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Synthesis, ring transformations, IR-, NMR and DFT study of heterocycles with two ferrocenyl units ☆

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ABSTRACT

Cyclization of 1,5-bis(ferrocenylmethylidene)thiocarbonohydrazide with DMAD afforded diastereomeric dimethyl-thiazole-4,5-dicarboxylates. The *cis*-isomer undergoes ring opening and recyclization to a thiazolone derivative. A further thiazolone was obtained from this precursor with ethyl chloroacetate employing a bifunctional organocatalyst. Due to its propensity to dehydrogenation evidenced by DFT calculations, the studied thiocarbonohydrazide underwent oxidative cyclizations under different conditions to yield a 1,3,4-thiadiazole and a 1,2,4-triazole derivative, respectively. Thermal isomerisation of 1,3,4-thiadiazole into 1,2,4-triazole was also observed. The DMAD-mediated cyclizations of the S-metylated thiocarbonohydrazide and the 1,5-bis(ferrocenylmethylideneamino)guanidine gave 1,2,4-triazole derivatives and a 4-pyrimidone, respectively. The structure of the new compounds was established by IR and NMR spectroscopy, including HMQC, HMBC and DEPT measurements. The solid state structure of a triazole was revealed by single crystal X-ray analysis.

1. Introduction

During the last decades the chemistry of ferrocenes has attracted remarkable attention due to their wide range of applications in material sciences, catalysis [1], biological studies and even in therapy [2]. Our group have also synthesized and characterized a variety of ferrocene-containing heterocycles [3,4] with potential and – in a few cases [3] – proved biological activity, including ferrocenyl-pyrazoles- and pyrazolines-, imidazoles-, diazepines-, oxazoles- and pyridazines. In our previous paper [4] we have reported facile DMAD-mediated cyclization reactions of the easily available thiosemicarbazones of formyl- and acetylferrocene and their S-methyl derivatives affording biologically promising sulfur heterocycles (thiazolone-, thiazole-, 1,3-thiazin-4-one and methylthio-substituted nitrogen heterocycles (imidazole-3-ones, pyrimidine-4-ones), respectively, carrying at least one carbomethoxy group which provides further possibility for a variety of coupling reactions including e.g. fixation to peptide carriers. Since according to the literature data numerous representatives of these heterocycles possess valuable pharmaceutical properties including anticancer effects [5–8], we continued this research by performing analogous syntheses of such sulfur- and nitrogen heterocycles which incorporate two ferrocenyl groups expected to display enhanced biological activity in ongoing biological tests on tumourous cell lines.

2. Results and discussion

The cyclization of 1,5-bis(ferrocenylmethylene)carbonohydrazide **1** with DMAD was conducted employing argon atmosphere and MeCN as solvent at reflux temperature (Method A, Scheme 1) to obtain novel sulfur heterocycles with two ferrocene units. The relatively short reaction (1 h) gave a thiazol-4-one (**2**) together with diastereomeric thiazole-dicarboxylates (*cis*-**3** and *trans*-**3**) in comparable yields (22% for **2**, 29% for *cis*-**3** and 25% for *trans*-**3**). When the reaction time was increased up to 5 h, the formation of *cis*-**3** could not be detected even in traces, while the yield of **2** considerably increased (69%) with the simultaneous decrease in the yield of *trans*-**3** (10%). Accordingly, more prolonged treatment (8 h) resulted **2** as a sole product in good yield (77%). These experiments refer to the mechanism with the primary conjugate addition of the sulfur centre on the activated carbon–carbon triple bond followed by the reversible cyclization of primary adducts *Z*-**I** and *E*-**I** leading to the formation of the mixture of *trans*-**3** and *cis*-**3** as isolable products. The irreversible cyclization of *Z*-**I** gives thiazolone **2** as final product. In another pathway intermediate *Z*-**I** can also be formed by the epimerization of the less stable *cis*-**3**

☆ Study on ferrocenes. Part 22. Part 21. see Ref. [4].

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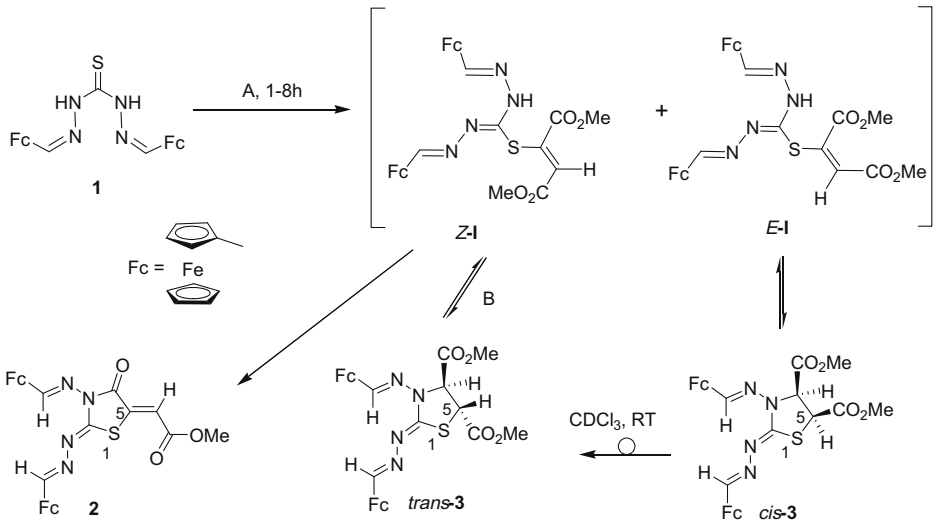


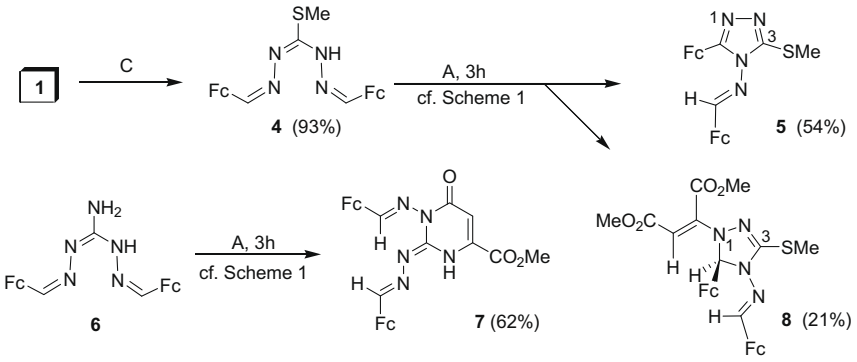
A: DMAD, MeCN, reflux, Ar; B: MeCN, reflux, 8h, Ar.

Scheme 1.

and the reversible ring opening of the resulted *trans*-**3**. As an experimental evidence for this assumed mechanism, epimerization *cis*-**3** → *trans*-**3** taking place in $CDCl_3$ at RT could be detected by ^1H NMR spectroscopy. In accordance with the above transformation *trans*-**3** → **2** could be achieved in excellent yield (91%) by prolonged heating (8 h) in MeCN (Method B, Scheme 1). It is worth to note that the analoguous cyclization of the diphenyl analogue of **1** effected by DMAD has been reported to afford a thiazolone analogous to **2** as a single isolable product without being contaminated by thiazole-dicarboxylates [9].

