THESIS OF THE DISSERTATION:

Synthesis and study of new heterocyclic ferrocene derivatives

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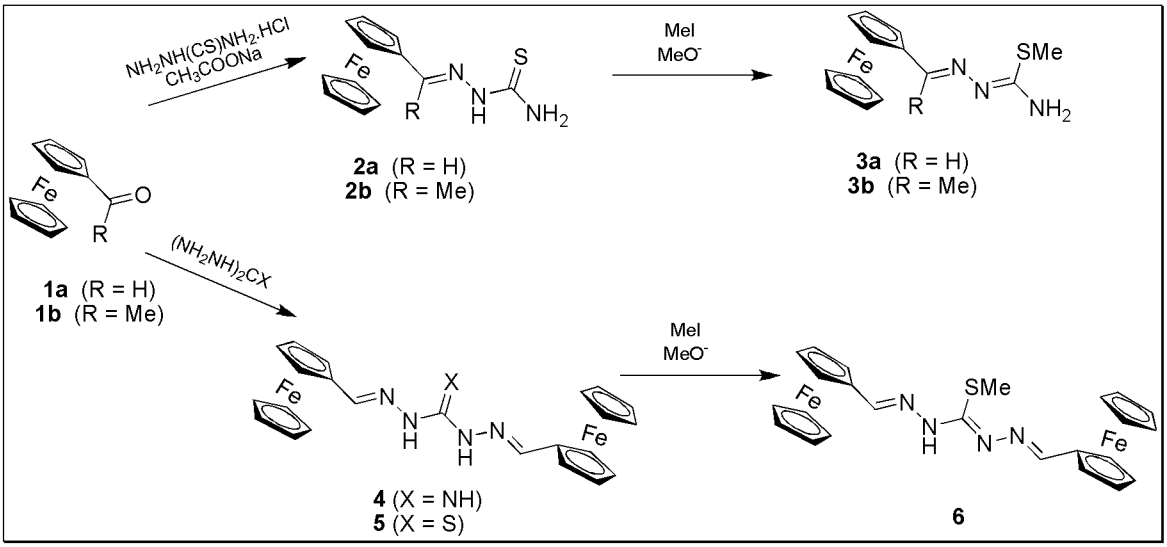
1. Aims

I set the synthesis of heterocyclic ferrocenes as an aim, which ones easily can be derivatized and available from easily accessible starting materials. Formyl- and acetyl-ferrocene were chosen as precursors. Their reactions with hydrazine derivatives (e.g. thiosemicarbazide) afforded nitrogen- and sulfur containing open chained intermediates which readily underwent cyclizations by the effect of the easily available dimethyl acetylenedicarboxylate. The targeted compounds are substituted with one or two ester functions and can be coupled with appropriate peptides and sacharides. This conjugates could be valuable subjects of further studies, because of the biological activity of the heterocyclic unit and the membrane transport properties of the ferrocenyl group combined with the pharmacological potential of the carrier.

