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Ferrocenyl pyrazolines: Preparation, structure, redox properties and DFT study on regioselective ring-closure ☆

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ABSTRACT

Cyclocondensation of 1-phenyl-3-ferrocenyl-2-propen-1-one (**1**) with RNHNH2 hydrazines and the substituent-dependent product distribution were investigated. With methylhydrazine, formation of two regioisomeric pairs of pyrazolines and pyrazoles was observed. The ratio of the products varied with the solvent and temperature. Transformation of 5-ferrocenyl-N-substituted pyrazolines into pyrazoles was systematically studied and DDQ was found to be the most suitable reagent. Mechanism of the cyclization reactions taking place under kinetic- and thermodynamic controls was supported with DFT calculations. The energy-dependence of the transformation of pyrazoline to pyrazole was investigated also by EI MS. Structure determination of the new compounds was performed by IR, MS and NMR methods including 2D-HMQC, 2D-HMBC, DEPT and DIFFNOE measurements. For two compounds structures were also proved by X-ray diffraction.

1. Introduction

Among the nitrogen heterocycles the 1-*H* pyrazoles and their 4,5-dihydro-derivatives have outstanding synthetic and biological significance [2]. Some of them have antibacterial, antimycotic or anticancer effect and several 1,3,5-triaryl-pyrazoles are used as anti-inflammatory and anti-rheumatic agents [2,3]. Recently new pyrazole derivatives were prepared as reverse transcriptase inhibitors for the treatment of HIV disorders [4]. Several 1-methyl-3,5-diaryl-pyrazoles were patented as γ-secretase inhibitors and were claimed useful for the treatment of Alzheimer's disease [5]. Furthermore, series of substituted phenylpyrazoles were developed as very effective and selective inhibitors of factor Xa, an important serine protease [6].

4,5-Dihydro-1-*H*-pyrazoles can be prepared advantageously by reacting 1,1′-diaryl-prop-2-en-1-ones (chalcones, Ar–CH=CH–CO–Ar′) with hydrazine derivatives [2,7,8]. Incorporation of the three-dimensional ferrocenyl group instead of a flat aryl or hetaryl substituent into the molecule can result in favourable change of biological properties [9–11]. Ferrocenyl-substituted pyrazoles are intensively studied nowadays by numerous research groups [6,8,10,12]. In our group also several ferrocene containing pyrazole derivatives were recently prepared as potential biologically active molecules [7,13–15].

Earlier studies indicated, that cyclocondensation of diarylpropenones with hydrazines may lead to pyrazolines and/or pyrazoles, depending on the reaction conditions [2,16]. The present work aimed detailed investigation on the formation of ferrocenyl pyrazolines having different substituents at $N-1$, starting from the easily available 3-ferrocenyl-1-aryl-propenones. Furthermore, we aimed a comparative study on the transformation of the pyrazolines into the corresponding pyrazoles. The experimental results were supported also by DFT calculations. As the stereochemistry has an important role in bioactivity, to clear the 3D-structures NMR-measurements, and in the case of some molecules also X-ray analysis were carried out.

2. Results and discussion

2.1. Syntheses

Reaction of 3-ferrocenyl-1-phenyl-prop-2-en-1-one (**1**) with aqueous hydrazine in ethanol resulted in 5-ferrocenyl-3-phenyl-4,5-dihydro-1*H*-pyrazole (**2a**) in good yield, in accordance with earlier findings [17]. These types of pyrazolines with free NH group were described occasionally as unstable materials, but they are more stable in the dry state [8]. Acetylation of **2a** can be advanta-

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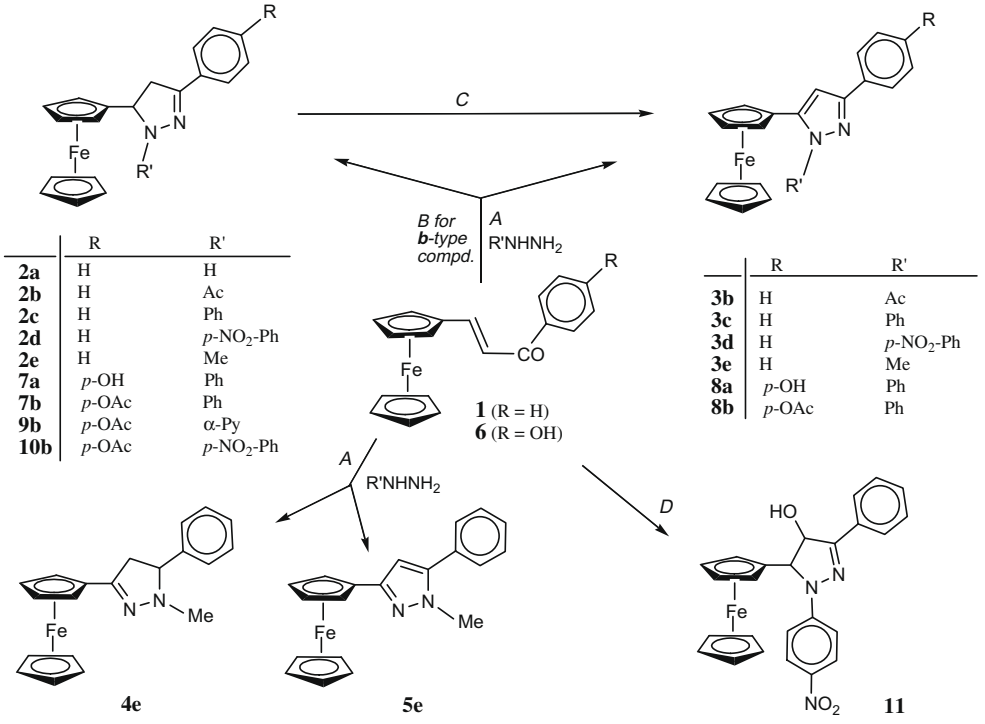
geously carried out with acetic anhydride in pyridine at 0 °C, resulting in the stable *N*-acetyl derivative **2b** in good yield (Scheme 1). We found this mild acetylation method a good alternative to previous procedures which used boiling acetic anhydride for the preparation of *N*-acetyl-pyrazolines [17,18].

The *N*-phenyl-pyrazoline **2c** was prepared by reacting **1** with phenylhydrazine in acetic acid–ethanol–water [18a], and the new *N*-(*p*-nitrophenyl)-pyrazoline (**2d**) was prepared analogously. In this latter case a 4-hydroxylated pyrazoline (**11**) as by-product could also be isolated. Formation of **11** can be explained by radical oxidation in the presence of *p*-nitrophenylhydrazine having been in excess in the reaction mixture.

To find the best procedure for the transformation of ferrocenyl-pyrazolines to pyrazoles, compounds **2c** and **2d** were used as model compounds. A variety of reagents were published for the dehydroaromatisation of pyrazolines [2,19], but in our case – because of the sensitivity of the ferrocenyl group to oxidation – only some of the methods seemed to be applicable. Our first attempts, to carry out the transformation of pyrazolines with *N*-bromo-succinimide (NBS) in analogous circumstances as described [20], gave poor results. By reacting **2c** with NBS in carbon tetrachloride as solvent, using pyridine as base, **3c** was formed in 29% yield even with a significant excess of the reagent. From **2d** the pyrazole **3d** was isolated only in 8% yield with NBS. Next, we tried the dehydroaromatisation of **2c** by sonication-assisted oxidation with copper(II) nitrate trihydrate, which has recently been published as advantageous reagent for such type of transformations [21]. However, employing this method, **3c** could be prepared only in moderate yield (37%).