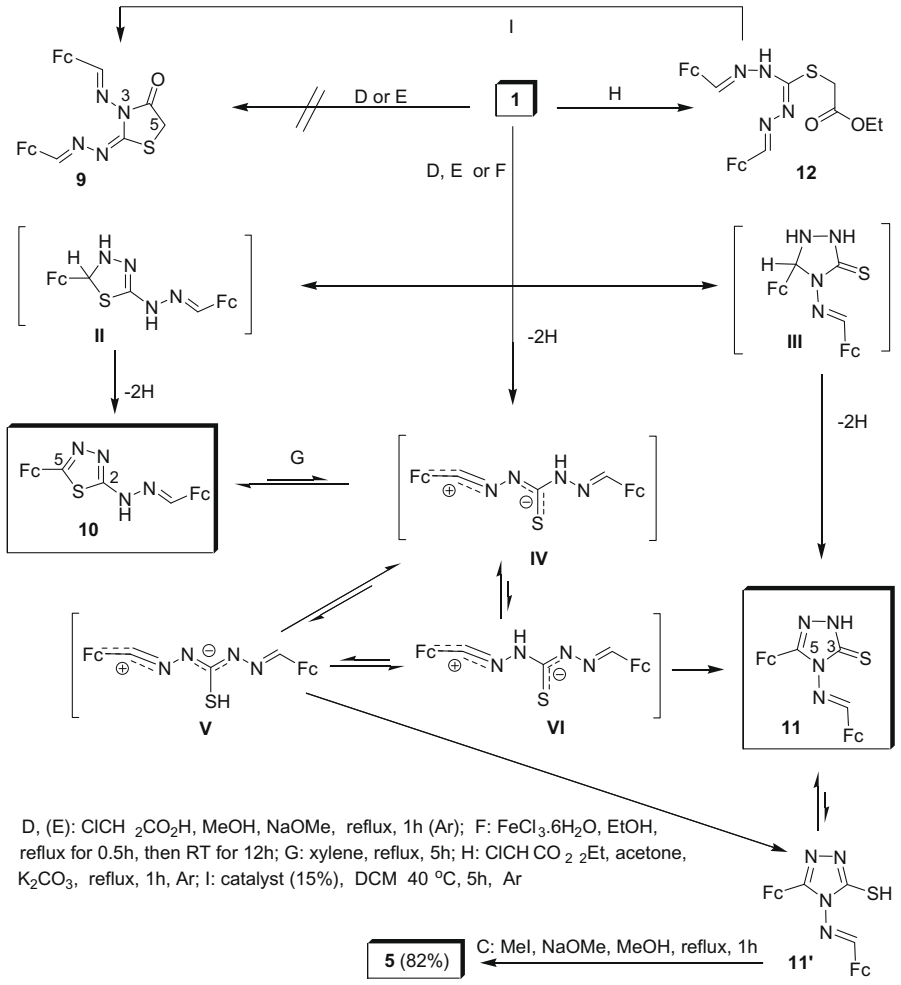
Searching for expedient ways to purely nitrogen heterocycles with two ferrocene moieties we attempted DMAD-mediated cyclizations of the methylthio derivative **4**, which was obtained by standard alkylation procedure (Method C) from **1**, and the bis-ferrocenyl-hydrazone of *N,N′*-diaminoguanidine **6**, respectively (Scheme 2). Under the conditions of Method A (see in Section 1) **4** underwent 1,5-cyclization associated either with dehydrogenation or conjugate addition on the reagent resulting in triazole **5** (54%) and triazoline **8** (21%), respectively (Scheme 2). The basic guanidine precursor **6** with enhanced affinity to the electrophilic reagent afforded pyrimidone **7** isolated as single product (Scheme 2) with acceptable yield (62%).

In order to get a further diferrocenylthiazolone **9** related to **2** without substituent at pos. 5 we attempted the chloroacetic acid-mediated cyclization of **1** involving S-alkylation and subsequent intramolecular acylation (Scheme 3). To our surprise, the treatment of **1** under the conditions employing NaOMe as base in refluxing methanol (Method D) led to the formation of [1,3,4]thiadiazole **10** (32%) and [1,2,4]triazole-3-thion **11** (9%) without being accompanied by the desired thiazolone **9**, but contaminated by a considerable amount of tarry substances. When the reaction was conducted in degassed methanol under argon for 1 h (Method E), a very similar product distribution with somewhat higher yields (40% for **10** and 14% for **11**) was observed suggesting that the reagent might presumably act as an oxidant. Better yields of the cyclic products (62% for **10** and 27% for **11**) were achieved when the oxidation of **1** was carried out by $FeCl_3$ in ethanolic solution (Method F, Scheme 3) representing the conditions employed for the preparation of the diaryl analogues of **10** [10]. Supporting the triazole structure of **11**, its methylation by method C took place smoothly to give methylthiotriazole **5** (Scheme 3) in good yield (82%) which was previously identified as major product in the DMAD-mediated oxidative cyclization of **4** (Scheme 2). Accordingly, alternative intramolecular addition either by the sulfur or one of the nitrogen atoms on the C=N bond and subsequent dehydrogenation (**1** → **II** → **10** and **1** → **III** → **11**, respectively, Scheme 3) can be considered as possible, but not exclusive pathways for the formation of **10** and **11**. Intermediate **IV** must also be taken into



C: MeI / NaOMe, MeOH, reflux 1h, Ar

Scheme 2.

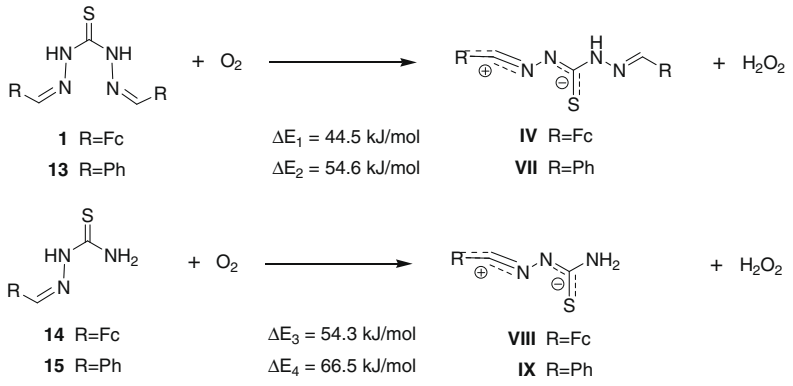


Scheme 3.

