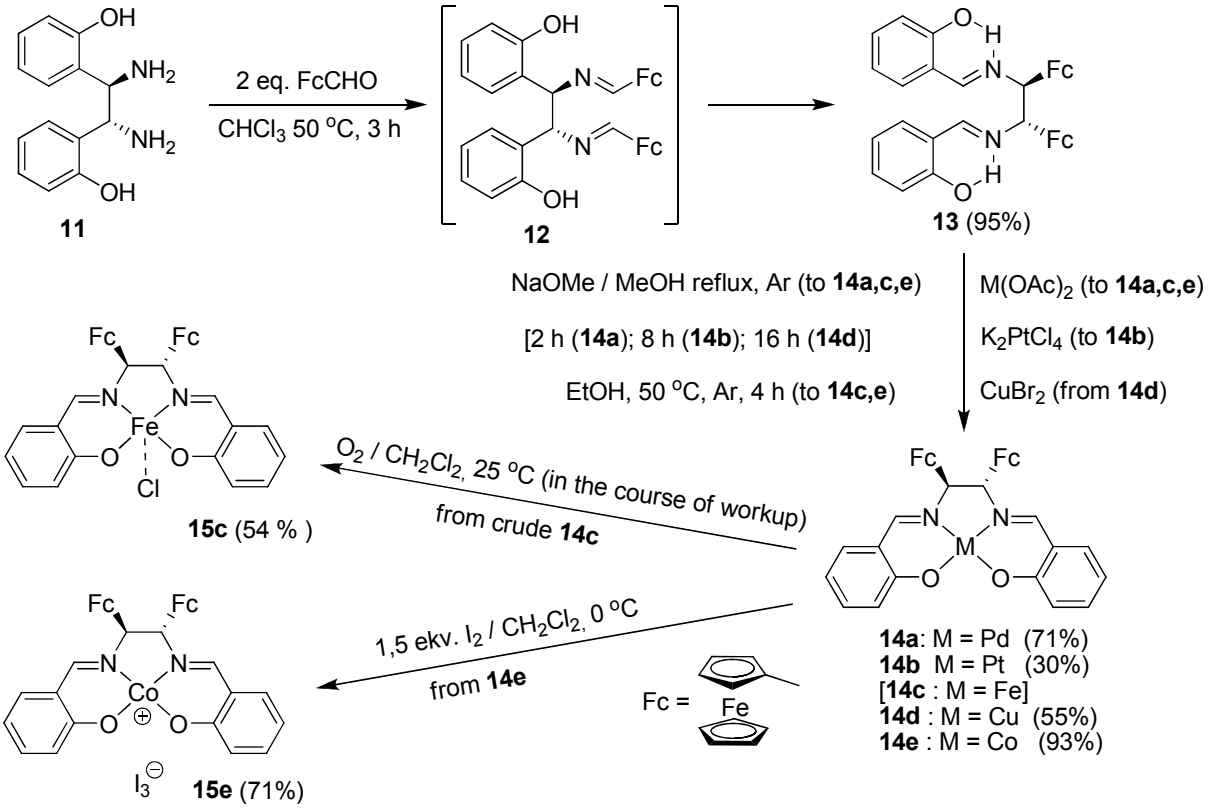
The structures of ferroceno[*g*]indazoles were exactly disclosed by NMR spectroscopy and single crystal x-ray diffraction. The reactivity of chalcone precursors dependent on the aryl substituent was also interpreted by theoretical modelling.



Scheme 4

3.3. Synthesis, structure determination and theoretical modelling of a novel chiral salen ligand with two attached ferrocenyl group and its transition metal complexes [3]

By means of diastereoselective *diaza*-Cope rearrangement of a diimine (**12**, Scheme 5) *in situ* formed from the chiral 2,2'-((1R,2R)-1,2-diaminoethane-1,2-diyl)diphenol (**11**) and 2 equivalents of formylferrocene, I prepared a novel chiral salen type ligand (**13**) of C_2-symmetry. Employing ligand-exchange and oxidation reactions, the synthesis of a series of its transition metal complexes (**14a,b,d,e**, **15c** and **15e**) were also achieved (Scheme 5). The structures of the novel complexes were determined by NMR spectroscopy and single crystal x-ray diffraction. Contrary to the facile spontaneous oxidation of **14c**, leading to a pentacoordinated iron(III)-chloro complex **15c**, the oxidation of the cobalt(II)-complex **14e** could be achieved by iodine at 0 ^{o}C to obtain cobalt(III)-complex salt **15e** in good yield (71%). The electronic structures of the iron(II)- and cobalt(II)-complexes (**14c** and **15c**, respectively) having control on their sensitivity towards oxidation were disclosed by theoretical modelling.



Scheme 5.

3.4. Preliminary results of biological tests

On selected human cancer cell lines the *in vitro* evaluation of representative members of the classes of novel compounds prepared in my research are recently being in progress in the frame of an ongoing cooperation. According to encouraging preliminary results of these tests, none of the tested compounds exhibited citotoxicity on liver cell line HepG2. The investigation of citotoxic properties is also in progress. On the basis on the measurements carried out so far, promising results are expected in this regard, too.

The thesis is based on the following publications:

[1] Kiss, K.; Csampai, A.; Sohar, P. New ferrocenyl-substituted heterocycles. Formation under Biginelli conditions, DFT modelling, and structure determination *Journal of Organometallic Chemistry* **2010** 695(15-16), 1852-1857.

[2] K. Kiss, T. Holczbauer, M. Czugler, Vasile-Ludovic Kocsis, Luminița Silaghi-Dumitrescu, A. Csámpai, 2-Arylideneferroceno[*e*]cyclohexanones and related 3-aryl-3,3a,4,5-tetrahydroferroceno[*g*]indazoles: synthesis, NMR-, DFT- and x-ray analysis.

Journal of Organometallic Chemistry (beküldve; reg. szám: JORGANCHEM-D-12-00567)

[3] K. Kiss, T. Holczbauer, M. Czugler, P. Sohar, A. Bodor, A. Csámpai Synthesis, IR-, NMR-, DFT- and X-ray analysis of novel C2-chiral diferrocenylesalen complexes *Journal of Organometallic Chemistry* **2012** 706-707, 46-51.

Poster- and oral presentations associated with the research discussed in the thesis

Poster presentation:

Kolos Kiss, Antal Csámpai, Pál Sohár, New ferrocenyl-substituted heterocycles. Formation under Biginelli conditions, DFT-modelling, and structure-determination
Board Number: VIIa.121 Reference Code: 5576_1462
3rd European Chemistry Congress , 2010. Aug. 29 – Sept. 2. Nürnberg, Germany

Oral presentations:

Kiss Kolos, Csámpai Antal, Sohár Pál, Eredmények formil- és 1,1'-diformil-ferrocénnel végzett Biginelli-reakciók köréből.
Heterociklusos Kémiai Munkabizottsági Konferencia, Balatonszemes, 2009. május 20-22.

Kiss Kolos, Csámpai Antal, Czugler Mátyás, Ferrocén-szubsztituált heterociklusok szintézise egyedényes eljárással, Dihidropiridinek szintézise Hantzsch-reakcióval
Heterociklusos Kémiai Munkabizottsági Konferencia, Balatonszemes, 2010. május 19-21.

Kolos Kiss, Antal Csámpai, Novel C_2-chiral diferrocenyl-salen complexes
10th Ferrocene Colloquium
2012. Febr. 15-17., Braunschweig, Germany