As quinone-type reagents in some cases proved to be also suitable for oxidation of pyrazolines [2,14,19,22], we resorted to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and investigated the aromatisation propensity of 5-ferrocenyl-3-phenyl pyrazolines **2b–d**. The *N*-phenyl-derivative **2c** reacted smoothly with 1.2 equiv. of DDQ even at RT, in dichloromethane or in benzene solution and gave the desired pure, crystalline pyrazole **3c** in about 80% yield. The progress of the reaction could be followed visually not only by TLC, but also by the amount of the precipitated greyish-green solid (quinone–hydroquinone-type complex). Under similar conditions **2d** did not react at all, even after addition of 2.0 equiv. of DDQ to the mixture. However, in toluene at reflux temperature, in the presence of 1.2 equiv. of DDQ, the reaction was complete within 2 h and **3d** could be isolated after purification in 76% yield. The *N*-acetyl-pyrazoline **2b** reacted also moderately, the dehydroaromatisation has been carried out only at higher temperature (~80 °C) in benzene or in toluene solution, by gradual addition of the solution of 1.3 equiv. of DDQ, and pyrazole **3b** was isolated in 42% yield. From our findings it can be seen, that pyrazolines **2b** and **2d**, having electron-withdrawing substituent at the N atom, show decreased reactivity towards oxidation with DDQ in non-polar solvents.

We investigated the reaction of **1** with methylhydrazine, too, under different conditions and observed formation of more complicated mixtures. Two regioisomeric pairs of *N*-methyl-pyrazolines (**2e** and **4e**) and *N*-methyl-pyrazoles (**3e** and **5e**) could be identified as hitherto unknown new compounds, but the ratio of the products varied depending on the solvent and temperature. All reactions were conducted under nitrogen. In boiling ethanol, with 6.5 equiv. of methylhydrazine (added in two portions), the main isolated products were 5-ferrocenyl-pyrazoline **2e** (23% yield) and 3-ferrocenyl-pyrazole **5e** (43% yield). Although the "reverse" 3-ferrocenyl-pyrazoline (**4e**) could be indicated by TLC in notable amount in the mixture, during work-up and purification a significant part of that was transformed into the corresponding pyrazole **5e** even when chromatography on Silica gel was made



	R	R'
2a	H	H
2b	H	Ac
2c	H	Ph
2d	H	*p*-NO_2-Ph
2e	H	Me
7a	*p*-OH	Ph
7b	*p*-OAc	Ph
9b	*p*-OAc	α-Py
10b	*p*-OAc	*p*-NO_2-Ph

	R	R'
3b	H	Ac
3c	H	Ph
3d	H	*p*-NO_2-Ph
3e	H	Me
8a	*p*-OH	Ph
8b	*p*-OAc	Ph

Reaction conditions:A) Hydrazinolysis of **1** or **6** with $RNHNH_2$: EtOH, RT for **2a**; AcOH, reflux for **2b**; AcOH-EtOH-H_2O, reflux for **2c**, **2d**, **7a+8a**, **9a**, **10a**; MeOH, 40°C for **2e-5e**; toluene, reflux for **4e+5e**; *B*) Acetylation of **2a, 7a, 9a** and **10a** to **2b**, **7b**, **9b** and **10b** with Ac_2O in pyridine at 0°C; *C*) Dehydroaromatization of pyrazolines **2** to pyrazoles **3** *a)* with $Cu(NO_3)_2.3H_2O$ under sonication, CH_2Cl_2 for **3c**; *b)* N-bromo-succinimide, CCl_4, reflux for **3c** and **3d**; *c)* DDQ, CH_2Cl_2 or toluene, RT for **3c**; toluene, reflux for **3b**, **3d** and **8b**; partial spontaneous oxidation during the reaction for **8a**, **3e** and **5e**; *D*) **11**: by-product at the preparation of **2d**.

Scheme 1.

under nitrogen. During purification of the yellow crude products reconversion to chalcone **1** was also observed. This fact indicates that some of the first steps of the reaction should be reversible.

When reaction of **1** was carried out with 6.5 equiv. of methylhydrazine in methanol below 40 °C, the main product was **2e**. In the next experiment, the solvent was changed to toluene, and solution of methylhydrazine (5.5 equiv.) was added to the boiling solution of **1** in two portions. In that case the main product was the "reverse" pyrazoline **4e** and during the reaction the amount of **5e** was gradually increasing. During purification by column chromatography this spontaneous dehydroaromatisation process was continued, affording **5e** in 58% yield, while **4e** was isolated in pure form only in 8% yield. The regioisomeric **2e** and **3e** were present only in a fewer amount. Our observations suggest that 1-methyl-3-ferrocenyl-pyrazoline **4e** is formed under thermodynamic control.

2.1.1. DFT study on cyclization reactions

In order to propose reaction mechanisms being in accord with our experimental observations, four possible pathways (A–D, Scheme 2) were taken into account for the formation of pyrazolines with alternative substitution patterns. On the basis of our earlier results [15] it can be assumed that cyclizations conducted at lower temperature in protic media take place along pathway A *via* the fast orbital-controlled conjugate addition of the substituted nitrogen leading to β-adducts type **I** of which cyclization and subsequent dehydration result in 3-ferrocenyl-pyrazolines (**I** → **V** → **2a**–**e**, **7a**,**b**). By means of theoretical modelling of simplified models (1-arylprop-2-en-1-ones) we have earlier shown [15] that kinetically controlled cyclization of neutral chalcones with methylhydrazine proceeds through β-adducts analogous to **I**. Following the same way of interpretation, employing simple FMO theory [23] within the frame of DFT [24] which proved to be sufficient to account for positional selectivity [15,25], the local electrophilicity inside the enon moiety was characterized by the relevant LUMO electron deficiency values concentrated on the potential electrophilic centra (Σc^2_{LUMO} on C-β and *C*═O) in the optimized structure of **1** obtained at B3LYP level of theory [26] using 6−31G(d,p) basis set [27]. In keeping with our preparative experiments, the results (Σc^2_{LUMO} = 0.193 for C-β and 0.150 for *C*═O) suggest that **1** has increased reactivity on the β-carbon atom in the orbital-controlled [28] addition towards the more nucleophilic methylated nitrogen of methylhydrazine (Σc^2_{HOMO} = 0.244 on NHMe and 0.076 on NH_2 as calculated by the same method).

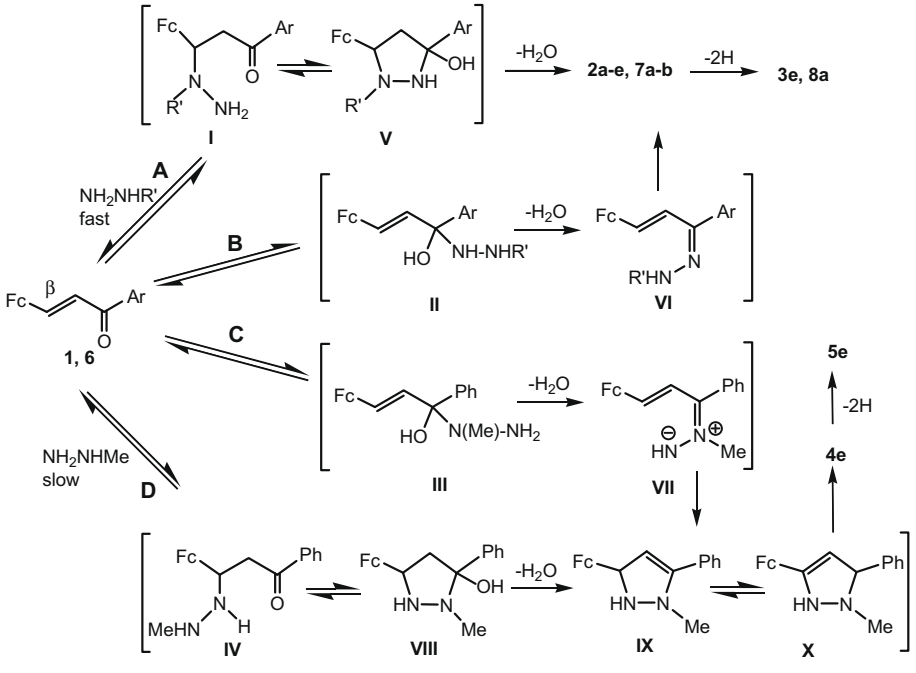
Corroborating with the formation of **4e** at elevated temperature, the free energy data obtained for the primary adducts (**I**–**IV**, R′ = Me, Ar = Ph, Scheme 2, Table 1) suggest that under thermodynamic control the reaction of **1** and methylhydrazine must proceed along pathway D *via* the most stable adduct **IV** with slightly increased entrophy resulted from nucleophilic attack of the NH_2 group on the β-carbon atom, which undergoes cyclocondensation and sequentional tautomerization affording the pyrazoline with reversed substitution pattern (**IV** → **VIII** → **IX** → **X** → **4e**). The relative free energy values also demonstrate that allyl alcohol type intermediates **II** and **III** formed upon the addition on the carbonyl group of **1** are less stable by ca 55–75 kJ/mol than the β-adducts referring to the little contribution of pathways **1** → **II** → **VI** → **2e** and **1** → **III** → **VII** → **4e**, respectively, to the formation of pyrazoline products.