account for the transformations **1** → **10** and **1** → **11** as nitrilimines analogous to **IV** have also been proposed for the iron(III)chloride-mediated oxidative cyclization of diaryl-substituted thiocarbonohydrazides affording [1,2,4]thiadiazoles [10]. The view about the transitional formation of **IV** was also supported by the following experiment. Although **10** was the major product in each oxidative cyclization discussed here (Methods D–F), on heating in refluxing xylene for 5 h under argon (Method G, Scheme 3) this heterocycle got converted into **11** in mediocre yield (50%), as the reaction was again accompanied by the formation of tarry substances. In accord with this experiment, the energy values obtained for these two isomers by DFT calculations [11] at B3LYP/6-31G(d,p) level of theory show that the triazole is more stable than the thiadiazole [ΔE(**11**–**10**) = −55.5 kJ/mol] pointing to that the oxidative cyclizations take place under kinetic control. Isomerization **10** → **11** presumably proceeds through the reversible endothermic ring opening to nitrilimine **IV** [ΔE(**IV**–**10**) = 131.7 kJ/mol]. In principle this intermediate can undergo two types of endothermic reversible proton migrations giving two tautomers **V** and **VI**, respectively [ΔE(**IV**–**V**) = 46.8 kJ/mol, ΔE(**IV**–**VI**) = 110.4 kJ/mol] of which exothermic cyclizations construct directly [1,2,4]triazole ring [**V** → **11**′ (ΔE = −156.7 kJ/mol) and **VI** → **11** (ΔE=−187.2 kJ/mol)]. In accord with the spectroscopic data (discussed later) the energetics calculated for **11** and **11'** show that the triazole-thion structure is more stable than the thiol tautomer [ΔE(**11**′–**11**) = 75.7 kJ/mol]. Comparing the energetics calculated for the possible elementary steps it can be suggested that the pathway including intermediates **IV**, **V** and **11**′ seems to be the most likely for the thermal isomerization **10** → **11** carried out under the conditions of method G.

Avoiding undesired oxidative transformations we found a convenient synthetic route to diferrocenylthiazolone **9** which proceeds through the primary S-alkylation of **1** with ethyl chloroacetate using K_2CO_3 as base and acetone as solvent to obtain ester **12** (Method H, Scheme 3). In the second step **12** was cyclized under mild conditions by the bifunctional organocatalyst N-(2-dimethylamino)-cyclohexyl-N′-[3,5-bis(trifluormethyl]phenylthio-urea developed by Takemoto and co-workers [12] (Method I: Scheme 3).

The relative stability of intermediate **IV** was interpreted by B3LYP/6-31 G(d,p) modelling. The energetics of the hypothetical oxygen-mediated dehydrogenations of selected models **1**, **13**, **14** and **15** (Scheme 4) indicate that the contribution to the stabilization of nitrilimines **IV**, **VII–IX** highly depends on the number and the structure of the terminal substituents. In keeping with our expectations, due to the presence of two ferrocenyl groups nitrilimine **IV** was found to be the most stable intermediate studied in this series. As it can be concluded from the almost identical values calculated for ΔE_2 and ΔE_3 (Scheme 4) the contribution to nitrilimine-stabilization from one ferrocenyl group is approximately equivalent to that provided by two phenyl groups. In accord with the calculated ΔE values facile thiazolone-forming cyclizations of **13** and **14** with chloroacetic acid have been reported [13,14].



Calculated energetics [B3LYP / 6-31 G(d,p)] representing substituent-dependency for the dehydrogenation of models **1**, **13**–**15**.

Scheme 4.

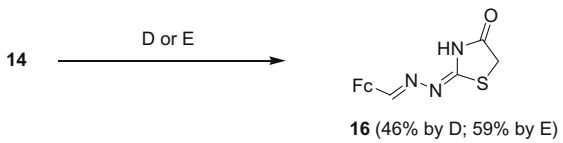
In order to gain further support for the substituent-dependency of the studied models to undergo dehydrogenation, we reacted **14** with chloroacetic acid using the conditions of Methods D and E, respectively, and obtained thiazolone **16** in acceptable yields (Scheme 5).

It is worth to compare the structures of two precursor/intermediate pairs **1**/**IV** and **13**/**VII**, respectively, resulted from geometry optimization as global minima. While the coplanar structure of **13** is retained in **VII**, on dehydrogenation of **1** the coplanarity of the substituted Cp rings ceased to exist and a twisted conformation with almost perpendicular ferrocenyl groups (interplanar angle between their Cp rings: $\Theta = 97.1°$) is adopted by **IV** (Fig. 1). The stability of intermediate **IV** might be at least partially ascribed to weak bonding overlaps between iron-centred d-type donor ferrocene-orbitals and the acceptor π^*-orbital of the linear electron-deficient nitrilimine group (Fig. 2). Analogous interactions are well-documented for a number of related ferrocene derivatives containing strong π-acceptor moiety directly attached to the ferrocenyl group [15]. The same structural difference was disclosed by DFT analysis of model pairs **14**/**VIII** and **15**/**IX** (Scheme 4).

3. Structure determination

The supposed structures of our new compounds can be deduced unambiguously from the spectral data (Tables 1–4). Only the following additional remarks are necessary:

In **2** a very stable planar conformation, stabilized by a chelate-type H-bond-like six-membered interaction between the azomethine-H in the side chain in Pos. 2, is plausible and with the S atom and ester carbonyl O simultaneously on the one hand and between the other azomethine-H (FcCH=N group in Pos. 3) and the O atom of the amide group or the N atom attached to C–2. Accordingly, *v*C=O IR frequencies have unusually low values (1705 and 1609 cm^{-1}), while the ^1H NMR signals of the N=CH groups in **2** are downfield-shifted (8.43 and 8.75 ppm, respectively) relative to those of **1**.



D: $ClCH_2CO_2H$, MeOH, NaOMe, reflux 1h;
E: $ClCH_2CO_2H$, MeOH, NaOMe, reflux 1h, Ar

Scheme 5.

The isomeric structures of compounds *cis*-**3** and *trans*-**3** follows straightforwardly from the values of vicinal couplings of H-4 and H-5 being 7.7 and 3.0 Hz, respectively, due to ~ 0° and ~144° dihedral angles [16]. Further proofs are the chemical shifts of these H's, which are higher in the *trans* isomer (by 0.39 and 0.35 ppm, respectively) as a consequence of the anisotropic neighbouring effect of the ester group on the same side of the ring, resulting in downfield shift [17a].

The oxidative ring closure, thus the structure of **5** follows from the absence of the NH and one of the CH=N–hydrogens as confirmed by the ^1H NMR spectrum and the absence of ^1H- and ^{13}C NMR signals of the DMAD moiety.

The six-membered structure of compound **7** is supported by the ^1H–^{15}N-HMBC spectrum in which a cross-peak between the olefinic CH (6.05 ppm) and the N atoms of the amide and NH groups, respectively (at 152 and 129 ppm) prove three-bond interactions. The other regioisomer (with the amide C=O and the ester-substituted sp^2 C in the ring in reversed positions) can be excluded on the basis of the ^{15}N NMR shifts: Fc–CH=N group is attached to the amide-NH and its signal lies at 152 ppm, downfield-shifted relative to the NH, having signal at 129 ppm as confirmed by the ^1H–^{15}N-HMBC cross-peaks. The extremely downfield-shifted signal of the azomethine-H of the FcCH=N group attached to the sp^3 N atom is explainable by the anisotropy of the coplanar amide carbonyl [17b] and a chelate-like H-bond between them.