2. Results

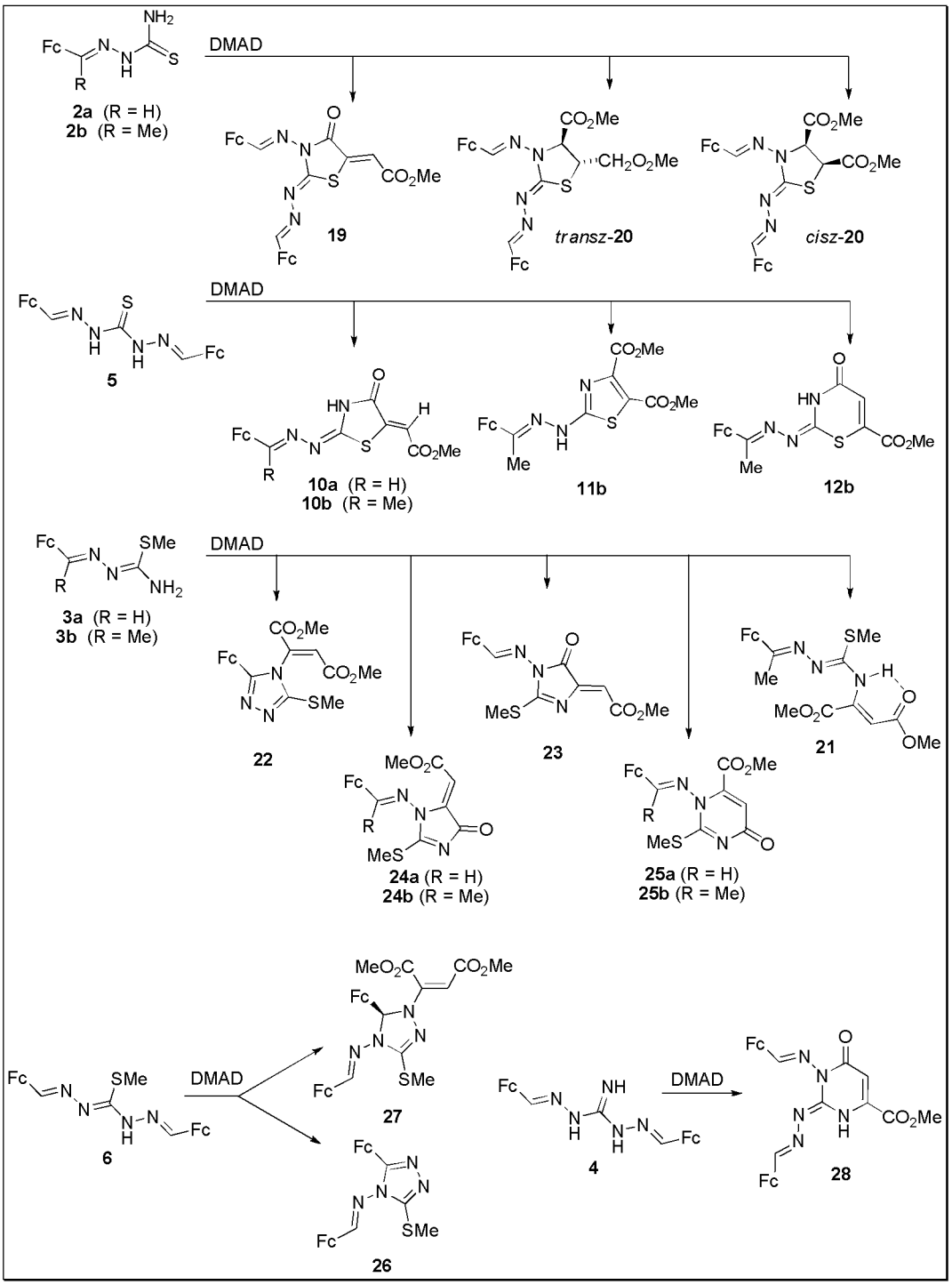
2.1. Introduction, keyintermediates

Formyl- and acetyl-ferrocene were condensed with thiosemicarbazide and formyl-ferrocene with thiocarbonodihydrazide and diamino-guanidine. The reactions afforded intermediates **2a**, **2b**, **5** and **4** respectively. Their subsequent methylation gave the S-methylated analogs (**3a**, **3b**, **6**). All of these intermediates were reacted with DMAD and yielded heterocycles substituted with SMe moiety or heterocycles with the sulfur incorporated in the ring depending on the structure of the intermediate with SMe- or thioxo group. Furthermore I studied the oxidative cyclizations of the symmetric bis-hydrazone **5**.

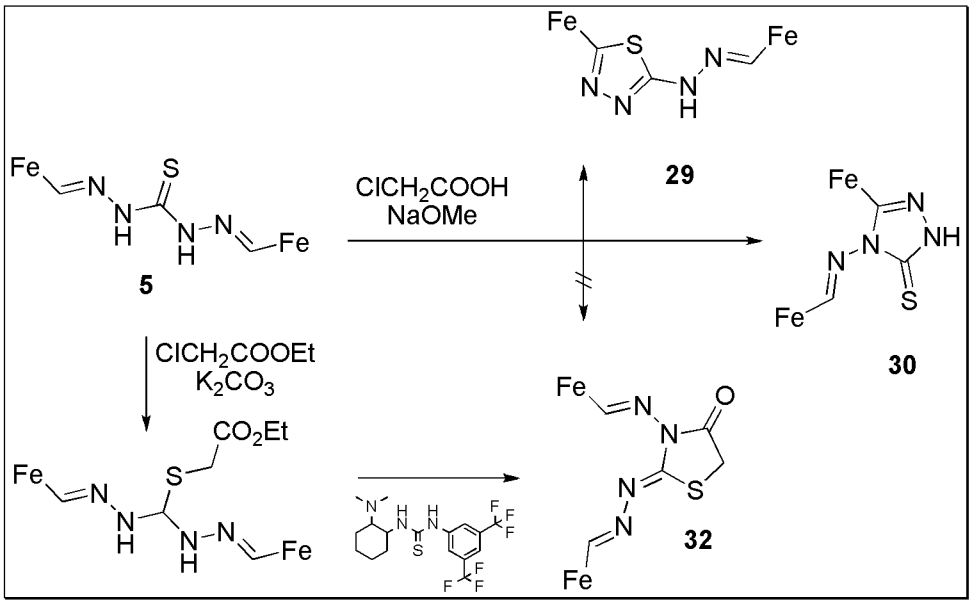


2.2. Cyclisations with DMAD and Oxidative cyclisations

1) Key-intermediates below (**2a**, **2b**, **3a**, **3b**, **4**, **5**, **6**) were reacted with DMAD in refluxing acetonitrile under inert atmosphere. The reactions were monitored by TLC and the products were isolated and purified by column chromatography.



2) Synthesis of thiazolidine **32** was attempted *via* the alkylation of **5** with chloroacetic acid followed by intramolecular cyclization in refluxing methanol with NaOMe as base. Instead of the desired product, the isolated compounds were identified as thiadiazol **29** and triazole-thion **30**.



3) The oxidative cyclizations were studied under various conditions and a few oxidative agents were tested. Finally the original aim (synthesis of **32**) was also successfully achieved as shown above.

4) DFT calculations were applied to investigate the relative stability of the products, the mechanism of the interconversion and the stabilizing effect of ferrocenyl moieties on the transition states.

5) The structures of the isolated compounds were determined by NMR (^{1}H, ^{13}C, ^{15}N one and two dimensional techniques, DEPT, COSY, HMQC, HMBC and DIFFNOE measurements) and IR spectroscopy, X-ray diffraction, various DFT calculations and additional preparative experiments.

6) Possible routes were suggested for the studied reaction mechanisms and the intermediates (both isolated and modeled theoretically) of these pathways were discussed.

2.3. List of Publications

1 B. Fábián, V. Kudar, A. Csámpai, T. Zs. Nagy, P. Sohár *J. Organomet. Chem.* **692** (2007) 5621. Number of independent citations: 10

2 B. Fábián, A. Csámpai, T. Zs. Nagy, M. Czugler, P. Sohár *J. Organomet. Chem.* **694** (2009) 3732. Number of independent citations: 1

3 B. Fábián, V. Kudar, A. Csámpai, P. Sohár *„Ferrocenil - tioszemikarbazon származékok változatos reakciói dimetil-acetilén-dikarboxiláttal" 2006, Balatonszemes – MTA Heterociklusos Munabizottsági Ülés (oral presentation)*