In principle alternative pathways B and C can not be ruled out completely for the formation of **2a**–**e, 7a**,**b** and **4e**, respectively, but they might play only negligible roles in these cyclization reactions.

The regioisomeric pyrazolines (**2e** and **4e**), both in crude mixture or in isolated crystalline form, were transformed into the corresponding pyrazole compounds (**3e** and **5e**) with DDQ in good yield.

It is noteworthy, that pyrazoline → pyrazole transformation was also observed during MS measurements of several models (see later).

In order to get new ferrocenyl-aryl-heterocycles having functionalisable groups at the phenyl moiety and also for biological purposes, some further pyrazoline derivatives were prepared. From 3-ferrocenyl-1-(*p*-hydroxyphenyl)-prop-2-en-one (**6**) [14] with 4.5 equiv. of phenylhydrazine in boiling acetic acid–ethanol–water mixture the *N*-phenyl-5-ferrocenyl-pyrazoline derivative (**7a**) was



Ar = Ph, *p*-HO-Ph; R' = H, Me, Ph, *p*-NO_2-Ph, α-Py

Scheme 2.

Table 1
Free energy-, entrophy- and ZPE[a] values of **I–IV** (Ar = Ph).[b]

	G (au)	*S* (cal/molK)	*G*–*G*(**III**) (kJ/mol)	ZPE (kJ/mol)
I	−2223.387466	156.85	−63.89	999.66
II	−2223.371006	158.92	−8.43	996.82
III	−2223.367793	156.98	0	996.57
IV	−2223.392133	162.51	−76.14	997.91

[a] Zero-point energy.
[b] Calculated by B3LYP/6-31G(d,p).

formed as main product in 58% yield and the corresponding pyrazole (**8a**) was isolated as minor product in 6.3% yield. The 5-ferrocenyl-3-(*p*-hydroxyphenyl)-pyrazoline **7a**, on standing at RT, slowly decomposes, but in refrigerator in inert atmosphere it could be stored for longer time. Acetylation of **7a** with acetic anhydride in pyridine at 0 °C led to the corresponding 5-ferrocenyl-3-(*p*-acetoxyphenyl)-pyrazoline (**7b**) as stable product in good yield. In a similar way, reaction of **6** with *p*-nitrophenylhydrazine or with 2-hydrazinopyridine and subsequent acetylation of the crude products resulted in the corresponding stable 5-ferrocenyl-3-(*p*-acetoxyphenyl)-pyrazolines **9b** and **10b**. Pyrazoline **7b** was converted to the corresponding pyrazole **8b** with 1.8 equiv. of DDQ, by refluxing in benzene, in good yield (72%). The structures of all new compounds were determined by NMR, IR, MS and in case of compounds **2d** and **8a** also by X-ray diffraction.

2.2. Structures and spectroscopy

2.2.1. NMR spectroscopy

The structures of the new compounds follow from the spectral data (Tables 2–4) straightforwardly. Only a few additional remarks are necessary:

The methyl singlet of the acetyl group in the ^{1}H NMR spectrum of **3b** is downfield-shifted by 0.61 ppm compared to **2b** as a consequence of the acidic character (−*I*-effect) of N−1 in the heteroaromatic pyrazole ring, while this N atom has a slightly basic nature in the pyrazoline ring. The same reason explains the high frequency of the amide-I band of **3b** (1735 cm^{-1}, while this band is at 1649 cm^{-1} in the IR spectrum of **2b**.)

The N-methyl ^{1}H NMR signal of **3e** and **5e** is also significantly downfield-shifted, which is characteristic of heteroaromatic systems [29a] relative to **2e** (by 1.31 and 1.14 ppm) or **4e** (by 1.40 and 1.23 ppm). The difference (upfield-shift in **4e** and **5e** by 0.09 and 0.17 ppm) between the regioisomeric pairs **2e**–**4e** and **3e**–**5e** is due to the anisotropic shielding [29b] of the benzene ring in pos. 5 in **4e** and **5e**.

The C/H−2′,5′ and C/H−3′,4′ atom pairs give separated signals for pyrazolines (except for ^{1}H NMR signals of **2a**,**b** because of accidental isochrony [29c]) due to molecular asymmetry (C−5, for **11** also C−4 are chiral centra).

The C−1′ chemical shift is significantly higher for pyrazolines (86–91 ppm, while 75.4 ± 0.2 ppm for pyrazoles) in accord with the literature, because of the different α-effects [29d,30] of sp^3 and sp^2 carbon substituents [31]. The only irregular shift (78.3 ppm) of **4e** is a further proof of the isomeric structure. In accord, the C−1 line of the 5-phenyl group is also downfield-shifted as the consequence of sp^3-type carbon-substituent (141.5 ppm, while all other compounds have line in the 122.4–134.2 ppm interval).

The structure of **11** was deduced from the following facts:

Apart from the signals of the phenyl, *para*-nitro-phenyl and ferrocenyl substituents, three hydrogens are present in this molecule one of which is a hydroxyl-H (as proved by the HMQC measurement and the broad shape of its doublet signal in the ^{1}H NMR spectrum). The doublet split of this signal confirms the presence of a CHOH group in accordance with the downfield-position of the C-line (69.7 ppm). Here, it is to be noted, that the assignments of the pyrazoline C's and H's were proved by HMQC and

Table 2
^{1}H NMR data[a] of compounds **2a–e**, **3b–e**, **4e**, **5e**, **7a**,**b**, **8a**,**b**, **9b**, **10b** and **11**.[b]