The structure of **8** is obvious from the presence of two carbomethoxy and the methine groups (see e.g. the ^1H- and ^{13}C NMR lines of the latter at 6.09 and 75.0 ppm, respectively). The *E* configuration of the –CE=CHE side chain (E=CO_2Me) was found out by a DIFFNOE measurement which proved the proximity of the ring-methine (H-5) and the olefinic H atoms. The upfield lying N=CH signal at 7.26 ppm (the corresponding values of the other compounds fall into the interval 7.93–9.32 ppm) is probably the consequence of the anisotropic shielding of the C(sp^3)–Fc moiety being in steric proximity.

The three carbon lines – disregarding the signals of the ferrocene moieties – confirmed ring closure of the starting compound **1** without the participation of the reaction partner in the reactions resulted in **10** and **11**. Thus, only the thiadiazole (**10**) and triazolethione structures (**11**) should be considered. The ^{13}C NMR chemical shifts suggest hetero aromatic structure **10** on the basis of two downfield lying lines (at 169.3 and 183.6 ppm) and of one much

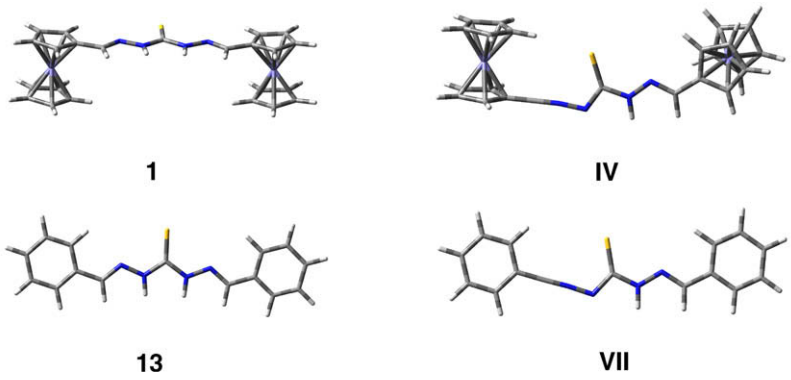


Fig. 1. Structures of model pairs **1**/**IV** and **13**/**VII** optimized at B3LYP/6-31 G(d,p) level of DFT.

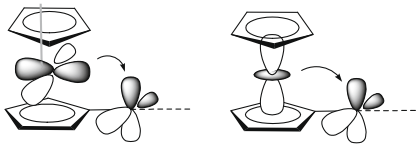


Fig. 2. Simplified illustration of the interactions between iron-centred d-type donor orbitals and the vertically oriented acceptor π*-orbital of the nitrilimine motiety in **IV** and **VII**.

more shielded carbon (its line is at 145.9 ppm) characteristic of a CH=N–NH group (see below). The significant downfield shift of the ^{1}H- and ^{13}C NMR signals of the CH group in **11** is explainable by the anisotropy of the thiocarbonyl group [17c] and for the ^{1}H NMR signal also by a weak H···S= bond. In the partly saturated ring the C=N carbon and the thiocarbamide carbon have upfield-shifted lines (at 150.1 and 161.9 ppm) as compared to **10**. Hence, the assignments of the ^{1}H- and ^{13}C NMR spectra to the two structures **10** and **11** are straightforward. Triazole **11** was also indirectly identified through its S-methyl derivative **5** analyzed by single crystal X-ray diffraction (see later).

For compound **12** the S-alkylation is unquestionable due to chemical shift (32.8 ppm) of the SCH_2 group. Similarly, the carbon shift of the SCH_2 group in **16** appears in the expected interval at 33.8 ppm [17d,18a].

As a result of molecular asymmetry (presence of chiral centra) the chemical non-equivalence of the atom-pairs H/C-2,5 and H/C-3,4 in ferrocene moieties for compounds *cis*-**3**, *trans*-**3** and **8** is noteworthy.

The signal of the substituted C of ferrocene is upfield-shifted in compounds **5** and **11** (71.0 and 70.1 ppm, respectively, while values of 75.6–80.6 ppm were measured for the other cases) because the ferrocenyl groups are attached in these compounds to the aromatic triazole ring. Again, in the ^{13}C NMR spectrum of **8** this signal is downfield-shifted to 83.6 ppm, as also expectable [18b][18b], due to the neighbouring sp^3 carbon.

Table 1
^{1}H NMR data[a,b] of compounds **1**, **2**, *trans*-**3**, *cis*-**3**, **412** and **16**.[c]

Compound	SCH_3 *s* (3H)	OCH_3 *s* (3H)	N=CH *s* (1H)[d]	N=CH *s* (1H)[e]	H-2-5[f]	H-2,5 (2H)	H-3,4 (2H)	H-2-5[f]	H-2,5 (2H)	H-3,4 (2H)	NH *s*, *br*
					Cp ring[d]			*Cp* ring[e]			
1	–	–	–	8.17	4.25	4.72	4.45	–	–	–	10.99
2	–	3.89	8.43	8.75	4.37	4.72	4.46	4.20	4.84	4.58	–
trans-**3**[g]	–	3.83, 3.84	8.28	8.66	4.21	4.61	4.37	4.23	4.63	4.40	–
cis-**3**[g]	–	3.80, 3.81	8.25	8.82	4.31	4.61	4.38	4.20	4.67	4.43	–
4	2.30	–	8.14	8.06	4.21[h]	4.79	4.43	4.21[h]	4.54	4.38	10.50
5	2.78	–	–	8.45	4.15[i]	4.91	4.35	4.37[i]	4.86	4.66	–
6	–	–		7.95	–	–	–	4.20	4.71	4.39	11.6[j]
7	–	3.82	8.33	9.23	4.31	4.64	4.45	4.20	4.75	4.52	8.97
8[g]	2.53	3.71, 3.98	–	7.26	4.15[i]	4.49	4.33	4.24[i]	4.26	4.15	–
9	3.82[k]	–	8.62	8.32	4.34	4.80	4.53	4.16	4.65	4.39	–
10	–	–	–	7.93	4.20[i]	4.81	4.47	4.24[i]	4.63	4.44	12.0
11	–	–	–	9.32	4.41	4.84	4.47	4.12	4.91	4.70	13.8
12	3.72[k]	4.10[l]	8.00	8.04	4.16[i]	4.74	4.40	4.19[i]	4.52	4.36	10.57
16	3.84[k]	–	8.20	–	4.20	4.65	4.46	–	–	–	11.8

[a] In $CDCl_3$ or DMSO-d_6 (**1**, **6**, **11**, **12** and **16**) solution at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz.
[b] Further ^{1}H NMR signals: =CH, *s* (1H): 6.96 (on C-5 in **2**), 6.05 (Pos. 5, **7**), 4.88 (side chain, **8**); H-5: 4.24, *d*, *J*: 3.2 (*trans*-**3**), 4.59, *d*, *J*: 7.7 (*cis*-**3**), 6.09, *s* (**8**); H-4, *d*: 5.40 (*trans*-**3**), 5.01 (*cis*-**3**), CH_3 (*t*, **12**): 1.20 (*J*: 7.2).
[c] Assignments were supported by HMQC (except for **16**) and H,C-HMBC (except for **6**), for *trans*-**3** also by 2D-COSY, for *trans*-**3**, *cis*-**3** and **8** by DIFFNOE measurements.
[d] Fc–CH=N–N= group, for **8** and **11** Fc attached to the sp^3 or sp^2 C in the heteroring.
[e] Fc–CH=N–N(sp^3).
[f] Unsubstituted Cp ring, interchangeable assignments.
[g] Due to molecular asymmetry (presence of chiral centra) the 2,5- and 3,4-H pairs of subst. Cp rings in Fc are chemically non-equivalent in each case. Counterparts of lines given in the Table: H-2,5: 4.65[d], 4.69[e] (*trans*-**3**), 4.65[d], 4.71[e] (*cis*-**3**), 4.54[d], 4.37[e] (**8**), H-3,4: 4.34[d], 4.22[e] (**8**).
[h] Overlapping signals.
[i] Interchangeable assignments.
[j] 3H.
[k] CH_2.
[l] OCH_2.

Table 2
^{13}C NMR chemical shifts[a] of compounds **1**, **2**, *trans*-**3**, *cis*-**3**, **412** and **16**.[b]

Compound	SCH_3	OCH_3	C-1-5 Cp[c,d]	C-1 Substituted *Cp* ring[d]	C-2,5 Substituted *Cp* ring[d]	C-3,4 Substituted *Cp* ring[d]	C-1-5 Cp[c,e]	C-1 Substituted *Cp* ring[e]	C-2,5 Substituted *Cp* ring[e]	C-3,4 Substituted *Cp* ring[e]	C-2 Hc[f]	CH=N group[d]	CH=N group[e]	C=O or C=S[g]
1	–	–	69.9	79.9	68.6	70.9	–	–	–	–	–	–	148.4	174.4
2	–	52.9	69.9[h]	77.9	69.3	71.7	70.7	75.4	69.9[h]	72.8	155.3	162.0	170.4	166.9
trans-**3**[i]	–	53.5, 53.9	69.9[j]	79.4	68.7[k]	70.88[l]	69.7[j]	79.2	68.51[k]	70.7[l]	160.6	156.3	153.3	170.05, 170.07
cis-**3**[i]	–	53.1, 53.6	70.0[j]	79.3	68.4	70.73	69.7[j]	78.2	68.5	71.15	162.9	156.4	160.1	168.7, 169.0
4	13.2	–	69.8[h]	80.6	68.9	70.7	69.8[h]	80.7	67.7	70.4		154.3	143.0	–
5	15.8	–	70.01[j]	71.0	68.7	69.97	70.4[j]	75.5	69.7	72.9	153.2	–	168.4	–
6	–	–	–	–	–	–	69.7	81.0	68.2	70.5	–	–	146.9	–
7	–	52.4	70.3[j]	78.5	68.8	71.4	69.8[j]	77.6	69.0	72.0	148.0	159.4	162.1	165.2
8[i]	13.6	51.7, 53.3	70.1[j]	86.3	68.1	68.4[h]	69.7[j]	79.6	67.4	70.46	75.0	–	140.6	164.4, 167.7
9	31.5[m]	–	70.6[j]	75.6	69.83	72.5	69.80[j]	78.5	69.0	71.2	158.9	170.4	160.0	168.1
10	–	–	70.7[j]	76.4	68.4	70.6	69.8[j]	80.2	67.9	70.8	183.6	–	145.9	–
11	–	–	71.0[j]	70.1	68.7[n]	70.9[n]	70.3[j]	76.1	69.9[n]	73.1[n]	–	–	170.7	161.9
12	32.8[m]	61.5[o]	69.80[j]	80.4	69.0	70.9	69.76[j]	80.6	67.8	70.6	–	154.8	143.4	170.2
16	33.8[m]	–	70.0	79.3	68.9	71.4	–	–	–	–	175.0	157.7	–	162.8

[a] In $CDCl_3$ or DMSO-d_6 (**1**, **6**, **11**, **12** and **16**) solution at 125.7 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm). Further lines: =CH– (in side chain): 116.3 (**2**), 85.2 (**8**); C-5[f]: 141.6 (**2**), 43.6 (*trans*-**3**), 44.4 (*cis*-**3**), 146.3 (**5**), 101.7 (**7**) 154.6 (**8**), 169.3 (**10**), 150.1 (**11**); C=O (lactame): 161.5 (**2**), 157.1 (**7**); C-4[f]:67.2 (*trans*-**3**), 67.8 (*cis*-**3**); –N=C(S or NH_2)–NH– group: 159.4 (**4**), 173.0 (**6**), 157.9 (**12**); C-6[f]: 138.5 (**7**); N–C= (*quat*., side chain): 149.4 (**8**); CH_3(OEt, **12**): 15.1.

[b] Assignments were supported by HMQC (except for **16**) and ^{1}H,^{13}C-HMBC (except for **6**, for **2**, *trans*-**3**, **4**, **7**, **8** and **11** also by ^{1}H,^{15}N-HMBC), for *trans*-**3**, *cis*-**3**, **4**, **7–9**, **11** and **12** also by DEPT measurements.

[c] Unsubstituted Cp ring.

[d] Fc–CH=N–N= group, for **8** and **11** Fc–C(sp^3) and Fc–C_{quat}(sp^2), respectively.

[e] Fc–CH=N–N(sp^3) group.

[f] Hc = in heteroring.

[g] Ester, C=S for **1** and **11**, lactame for **9**.

[h] Two overlapping lines.

[i] Due to molecular asymmetry (presence of chiral centra) the 2,5- and 3,4 C-pairs of subst. Cp rings in Fc are chemically non-equivalent. The counterparts of the lines given in the table: C-2,5: 68.53[h,j] (*trans*-**3**), 68.8[d], 69.2[e] (*cis*-**3**), 68.0[d], 68.4[e,h] (**8**), C-3,4: 70.8[l] and 70.93[l] (*trans*-**3**), 70.78[d], 71.19[e] (*cis*-**3**), 69.0[d], 70.5[e] (**8**).

[j,k,l] Interchangeable assignments.

[m] SCH_2.

[n] Broad.

[o] OCH_2.

Table 3
Characteristic IR frequencies [cm^{-1}] of compounds **1**, **2**, *trans*-**3**, *cis*-**3**, **4–12** and **16** (in KBr discs).

Compound	*v*NH[a] band	*v*C=O band	Amide-I band	*v*C=N-type band[b]	*v*C–O bands	v_{as}Cp–Fe–Cp and tilt of Cp
1	3300–2750	–	–	1606, 1524	–	482
2	–	1705	1625	1609	1241, 1198	500, 485
trans-3	–	1761, 1737	–	1611	1227, 1201, 1170	483
cis-3	–	1740	–	1614, 1568	1213, 1002	498
4	3237, 3120	–	–	1549, 1520	–	481
5	–	–	–	1582, 1557	–	502, 485
6	3500–2000	1710	–	1665	–	505, 482
7	~3410	1730	1638	–	1247, 1155	~500, 484
8	–	1749, 1697	–	1589, 1556	1221, 1152	~500, 485
9	–	–	1719	1613	–	531
10	3000–2500	–	–	1600, 1584	–	497, 483
11	3500–2000	–	–	1587	–	504, 482
12	~3300	1737	–	–	1284, 1106	484
16	3500–2000	–	1718	1631	–	511, 479

[a] Diffuse (**1**, **6**, **10**, **11**, **16**), broad (**4**, **7**, **12**).