Compound	CH_3[c] *s* (3H)	CH_2 (Pos. 4)[d]	H−5[e]	H−2′,5′	H−3′,4′	H−1−5	H−2′,6	H−3,5	H−4	H−2,6	H−3,5	H−4	OH *s* (1H)
		Pyrazoline ring		Substituted Cp ring		Cp[f]	3/5-Phenyl/aryl group[g]			N-aryl/α-pyridyl ring[h]			
2a	–	3.05, 3.34	5.85	4.67	4.15	4.21	7.67	∼7.4[i]	–	–	–		
2b	2.19	3.56, 3.82	5.37	4.39	4.14	4.18	7.87	∼7.5[i]	–	–	–	–	
2c	–	3.78, 3.82	5.06	4.15[i], 4.24	4.15[i]	4.17	7.86	7.47	7.39	7.22	7.27	6.85	–
2d	–	3.85, 4.04	5.49	4.21, 4.58	3.91, 4.13	4.24	7.94	7.53	7.49	7.24	8.07		–
2e	2.67	3.15, 3.57	3.91	4.25, 4.33	∼4.19	4.22	7.68	7.39	7.33	–	–	–	–
3b	2.80	6.85	–	4.72	4.36	4.16	7.90	7.47	7.41	–	–	–	–
3c	–	6.85	–	4.22[i]		4.12	7.95	7.45[i]	7.36	∼7.45[i]		7.42	–
3d	–	6.93	–	4.32	4.28	4.18	7.93	7.47	7.39	7.56	8.21	–	–
3e	3.98	6.82	–	4.68	4.40	4.19	7.80	7.39	7.28	–	–	–	–
4e	2.58	2.81, 3.34	3.94	4.52, 4.55	4.33	4.17	7.47	7.38	7.30	–	–	–	–
5e	3.81	6.53	–	4.65	4.25	4.05	7.56	7.50	7.44	–	–	–	–
7a	–	3.68, 3.86	5.13	3.96, 4.42	4.10, 4.15	4.22	7.70	6.88	–	7.09	7.17	6.70	9.80
7b	2.30	3.74, 3.92	5.23	3.98, 4.44	4.10, 4.15	4.23	7.88	7.24	–	7.13	7.18	6.73	–
8a	–	7.01	–	4.27	4.20	4.13	7.71	6.54	–	7.41	7.52	7.49	9.53
8b	2.32	6.79	–	4.21[i]	4.19[i]	4.09	7.92	7.16	–	∼7.42[i]			–
9b	2.22	3.57, 3.77	5.52	3.91, 4.47	3.97, 4.02	4.12	7.83	7.17	–	7.16	7.46	6.61	–
10b	2.22	3.75, 3.96	5.40	3.84, 4.49	4.03, 4.11	4.15	7.89	7.15	–	7.20	7.98	–	–
11	–	5.86	4.95	3.87, 4.34	4.15, 4.25	4.17	8.02	7.45	7.50	7.19	8.12	–	2.44[k]

[a] In $CDCl_3$ (**2a,c**, **3b–d**, **8b** and **11**) or DMSO-d_6 (**2b**,**d**,**e**, **3e**, **4e**, **5e**, **7a**,**b**, **8a, 9b** and **10b**) solution at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz.
[b] Assignments were supported by HMQC (except for **3b**,**e**) and for **2a**,**b** and **7a** also by COSY measurements.
[c] Acetyl (**b**-type compounds) or N-methyl group (**e**-type compounds).
[d] Two *dd*'s (2 × 1H), ^2J: 17.9 ± 0.1 (**2b–d**), 16.2 (**2e**, **4e**), 17.3 (**7a**,**b**), 17.7 (**9b**), ^3J (upfield *dd*): 4.0 ± 0.2 (**2b**,**d**), 6.0 (**2c**), 13.6 (**2e**), 14.6 (**4e**), 5.2 (**7a**,**b**), 4.5 (**9b**), ^3J (downfield *dd*): 11.5 ± 0.2 (**2b–d**, **7a**,**b**, **9b**), 9.8 (**2e**, **4e**), coalesced to ∼*d* and ∼*t* (**2a**, **10b**), ∼*d* for **11**, *J*: ∼8, *s* (1H) for pyrazoles (**3b–e**, **5e**, **8a**,**b**).
[e] *dd* (1H), coalesced to ∼*d* (**10b**), *d*, *J*: 1.5, (**11**).
[f] Unsubstituted cyclopentadiene ring.
[g] Pos. 5 for **4e** and **5e.**
[h] H-3-5 signals (α-pyridyl, ∼*d*, ∼*dt*, ∼*t*) for **9b,** H−6: 8.05, ∼*d*.
[i] Coalesced signals.
[k] ∼*d*, *J*: ∼8.

Table 3
^{13}C NMR chemical shifts (in ppm, $\delta_{TMS} = 0$ ppm)[a] of compounds **2a–e**, **3b–e**, **4e**, **5e**, **7a**,**b**, **8a**,**b**, **9b**, **10b** and **11**.[b,c]

Compound	CH_3[d]	C–3	C–4	C–5	C–1′	C–2′,5′	C–3′,4′	C–1–5 *Cp*[e]	C–1	C–2,6	C–3,5	C–4	C–1	C–3,5	C–3,5	C–4
		Pyrazoline ring			Substituted *Cp* ring				3-/5-Phenyl/aryl group[f]				N-phenyl/α-pyridyl[g] ring			
2a	–	151.7	40.7	59.6	90.9	66.4, 66.8	68.5, 68.7	68.9	133.4	126.5	128.9	129.1	–	–	–	–
2b	22.6	155.4	40.0	55.9	88.2	66.6, 70.9	68.5, 68.6	69.4	132. 2	127.5	129.7	131.1	–	–	–	–
2c	–	147.8	42.6	59.8	91.0	68.5, 68.8	67.4, 68.1	69.1	133.3	126.2	129.1	129.0	145.8	114.6	129.2	119.7
2d	–	154.1	42.4	58.8	88.9	66.5, 70.1	68.6, 69.2	69.6	132.3	127.4	129.8	130.8	149.3	113.2	126.5	138.5
2e	41.5	149.8	40.4	68.9	86.0	66.8, 70.3	68.6, 69.0	69.4	133.8	126.5	129.4	129.2	–	–	–	–
3b	24.6	153.4	109.6	146.8	75.4	69.3	69.13	70.3	132.3	126.6	129.2	129.5	–	–	–	–
3c	–	152.1	104.2	143.5	75.3	69.05[h]	69.13[h]	70.3	133.6	126.2	129.0[i]	128.3[i]	140.5	126.7	129.2[i]	128.5[i]
3d	–	153.4	107.4	143.7	75.6	69.5	70.1	70.5	132.9	126.4	129.2	128.9	145.4	125.3	124.6	146.4
3e	38.9	149.4	103.4	142.8	75.4	68.7	69.7	70.2	134.2	125.8	129.4	128.2	–	–	–	–
4e	42.4	150.9	45.0	73.5	78.3	67.3, 67.6	70.0, 70.1	69.96	141.5	128.3	129.4	128.4	–	–	–	–
5e	38.3	149.3	104.4	144.5	79.9	67.1	68.9	70.1	131.1	129.3	129.7	129.2	–	–	–	–
7a	–	149.1	42.5	59.2	90.5	66.9, 70.1	68.1, 68.7	69.5	124.4	128.3	116.5	159.1	145.9	114.3	129.5	119.0
7b	21.8	147.8	42.2	59.7	90.1	66.9, 70.3	68.1, 68.9	69.5	131.0	127.7	123.1	151.5	145.4	114.7	129.6	119.6
8a	–	151.6	104.1	143.4	75.5	69.4	68.0	70.5	124.9	127.5	116.2	158.2	141.1	127.2	129.8	129.1
8b	21.6	151.3	104.1	143.6	75.2	69.07[h]	69.11[h]	70.3	131.5	126.7	122.1	150.8	140.8	127.3	129.2	128.6
9b	21.8	150.6	40.4	57.7	89.0	66.9, 71.3	68.4	69.4	130.7	128.1	123.1	151.9	156.1	109.5	138.1	115.1
10b	21.8	153.4[h]	42.4	58.9	88.8	66.5, 68.5	69.2, 70.3	69.7	129.9	128.6	123.3	152.5[h]	149.2[h]	126.5	113.2	138.5
11[k]	–		83.4	67.9	~85	66.8, 68.5	68.8, 69.0	69.2		126.2	129.6	130.4		126.9	113.0	

[a] In $CDCl_3$ (**2a**,**c**, **3b–d**, **8b** and **11**) or DMSO-d_6 (**2b**,**d**,**e**, **3e**, **4e**, **5e**, **7a**,**b**, **8a**, **9b** and **10b**) solution at 125 MHz.
[b] Assignments were supported by DEPT (except for **3e** and **11**), HMQC (except for **3b**,**e**) and HMBC (except for **2a**,**b**, **9b** and **10b**) measurements.
[c] Further signals: C=O: 170.9 (**3b**), 170.0 (**7b**, **9b** and **10b**), 169.8 (**8b**).
[d] Acetyl (**b**-type compounds) or N-methyl group (**e**-type compounds).
[e] Unsubstituted cyclopentadiene ring.
[f] Pos. 5 for **4e** and **5e.**
[g] α-Pyridyl (**9b**): C–2 - C–5, C–6: 148.1.
[h] Interchangeable assignments.
[i] Due to the low concentration of the measured solution the lines of quaternary carbons were not identifiable in the ^{13}C NMR spectrum.