[b] Thiocarbamide group (guanidine group for **6**).

[c] Overlapped maxima.

Table 4
^{15}N NMR chemical shifts[a] of compounds **2**, **4**, **7**, **8** and **11**.[b]

Compound	N(sp^3)	C_{quat}=N	>N–*N*=CH	=N–*N*=CH
2	191	306	293	336
4	155	264	306	330
7	129, 152[c]	254	298	328
8	161, 163	162	304	–
11	211	261	291	–

[a] In $CDCl_3$ (DMSO-d_6 for **11**) solution at 50.7 MHz. Chemical shifts in ppm (δNH_3 = 0 ppm).

[b] Assignments are based on ^{1}H^{15}N-HMBC measurements.

[c] NH.

Of course the azomethine ^{1}H NMR chemical shift depends on the character of the N-substituent: for CH=N–NH– groups we measured values between 143 and 148 ppm (**1**, **4**, **6**, **10** and **12**). In case of CH=N–*N* groups, where *N* is an imide type atom [=N–*N*(C=X)$_2$, X: O, S or N], the signal is shifted in the opposite direction (to ca. 170 ppm, c.f. the data stated for compounds **2**, **9** and **11**).

X-ray diffraction revealed the expected constitution of **5** (Fig. 3). Interplanar angles of the anchored *Cp* rings (atoms C4- > C8) and (C14- > C18) to each other and to the five-membered ring are ca. 71°, 63° and 11°, respectively. Sole existence of weak electrostatic interactions may be responsible for the relative weak cohesion between molecules in the crystal. Thus an indirect explanation for the

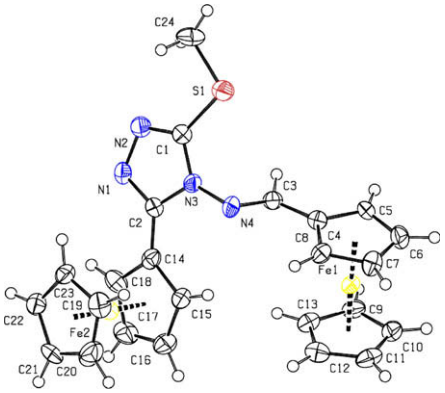


Fig. 3. A 50% atomic displacement probability plot of **5** in the crystal. Characteristic bond distances in the [1,2,4]triazole ring and its immediate vicinity (in Å): S(1)–C(1) 1.750(6), N(1)–N(2) 1.398(8), N(1)–C(2) 1.333(9), N(2)–C(1) 1.309(9), N(3)–N(4) 1.426(7), N(3)–C(1) 1.364(9), N(4)–C(3) 1.282(9), N(3)–C(2) 1.387(8), C(2)–C(14) 1.421(10) and C(3)–C(4) 1.447(9). Geometry around Fe metals involving ring centroids: Cg(2)–Fe(1) 1.657(3) Å, Cg(3)–Fe(1) 1.668(3) Å, Cg(2)–Fe(1)–Cg(3) 176.22(17)°, Cg(4)–Fe(2) 1.653(3) Å, Cg(5)–Fe(2) 1.658(3) Å, Cg(4)–Fe(2)–Cg(5) 178.15(18)°.

disposition for twining is given (see also Fig. 4, deposited). Most apparent of such feeble contacts, as represented by their D–H···A geometry, are C3–H3···$N2_{/2-x,-y,2-z/}$ at 0.96 Å, 2.45 Å, 3.31(1) Å, 150° and C11–H11···$N1_{/1/2+x,1/2-y,1/2+z/}$ 0.95 Å, 2.49 Å, 3.41(1) Å, 163°, respectively. A third such contact may be the almost exact placement of the S atom over the ring centre of a neighbouring triazole ring at a distance of ca. 3.91 Å.

4. Conclusion

Besides DMAD employing further activated acetylene components for the cyclization reactions of easily available diferrocenyl-thicarbonohydrazide and related precursors discussed in this contribution may open up facile synthetic routes to a variety of novel diferrocenyl-substituted S,N- and N,N heterocycles of potential biological interest. Our reaction conditions allow to control the product ratio of diastereomeric 2-hydrazono-thiazolidines and thiazolone by the choice of the reaction time. The two-step protocol involving organocatalytic intramolecular acylation can be considered as being applicable to the expedient syntheses of related thiazolones carrying aralkylidenehydrazono- and amino functionalities. The detected propensity of the investigated diferrocenyl-thiocarbonohydrazide to undergo oxidative cyclizations via ferrocenyl-stabilized nitrilimine intermediate must be taken into account during other manipulations with this easily accessible precursor. It was also evidenced by both theoretical and preparative methods that the related ferrocenylthio-semicarbazone has decreased sensitivity towards oxidation allowing more predictable reactions to be carried out.

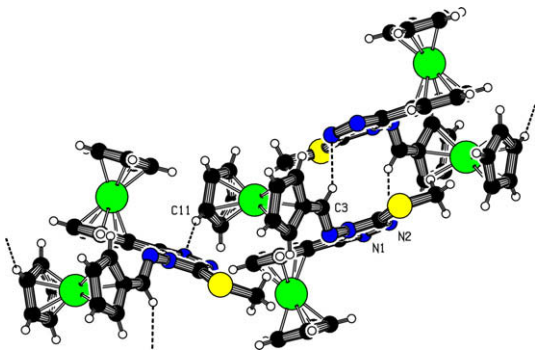


Fig. 4.

5. Experimental

All chemicals were obtained from commercially available sources and used without further purification (Aldrich, Fluka). Each flash silica gel column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). Melting points were determined with a Boethius microstage. The IR spectra were run in KBr disks on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The ^{1}H- and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 spectrometer at 500 (^{1}H), and 125 (^{13}C) with the deuterium signal of the solvent as the lock and TMS as internal standard. The ^{15}N NMR chemical shifts were obtained and assigned from the ^{1}H–^{15}N HMBC spectra with NH_3(liq) as external reference at 50 MHz. The standard Bruker microprogram NOEMULT to generate NOE and to get DIFFNOE spectra was used. DEPT spectra were run in a standard manner, using only a $\Theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-COSY, HMQC and HMBC spectra were obtained by using the standard Bruker pulse programs. All calculations were carried out with the Gaussian 03 suite of programs [19]. Optimized structures available from the authors were obtained by Becke's three-parameter hybrid functional together with the correlation functional of Lee, Yang and Parr [20] as implemented in GAUSSIAN 03 suite of programs using standardized 6–31 G(d,p) basis set including polarization functions [21]. X-ray diffraction experiment on selected single-crystals were executed at low temperatures (at T = 114(2) K and 135(2) K) on a Rigaku R_axis Rapid IP diffractometer.

5.1. General procedure for the synthesis of compounds *1* and *6*

Formylferrocene (21.4 g, 100 mmol) and the corresponding diamine component (55 mmol) ($(NH_2NH)_2CS$ or $(NH_2NH)_2NH.HCl$) were refluxed in abs. ethanol for 2 h. After evaporation the resulted crude materials were purified by flash column chromatography on silica using DCM as eluent. The isolated products were triturated with *n*-hexane, filtered off and dried under vacuo.