Table 4
Characteristic IR frequencies [cm^{-1}] of compounds **2a–e**, **3b–e**, **4e**, **5e**, **7a**,**b**, **8a**,**b**, **9b**, **10b** and **11** (in KBr discs).

Compound	*ν*C=O band[a]	$\nu_{as}NO_2$ and ν_sNO_2 band	*ν*C–O band	$\gamma C_{Ar}H$ band[b]	$\gamma C_{Ar}H$ band[b]	$\gamma C_{Ar}C_{Ar}$band[c]	ν_{as}Cp–Fe–Cp and tilt of Cp
2a	–	–	–	–	745	695	508, 490
2b	1649	–	–	–	762	691	510, 487, 462
2c	–	–	–	–	746, 758	707, 690	500, 484
2d	–	1595, 1318	–	836	763, 749	693	487
2e	–	–	–	–	761	696	490
3b	1735	–	–	–	769	693	502, 478
3c	–	–	–		764	694	503
3d	–	1519, 1341	–	854	769	690	501
3e	–	–	–	–	768	695	504
4e	–	–	–	–	774	702	509, 486
5e	–	–	–	–	775	706	509, 487
7a	–	–	–	833	751	693	496
7b	1761	–	1198, 1103	845	752	691	496, 479
8a	–	–	1263, 1236	836	767	698	505, 485
8b	1750	–	1215, 1203, 1017	851	767	690	532, 503
9b	1751	–	1195, 1008	855	913[d]	764[d]	512, 492
10b	1753	–	1198, 1002	840	–	–	526, 490
11	–	1507, 1495, 1305	–	834	–	–	489

Further bands: *ν*NH: 3308, sharp (**2a**), ~3420, broad (**7a**), 3600–3000, diffuse (**8a**), ~3400, broad (**11**).
[a] Amide (**2b**, **3b**) or ester group (**7b**, **8b**, **9b**, **10b**).
[b] *Para-di-* or *mono*-substituted benzene.
[c] *Mono*-substituted benzene.
[d] α-Pyridyl group.

HMBC measurements. e.g., The C–4 line (at 83.4 ppm) has long-range coupling to the *ortho*-H's of the phenyl group at 8.02 ppm. The downfield-position of the latter signal is proof of the conjugation of the phenyl with the C=N double bond.

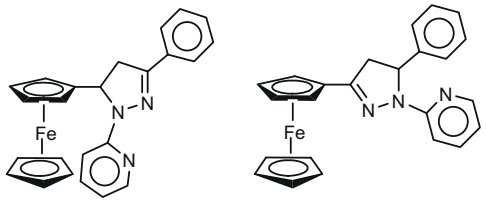
Taking the coupling between H–4 and H–5 and the C–1′ shift of the substituted Cp ring (confirming sp^3-type carbon-substitution) into consideration the structure of this intermediate is unambiguous.

It is noteworthy that the quaternary carbon lines, due to very low concentration of the solution of **11**, were not identifiable, however, the HMBC cross peaks to H–4 and H–2′,5′ enable us to determine the approximately position of line C–1′.

2.2.2. Electron impact mass spectrometry

The electron impact (EI) mass spectra of ferrocenyl pyrazolines and ferrocenyl pyrazoles were also recorded. Among them we comparatively studied regioisomeric pairs of some pyrazolines (**2e**, **4e** and **13a**, **13b** [7], see Schemes 1 and 3), as well as pyrazoles (**3e**, **5e**). For ferrocenyl–pyrazolines, including **2a–c**, were previously published MS data [32], but to our knowledge, no reports have appeared on ferrocenyl–pyrazoles.

In the mass spectra of ferrocenyl pyrazolines the molecular ion is present. These substances show medium fragmentation, mostly dominated by fragments due to the ferrocene moiety. Although there is no universal rule for any fragmentation pathways, a com-



Scheme 3.

mon spectral feature is the presence of a peak at 186 amu, which can be assigned to the ferrocene ion (FcH^+). This peak is absent in the spectra of ferrocenyl–pyrazoles. The $[M-2]^+$ ion can be found and in most cases is more intensive than that according to the ^{54}Fe isotope containing ion. The hydrogen molecule loss is rather unusual in EI MS. To clarify this point, energy dependent measurements were performed for compound **2c.** Varying the electron energy from 6 to 75 eV there is a strong dependence of the intensity of the $[M-2]^+$ ions peak on electron energy: at the lowest energies no fragmentation occurs, i.e. the $[M-2]^+$ peak is absent, then the intensity rises to a maximum after which it tends to a lower constant value, as other fragmentation pathways start up. Fig. 1 shows the energy dependence of some common peaks of ferrocenyl–pyrazolines.

An important question related to the studied molecules is the possibility to discriminate 5-ferrocenyl and 3-ferrocenyl compounds. The appearance of the ions at 212 ($FcC_2H_3^+$) or 211 ($FcCN^+$) amu is a good method to distinguish these compounds. $FcC_2H_3^+$ appears in case of 5-ferrocenyl-pyrazolines, whereas $FcCN^+$ is typical for 3-ferrocenyl compounds. Information about N−1 substitutent of the ring is given by the loss of the R′NH moiety, which usually occurs from the molecular ion.

Ferrocenyl pyrazoles show low degree of fragmentation. As mentioned before, the ferrocene ion is not present. In the case of pyrazoles it is hard to differentiate between 5-ferrocenyl and 3-ferrocenyl compounds. One difference between them is that 3-ferrocenyl-pyrazoles have higher degree of fragmentation than the isomer 5-ferrocenyl ones. Another way to distinguish these compounds is the appearance of the FcC_2H^+ ion at 210 amu in case of 5-ferrocenyl-pyrazoles, but usually it is of low intensity.

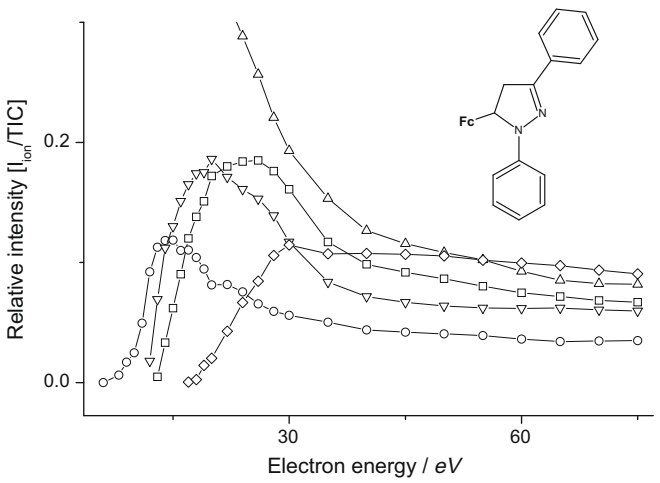


Fig. 1. Energy dependence of the intensity of some peaks of **2c** (△ – M^+, ○ – $[M-2]^+$, □ – $FcC_2H_3^+$, ▽ – FcH^+, ◇ – $CpFe^+$).

2.2.3. X-ray studies

X-ray crystal structure analysis of **2d** and **8a** revealed the structures depicted in Figs. 2 and 3, respectively. The selected bond parameters are listed in Table 5.

In both crystal structures the two cyclopentadienyl rings (C1–C2–C3–C4–C5 and C6–C7–C8–C9–C10) of the ferrocene moiety are parallel, the plane angle between them is 4.4(3)° in **2d** and 1.0(9)° in **8a**. The conformation of the ferrocene in both molecules is eclipsed.

The molecules of **2d** have chirality, but in the crystal there was a racemate. The conformation of N1 atom is nearly planar, as it also can be seen from the NMR shifts and from the sum of angles (356.9°). And because of this nitrogen atom planarity the pyrazoline ring is almost planar, it has only a little envelope structure with the C11 atom on the tip (0.125 Å above the plane of the other four atoms of the ring). The angle between the least-squares planes of the pyrazoline and the *p*-nitrophenyl rings is 16.8(4)°, and between pyrazoline and phenyl rings is 12.9(4)°.

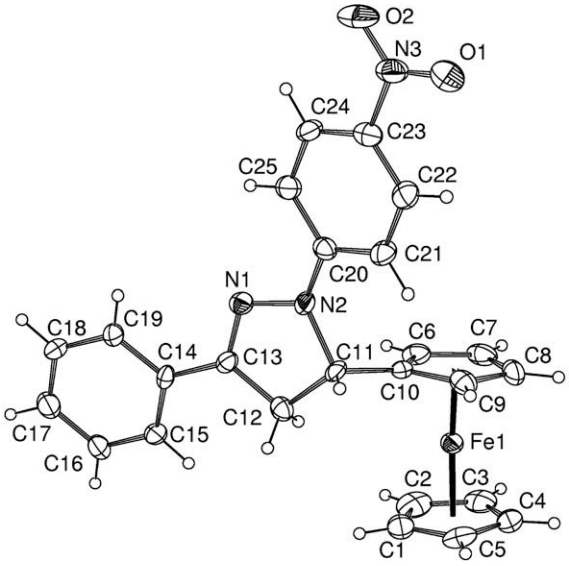


Fig. 2. The ortep drawing of compound **2d** (the ellipsoid probability is 30%). Only non-hydrogen atoms are labelled.

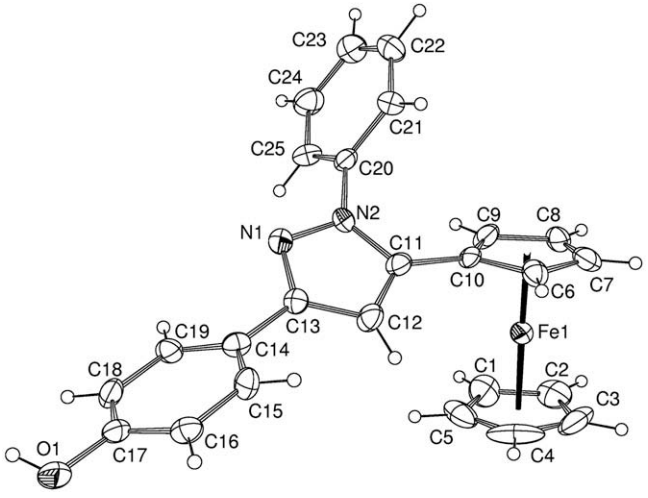


Fig. 3. The ortep drawing of compound **8a** (the ellipsoid probability is 30%). Only non-hydrogen atoms are labelled.

Table 5
Selected bond lengths, angles and torsion angles for **2d** and **8a.**

		2d	8a			2d	8a
Bond lengths [Å]	O(1)–C(17)		1.370(15)	Bond lengths [Å]	N(2)–C(20)	1.367(7)	1.413(16)
	C(23)–N(3)	1.480(8)			C(10)–C(11)	1.497(8)	1.475(16)
	N(1)–C(13)	1.303(6)	1.331(15)		C(13)–C(14)	1.438(8)	1.474(16)
	N(1)–N(2)	1.392(6)	1.368(13)		C(12)–C(13)	1.483(8)	1.396(16)
	N(2)–C(11)	1.504(7)	1.374(14)		C(11)–C(12)	1.548(8)	1.376(17)
	Compound	2d	8a		Compound	2d	8a
Angles [°]	C(13)–N(1)–N(2)	109.0(5)	105.5(10)	Torsion angles [°]	C(13)–N(1)–N(2)–C(11)	2.5(6)	−1.4(14)
	N(1)–N(2)–C(11)	113.0(4)	110.8(10)		C(13)–N(1)–N(2)–C(20)	163.9(5)	−178.5(11)
	N(1)–C(13)–C(12)	112.6(6)	111.2(11)		N(2)–N(1)–C(13)–C(12)	3.2(7)	0.8(14)
	N(1)–C(13)–C(14)	121.8(6)	120.7(11)		N(2)–N(1)–C(13)–C(14)	−178.3(5)	−176.6(11)
	C(12)–C(13)–C(14)	125.6(5)	128.0(12)		C(15)–C(14)–C(13)–N(1)	−168.0(6)	−144.3(13)
	C(11)–C(12)–C(13)	105.4(5)	105.9(12)		C(19)–C(14)–C(13)–N(1)	15.4(9)	37.5(18)
	N(2)–C(11)–C(12)	99.3(5)	106.5(11)		N(1)–N(2)–C(20)–C(25)	15.5(8)	−59.8(17)
	N(2)–C(11)–C(10)	110.8(5)	123.4(12)		N(1)–N(2)–C(20)–C(21)	−162.7(5)	120.9(13)
	C(12)–C(11)–C(10)	115.6(5)	129.8(11)		C(22)–C(23)–N(3)–O(1)	−0.8(9)	

In **8a** the aromatic character of the pyrazole moiety can be seen from the planarity of the ring and from the bond distances in it (see Table 5.). The extended conjugation including the cyclopentadienyl, pyrazole and the two phenyl moieties cannot realize because of sterical effects. The angle between the least-squares planes of the central pyrazole and the 4-hydroxy-phenyl rings is 37.4(6)°, and between the pyrazole and the phenyl rings is 57.8(6)°. In the crystals of **8a** the planar chirality appears, because of this the space group is acentric ($P2_12_12_1$).

The main crystal building forces are the dispersion interactions between the ferrocene and phenyl moieties, and the hydrogen bonds. In the crystal of **2d** the hydrogen bonded molecules (between C19–H19 and O2 [$2-x$, $1-y$, $1-z$] atoms) form dimers, while in the crystal of **8a** (hydrogen bond between the O1–H1A and N1 [$-x+1.5$, $-y+2$, $z-0.5$] atoms) these molecules form H-bonded chain. The parameters of the hydrogen bonds are summarized in Table 6. In both cases there are distinct layers of the apolar ferrocenes and the other three rings of the molecules, but in **2d** perpendicular, in **8a** parallel to the *ac* plane of the unit cell.

3. Experimental

General: IR spectra were recorded with a Bruker IFS-55 FT-spectrometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained at 500 and 126 MHz by a Bruker DRX-500 spectrometer in $CDCl_3$ or DMSO-d_6 solution, with the deuterium signal of the solvent as the lock and Me_4Si as internal standard. The standard Bruker micro program NOEMULT.AU to generate NOE was used with a selective pre-irradiation time. DEPT spectra were run in a standard manner, using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-HMQC spectra were obtained by using the standard Bruker pulse program HXCO.AU.

Electron impact mass spectra (70 eV) were recorded on a Kratos MS-80 and a Fisons TRIO 1000 mass spectrometer using direct evaporation. The source temperature was between 200 and 230 °C. During the energy dependent measurement the source temperature was kept at 80 °C and the electron energy varied from 6 to 75 eV. In the case of compounds **2e**, **4e** and **8b** the fragment compositions were confirmed by accurate mass measurements.