5.2. 1,5-Diferrocenymethylidenethiocarbonohydrazide (*1*)

Brown powder; yield: 22.25 g, 89%; mp 173–175 °C; Anal. Calc. for $C_{23}H_{22}Fe_2N_4S$ (498.22): C, 55.45; H, 4.45; N, 11.25; S, 6.44. Found: C, 55.42; H, 4.43; N, 11.29 S; 6.40%.

5.3. 1,3-Bis(ferrocenylmethylideneamino)guanidine (*6*)

Dark orange powder; yield: 20.40 g, 85%; mp 109–111 °C; Anal. Calc. for $C_{23}H_{23}Fe_2N_5$ (481.17): C, 57.41; H, 4.82; N, 14.55. Found: C, 57.32; H, 4.94; N, 14.70%.

5.4. General procedure for the reactions with DMAD (Method A)

The corresponding bis-ferrocenyl derivative (**1**, **4** or **6:** 4 mmol), and DMAD (0.71 g, 5 mmol) was dissolved in anhydrous and degassed MeCN (50 mL). The solution was refluxed under Ar for 1–8 h then evaporated to dryness. The solid residue was triturated with *n*-hexane and filtered off to remove the excess of DMAD. The deep orange powder was dissolved in DCM (50 ml) and extracted with water (3 × 50 mL). The organic layer was dried over Na_2SO_4, then evaporated. The residue was purified by column chromatog-

raphy on silica using chloroform as eluent. The separated products were crystallized with *n*-hexane.

5.5. Methyl 2-(ferrocenylmethylidenehydrazono)-3-(ferrocenylmethylideneamino)-4-oxothiazol-idin-5-ylidene)acetate (**2**)

Dark orange powder; yield: 0.535 g, 22% (from **1**, reaction time: 1 h); 1.677 g, 69% (from **1**, reaction time: 5 h) and 1.873 g, 77% (from **1**, reaction time: 8 h); mp 188–191 °C (decomposed); Anal. Calc. for $C_{28}H_{24}Fe_2N_4O_3S$ (608.29): C, 55.29; H, 3.98; N, 9.21; S, 5.27. Found: C, 55.35; H, 4.04; N, 9.13; S, 5.30%.

5.6. (4R*,5R*)-Dimethyl 2-(ferrocenylmethylidenehydrazono)-3-(ferrocenylmethylideneamino)-thiazolidine-4,5-dicarboxylate (cis-**3**)

Orange powder; yield: 0.742 g, 29% (from **1**, reaction time: 1 h); mp 145–149 °C; Anal. Calc. for $C_{29}H_{28}Fe_2N_4O_4S$ (640.33): C, 54.40; H, 4.41; N, 8.75; S, 5.01. Found: C, 54.47; H, 4.37; N, 8.79; S, 4.97%.

5.7. (4R*,5S*)-Dimethyl 2-(ferrocenylmethylidenehydrazono)-3-(ferrocenylmethylideneamino)-thiazolidine-4,5-dicarboxylate (trans-**3**)

Orange powder; yield: 0.640 g, 25% (from **1**, reaction time: 1 h); 0.256 g, 10% (from **1**, reaction time: 5 h); mp 162–164 °C; Anal. Calc. for $C_{29}H_{28}Fe_2N_4O_4S$ (640.33): C, 54.40; H, 4.41; N, 8.75; S, 5.01. Found: C, 54.30; H, 4.50; N, 8.84; S, 5.09%.

5.8. 3-Methylthio-4-(ferrocenylmethylideneamino)-5-ferrocenyl-4-H-1,2,4-triazol (**5**)

Orange powder; yield: 1.102 g, 54% (from **4**, reaction time: 3 h); mp 106–109 °C; Anal. Calc. for $C_{24}H_{22}Fe_2N_4S$ (510.21): C, 56.50; H, 4.35; N, 10.98; S, 6.28. Found: C, 56.60; H, 4.31; N, 11.06; S, 6.21%. Deep red plates suitable to single crystal X-ray analysis were obtained by recrystallization from EtOAc-*n*-hexane (1:10).

5.9. Crystal data and details of the structure determination of **5** (CCDC 727238)

Several crystals were tested with the use of both Cu- and Ag-radiations. Their asymmetric rhombic plate shape coupled with extensive twinning and/or rotational disorder in some *Cp*-groups hampered straightforward analysis for the Cu-radiation dat sets (low-resolution ($d_{min} \sim 1.2$ Å) and *R*-values around 10–12%). However the specimen selected for the Ag-radiation experiment gave better resolution and lower *R* values, reported here. Initial structure models obtained by direct methods (SHELXS-97, Sheldrick, 2008 [22]) was completed and refined by standard procedures to convergence (SHELXL-97, Sheldrick, 2008 [23]). $C_{24}H_{22}Fe_2N_4S$, F.W. 510.22, Ag Kα, $\lambda = 0.56089$ Å, $T = 136(2)$ K, monoclinic, $P2_1/n$ (No. 14), $a = 12.0043(8)$ Å, $b = 11.1630(5)$ Å, $c = 15.9721(8)$ Å, $\beta = 100.893(3)°$, $V = 2101.8(2)$ [Å^3], $Z = 4$, $D_{(calc)} = 1.612$ Mg/m^3, μ(Ag Kα) = 0.781 mm^{-1}, total and unique data, 10 844 and 3757, $R_{int} = 0.085$, data with $I > 2.0\sigma(I) = 3124$, $N_{ref} = 3757$, $N_{par} = 285$, $R = 0.08$, $wR^2 = 0.232$.

5.10. Dimethyl 2-(4-(ferrocenylmethylideneamino)-4,5-dihydro-3-(methylthio)-5-ferrocenyl-1,2,4-triazol-1-yl)maleate (**8**)

Orange powder; yield: 0.550 g, 21% (from **4**, reaction time: 3 h); mp 96–98 °C; Anal. Calc. for $C_{30}H_{30}Fe_2N_4O_4S$ (654.36): C, 55.07; H, 4.62; N, 8.56; S, 4.90. Found: C, 55.12; H, 4.55; N, 8.49; S, 4.93%.

5.11. Methyl 2-(ferrocenylmethylidenehydrazono)-1-(ferrocenylmethylideneamino)-1,2,3,6-tetra-hydro-6-oxopyrimidine-4-carboxylate (**7**)

Orange powder; yield: 1.465 g, 62% (from **6**, reaction time: 3 h); mp 110–112 °C; Anal. Calc. for $C_{28}H_{25}Fe_2N_5O_3$ (591.22): C, 56.88; H, 4.26; N, 11.85. Found: C, 56.99; H, 4.20; N, 11.94%.

5.12. Thermal transformation trans-**3** → **2** (Method B)

Thiazole-dicarboxylate *trans*-**3** (0.640 g, 1 mmol) was dissolved in anhydrous and degassed MeCN (15 mL) and the solution was refluxed under Ar for 8 h then evaporated to dryness. The oily residue was triturated with *n*-hexane and filtered off to obtain **2** as dark orange powder without any ferrocene-containing contamination as it was shown by silica-TLC analysis using chloroform and DCM-MeOH (100:1), respectively, as eluent. Yield: 0.553 g, 91%. Within experimental error the analytical and spectral data were identical with those listed under Method A.