The X-ray measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of carefully centred reflections. The crystals of **2d** and **8a** were mounted on a glass fibre. The data were collected at a temperature of 293 K using the ω/2θ scan technique. Crystal data for **2d**: $C_{25}H_{21}FeN_3O_2$, Fwt: 451.3, yellow plate, size: $0.5 \times 0.3 \times 0.1$ mm, monoclinic, space group $P2_1/n$ (No. 14), $a = 17.347(2)$ Å, $b = 6.000(4)$ Å, $c = 19.524(2)$ Å, $\beta = 94.98(1)°$, $V = 2024(1)$ Å^3, $Z = 4$, DC = 1.481 Mg/m^3, 3628 reflections, 3503 unique and $1344 > 2\sigma(I)$. Crystal data for **8a**: $C_{25}H_{20}FeN_2O$, Fwt: 420.2, orange plate, size: $0.75 \times 0.25 \times 0.07$ mm, orthorombic, space group $P2_12_12_1$ (No. 19), $a = 13.04(2)$ Å, $b = 25.17(2)$ Å, $c = 5.94(2)$ Å, $V = 1949(6)$ Å^3, $Z = 4$, DC = 1.432 Mg/m^3, 3818 reflections, 3221 unique and $1195 > 2\sigma(I)$. Data processing was carried out by use of the software supplied with the diffractometer. The linear absorption coefficient, μ, for Cu Kα radiation is 6.202 mm^{-1} for **2d** and 6.345 mm^{-1} for **8a**. An empirical absorption correction based on azimuthal scans of several reflections was applied. Structure solutions with direct methods were carried out with the teXsan Crystal Structure Analysis Package [33]. Refinements were carried out using the SHELXL-97 [34] program by the full matrix, least-squares method on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated based upon geometric evidence and their positions were refined by the riding model. The final $R_1 = 0.0545$ and $wR^2 = 0.1238$ for $3503 > 2\sigma(I)$ intensity data, number of parameters = 281, goodness-of-fit = 0.91 for **2d**. The final $R_1 = 0.0810$ and $wR_2 = 0.1874$ for $1195 > 2\sigma(I)$ intensity data, number of parameters = 263, goodness-of-fit = 0.93, absolute structure parameter Flack $x = 0.021(17)$ [35] for **8a**.

TLC was performed on aluminium plates precoated with Silica gel 60 F_{254} (E. Merck) and were developed with solvent or solvent mixtures: *A*, CH_2Cl_2; *B*, 7:3 *n*-hexane–EtOAc; *C*, 95:5 CH_2Cl_2–EtOAc; *D*, 4:1 CH_2Cl_2–EtOAc, the spots were detected visually or by UV light at 254 nm and 366 nm, respectively. Column chromatography was made on Silica gel (E. Merck, 0.020–0.043 mesh). M.p. data were measured in capillary tubes and are not corrected.

Syntheses: Formylferrocene, *p*-hydroxyacetophenone, phenylhydrazine, methylhydrazine, *p*-nitrophenylhydrazine, 2-hydrazinopyridine, *N*-bromo-succinimide and DDQ were purchased from Sigma–Aldrich. Procedures for the preparation of 3-ferrocenyl-1-aryl-prop-2-en-1-ones **1** [7,36] and **6** [14], respectively, were described earlier. Compounds **2a–c** were prepared by modification of known procedures [18].

Table 6
Hydrogen–bonds in **2d** and **8a.**

Donor–H···Acceptor	*d* (D–H)	*d* (H···A)	*d* (D···A)	<(D–H···A)
C19–H19···O2 (a) in **2d**	0.93	2.60	3.232(8)	125.4
O1–H1A··· N1 (b) in **8a**	0.82	2.09	2.898	167.2

Symmetry transformations: (a) $-x+2$, $-y+1$, $-z+2$; (b) $-x+1.5$, $-y+2$, $z-0.5$.

3.1. 5-Ferrocenyl-3-phenyl-4,5-dihydro-1H-pyrazole (**2a**)

To a stirred suspension of **1** (1.22 g, 3.86 mmol) was added dropwise 55% aqueous solution of hydrazine hydrate (16 mL) and the mixture was refluxed for 2.5 h, filtered and cooled. The separated pale yellow crystals of **2a** were filtered and washed with cold ethanol. Yield 1.15 g (90%), m.p. 105–107 °C (decomp.). In our experience, compound **2a** can be stored without decomposition for years in refrigerator. MS: 330 (100) $[M^+]$, 328(19) $[M-2]^+$, 314(6) $[M-R'NH]^+$, 265(4) $[M-C_5H_5]^+$, 263(5) $[M-2-C_5H_5]^+$, 227 (12) $[M-RPhCN]^+$, 212(34) $[FcC_2H_3]^+$, 186(51) $[FcH]^+$, 121(49) $[CpFe]^+$, 56(25) $[Fe]^+$.

3.2. 1-Acetyl-5-ferrocenyl-3-phenyl-4,5-dihydro-1H-pyrazole (**2b**)

3.2.1. Procedure A

To a cooled solution of acetic anhydride (0.8 mL) in dry pyridine (1 mL) was added compound **2a** (0.109 g, 0.33 mmol) and the mixture was stirred at 0 °C for 5 h, and then it was allowed to stand in refrigerator for 24 h. The solution was poured into ice–water and the solidified crude product (0.112 g, 91.1%) was purified by column chromatography using dichloromethane as eluent. Crystallization from ethanol gave yellow crystals of pure **2b** (0.094 g, 76.5%), m.p. 184–185 °C, R_f 0.24 (solvent *A*), lit. m.p. 180–181 °C [18b]. For an alternative recent preparation and X-ray data of **2b** see [12b] with lit. m.p. 184–185 °C. MS: 372(100) $[M^+]$, 370(8) $[M-H_2]^+$, 307(58) $[M-C_5H_5]^+$, 288(1) $[M-42]^+$, 287(8) $[M-43]^+$, 269(26) $[M-RPhCN]^+$, 212(4) $[FcC_2H_3]^+$, 186 (5) $[FcH]^+$, 121(23) $[CpFe]^+$, 56(15) $[Fe]^+$.

3.2.2. Procedure B

Realizing the reaction in larger scale, in some cases crystals of **2b** were spontaneously separated from the reaction mixture. After filtration and washing with cold ethanol–water (7:3), pure product was obtained in ~55% yield. The mother liquor of the reaction was worked up, as described in Section 3.2.1, resulting in further crop of **2b**, total yield 75%.

3.3. 5-Ferrocenyl-1,3-diphenyl-4,5-dihydro-1H-pyrazole (**2c**)

3-Ferrocenyl-1-phenyl-prop-2-en-1-one (**1**, 1.51 g, 4.77 mmol) and phenylhydrazine (1.75 g, 16.2 mmol) was added to a mixture of abs. ethanol (22 mL), dist. acetic acid (15 mL) and water (5 mL) and the reaction was boiled for 4 h under argon, by protecting from light. The separated yellow product was washed with cold ethanol–water and recrystallized from ethanol–water, to give pure **2c** as yellow needles (1.47 g, 76%), m.p. 158–159 °C; R_f 0.92 (solvent *A*). Anal. Calc. for $C_{25}H_{22}FeN_2$ (406.31): C, 73.90; H, 5.46; N, 6.89. Found: C, 73.45; H, 5.79; N, 6.73%. MS: 406(100) $[M^+]$, 404(39) $[M-H_2]^+$, 376(2) $[M-30]^+$, 374(8) $[M-30-2]^+$, 341(4) $[M-C_5H_5]^+$, 339(6) $[M-H_2-C_5H_5]^+$, 314(26) $[M-R'NH]^+$, 285(3) $[M-FeCp]^+$, 283(2) $[M-H_2-FeCp]^+$, 249(28) $[M-C_5H_5-R'N]^+$, 212(86) $[FcC_2H_3]^+$, 186(53) $[FcH]^+$, 121(97) $[CpFe]^+$, 56(29) $[Fe]^+$.