5.13. S-methylation of **1** and **11** (Method C)

Thiocarbonodihydrazide **1** or triazole-thion **11** (5 mmol) and iodomethane (0.71 g, 5 mmol) was added in turn to the solution obtained by dissolving sodium (0.115 g, 5 mmol) in methanol (25 mL). The reaction mixture was stirred and refluxed under argon for 1 h. The solvent was evaporated to dryness, and the solid residue was purified by flash column chromatography on silica, using DCM as eluent. The oily product resulted from the evaporation of the eluent was triturated with *n*-hexane, filtered off and dried to obtain **4** and **5**, respectively. Triazole **5** was obtained as deep orange powder. Yield: 2.092 g, (82%). Within experimental error the analytical and spectral data of this product were identical with those listed under Method A.

5.14. 1,3-Bis(ferrocenylmethylideneamino)-2-methylisothiourea (**4**)

Deep red powder. Yield: 2.380 g, 93%; mp 79–81 °C; Anal. Calc. for $C_{24}H_{24}Fe_2N_4S$ (512.24): C, 56.28; H, 4.72; N, 10.94 S, 6.26. Found: C, 56.37; H, 4.82; N, 11.02, S, 6.24%.

5.15. Reactions of **1** and **14** [4] with chloroacetic acid (Methods D and E)

(According to Method D the reaction mixture was exposed to air, while using Method E the reaction was conducted under Ar.) To a well stirred solution of NaOMe, made of methanol (25 mL) and sodium (0.047 g, 2 mmol), 2 mmol of the corresponding precursor and chloroacetic acid (0.189 g, 2 mmol) were added in sequence. The resulting mixture was heated at reflux temperature for 1 h. The solvent was evaporated, and the solid residue was partitioned between DCM (100 mL) and 10% $NaHCO_3$ (20 mL). The organic phase was washed with water (2×20 mL), dried over Na_2SO_4 and evaporated. The crude thiazolone **16** obtained from the reaction of **14** was purified by flash column chromatography on silica [eluent: DCM-MeOH (30:1)] followed by crystallization with ethanol. The crude residue obtained from the reaction of **1** was also subjected to flash column chromatography on silica [eluent:*n*-hexane-EtOAc (5:1)] to separate **10** (first band) and **11** (second band) which were crystallized with Et_2O. The crude residue obtained from each reaction was contaminated by black tarry substances removed by chromatography.

5.16. 2-Ferrocenyl-1-(5-ferrocenyl-1,3,4-thiadiazol-2-yl)hydrazine (**10**)

Orange powder; yield: 0.317 g, 32% (Method D); 0.396 g (40%) (Method E); mp 210–213 °C (decomp.); Anal. Calc. for $C_{23}H_{20}Fe_2N_4S$ (496.20): C, 55.67; H, 4.06; N, 11.29; S, 6.46. Found: C, 55.80; H, 3.98; N, 11.19; S, 6.50%.

5.17. 4-(Ferrocenylideneamino)-5-ferrocenyl-2H-1,2,4-triazole-3(4H)-thione (**11**)

Orange powder; yield: 0.089 g, 9% (Method D); 0.139 g, 14% (Method E); mp 235–238 °C; Anal. Calc. for $C_{23}H_{20}Fe_2N_4S$ (496.20): C, 55.67; H, 4.06; N, 11.29; S, 6.46. Found: C, 55.77; H, 4.15; N, 11.35; S, 6.56%.

5.18. 2-(2-Ferrocenylmethylidenehydrazono)thiazolidin-4-one (**16**)

Red microcrystals; yield: 0.301 g, 46% (Method D); 0.386 g, 59% (Method E); mp 232–235 °C (234–236 °C in Ref. [14]); Anal. Calc. for $C_{14}H_{13}FeN_3OS$ (327.18): C, 51.39; H, 4.00; N, 12.84; S, 9.80. Found: C, 51.10; H, 4.12; N, 13.02; S, 9.96%.

5.19. Oxidation of **1** by $FeCl_3$ (Method F)

At rt. **1** (0.996 g, 2 mmol) was added to $FeCl_3.6H_2O$ (1.350 g, 5 mmol) dissolved in EtOH (25 mL). The reaction mixture was refluxed for 30 min. then was stirred for 12 h at rt. After addition of water (100 mL) the dark precipitated solid was filtered off, thoroughly washed with water and dried. The separation and purification of **10** and **11** was carried out according to the procedure described in Methods D and E. Yield: 0.615 g, 62% (**10**); 0.268 g, 27% (**11**). Within experimental error the analytical and spectral data were identical with those listed under Methods D and E.

5.20. Thermal transformation **10** → **11** (Method G)

In dry degassed xylene (20 mL) **10** (0.496 g, 1 mmol) was suspended. The reaction mixture was refluxed under Ar for 5 h then evaporated to dryness. The crude product was purified by flash column chromatography on silica [eluent:*n*-hexane-EtOAc (5:1)] and crystallized with Et_2O to obtain **11** as dark orange powder. Yield: 0.248 g (50%). Within experimental error the analytical and spectral data of the single product were identical with those listed under Methods D and E.

5.21. 1,3-Bis(ferrocenylmethylideneamino)-2-(ethoxycarbonyl)methylisothiourea (**12**) (Method H)

To the stirred suspension made of **1** (2.491 g, 5 mmol), K_2CO_3 (0.345 g, 2.5 mmol) and anhydrous acetone (75 mL) ethyl chloroacetate (0.735 g, 6 mmol) dissolved in acetone (5 mL) was added dropwise at 25 °C over 5 min. The reaction mixture was then refluxed for 1 h and and evaporated to dryness. To the thick oily residue DCM (50 mL) was added, and the undissolved salts were removed by filtration. The solution was extracted with water (2×50 mL), dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on silica using DCM-MeOH (80:1) as eluent and recrystallized from cyclohexane to obtain orange powder; yield: 2.162 g, 74%; mp 82–85 °C; Anal. Calc. for $C_{27}H_{28}Fe_2N_4O_2S$ (584.29): C, 55.50; H, 4.83; N, 9.59; S, 5.49. Found: C, 55.42; H, 4.93; N, 9.64; S, 5.43%.

5.22. 2-(2-ferrocenylmethylidenehydrazono)-3-(ferrocenylmethylideneamino)thiazolidin-4-one (**9**) (Method I)

To the solution of the **12** (0.584 g, 1 mmol in 10 mL of DCM) Takemoto-catalyst (0.062 g, 0.15 mmol) was added and the solution was stirred at 40 °C under Ar for 5 h. The reaction mixture was evaporated and the product was purified by flash column chromatography on silica using *n*-hexane-EtOAc (5:1) and recrystallized from cyclohexane to obtain orange powder. Yield: 0.484 g, 90%;mp 115–117 °C; Anal. Calc. for $C_{25}H_{22}Fe_2N_4OS$ (538.22): C, 55.79; H, 4.12; N, 10.41; S, 5.96. Found: C, 55.88; H, 4.04; N, 10.51; S, 6.00%.

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