3.4. 5-Ferrocenyl-1-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole (**2d**)

3-Ferrocenyl-1-phenyl-prop-2-en-1-one (**1**, 1.00 g, 3.16 mmol) and 4-nitrophenylhydrazine was boiled in a mixture of ethanol (15 mL), distilled acetic acid (22 mL) and water (3 mL) for 3 h under argon, while TLC (solvent *A*) indicated complete reaction. After cooling dark yellow crystals separated, which were filtered and washed with cold ethanol–water to give pure **2d** (1.045 g, 73%). From the mother liquor further crop of **2d** was isolated and purified by column chromatography using dichloromethane as eluent, total yield 81%; m.p. 225–226 °C; R_f 0.85 (solvent *A*). Anal. Calc. for $C_{25}H_{21}FeN_3O_2$ (451.31): C, 66.53; H, 4.69; N, 9.31. Found: C, 66.35; H, 4.81; N, 9.43%. MS: 451(91) M^+, 449(23) $[M-H_2]^+$, 419(55), 314(29) $[M-R'NH]^+$, 248(23) $[M-C_5H_5-R'N]^+$, 212(100) $[FcC_2H_3]^+$, 210(26) $[FcC_2H]^+$, 186(73) $[FcH]^+$, 121(93) $[CpFe]^+$.

From the reaction a less moving component was also isolated by chromatography and was crystallized from petroleum ether to give brown crystals (**11,** 31 mg, 1.4%), m.p. 186–188 °C; R_f 0.24 (solvent *A*). MS ($C_{25}H_{21}FeN_3O_3$): 467 (M^+), 449 ($M-H_2O$). The pyrazole compound **3d** was also detected in the mother liquor.

3.5. 1-Acetyl-5-ferrocenyl-3-phenyl-1H-pyrazole (**3b**)

To a solution of 1-acetyl-5-ferrocenyl-3-phenyl-4,5-dihydro-1H-pyrazole (**2b**, 300 mg, 0.81 mmol) in benzene (20 mL) was dropped a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 100 mg) in benzene (8.5 mL) and the reaction mixture was heated to reflux temperature. After 1 h, an identical portion of DDQ solution was added and 1 h later further 35 mg DDQ in 3 mL benzene (total amount of DDQ 235 mg, 1.03 mmol, in 20 mL benzene, total reflux time 4 h), than the mixture was cooled to RT. It was filtered through Silica gel, washed with dichloromethane and the crude product was purified by repeated column chromatography using dichloromethane and then dichloromethane–ethyl-acetate 9:1 as eluent. Although a significant amount (130 mg) of the starting material **2b** was recovered, longer reaction time or reflux in toluene instead of benzene did not give better results. Product **3b** was crystallized from petroleum ether to give dark-orange rhomboid crystals (70 mg, reduced yield 42%), m.p. 133–134 °C; R_f 0.83 (solvent *A*). Anal. Calc. for $C_{21}H_{18}FeN_2O$ (370.23): C, 68.13; H, 4.90; N, 7.57. Found: C, 67.98; H, 4.99; N, 7.46%. MS: 370(65) M^+, 328(100) $[M-42]^+$, 263(10) $[M-42-C_5H_5]^+$, 207(4) $[M-42-FeCp]^+$, 121(35) $[CpFe]^+$, 56(14) $[Fe]^+$, 43(97) $[Ac^+]$.

3.6. 5-Ferrocenyl-1,3-diphenyl-1H-pyrazole (**3c**)

3.6.1. Method A: dehydroaromatisation with DDQ

To a stirred solution of 5-ferrocenyl-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (**2c**, 0,15 g, 0,37 mmol) in dichloromethane (6 mL) was added a solution of DDQ (0,11 g, 0,48 mmol) in dichloromethane (10 mL). In a few minutes dark greyish-green precipitate (quinone–hydroquinone complex) separated from the homogeneous reaction mixture. After 1 h stirring TLC (solvent *A*) indicated complete reaction. The solid was filtered and washed several times with dichloromethane. The filtrate was evaporated and purified by column chromatography using benzene as eluent. After evaporation pure **3c** (139 mg, 79%) was obtained as pale yellow syrup, which slowly crystallized from methanol, m.p. 100–101 °C; R_f 0.69 (solvent *A*). Anal. Calc. for $C_{25}H_{20}FeN_2$ (404.29): C, 74.27; H, 4.99; N, 6.93. Found: C, 74.72; H, 5.08; N, 6.96%. MS: 404(14) M^+, 339(9) $[M-C_5H_5]^+$, 121(4) $[CpFe]^+$, 56(6) $[Fe]^+$, 210(10) $[FcC_2H]^+$, 374 (100) $[M-30]^+$.

3.6.2. Method B: dehydroaromatisation with Cu(II)-nitrate and sonication

To a solution of pyrazoline **2c** (0.30 g; 0.74 mmol) in dichloromethane (10 mL) was added $Cu(NO_3)_2{\cdot}3H_2O$ (0.36 g, 1.48 mmol) and the reaction mixture was sonicated at RT and monitored by TLC (solvent *A*). After 2 h further amounts of $Cu(NO_3)_2{\cdot}3H_2O$ (0.18 g, 0.74 mmol) and dichloromethane (8 mL) were added and sonication was continued for 2 h, then the mixture was allowed to stand at RT for 14 h. Addition of newer portion of the reagent (0.74 mmol), sonication for further 2 h and standing at RT for 14 h resulted in complete reaction. The mixture was filtered, washed with dichloromethane, evaporated and purified by column chromatography using dichloromethane as eluent. Repeated

chromatography with toluene resulted in pure product as pale yellow syrup, which on trituration with cold methanol gave crystalline **3c** (0.11 g, 37%), m.p. 100–101 °C, identical with the product described in Section 3.6.1.

3.6.3. Method C: dehydroaromatisation with N-bromo-succinimide

To a suspension of pyrazoline **2c** (0.30 g; 0.74 mmol) in anhydrous carbon tetrachloride (15 mL) was added *N*-bromo-succinimide (NBS, 0.15 g, 0.84 mmol) and three drops of dry pyridine and the mixture was refluxed under nitrogen and was monitored by TLC (solvent *A*). After 4 h further amounts of NBS (0.075 g;0.42 mmol), CCl_4 (5 mL) and two drops of dry pyridine were added and after 10 h boiling, repeated addition of the same amount of reagents was carried out and boiling was continued for further 10 h. The hot solution was decanted from the separated dark-brown oil and extracted with hot carbon tetrachloride (2×8 mL). The united solutions were evaporated and the crude oily product was purified by column chromatography (toluene) to give pure **3c** (0.086 g, 29%), identical with the product described in Section 3.6.1.

*3.7. 5-Ferrocenyl-1-(4-nitrophenyl)-3-phenyl-1H-pyrazole **(3d)***

To the stirred solution of **2d** (40 mg; 0.088 mmol) in toluene (20 mL) was added dropwise a solution of DDQ (24 mg; 0.106 mmol) in toluene (12 mL) and the mixture was heated on a bath at 120 °C for 3 h and then further heated at 100 °C for 3 h, by that time greyish-green precipitate was separated from the homogeneous reaction mixture and TLC (solvent *A*) indicated complete reaction. The solid was filtered and washed several times with dichloromethane. The filtrate was evaporated and purified by column chromatography using dichloromethane as eluent and was crystallized by treating petroleum ether to give pure **3d** (30 mg, 76%) in the form of orange crystals, m.p. 183–184 °C, R_f 0.74 (solvent *A*). Anal. Calc. for $C_{25}H_{19}FeN_3O_2$ (449.29): C, 66.83; H, 4.26; N, 9.35. Found: C, 66.52; H, 4.37; N, 9.56%. MS: 449(14) M^+, 419 (100) $[M-30]^+$, 384(10) $[M-C_5H_5]^+$, 298(3) $[M-30-FeCp]^+$, 210(10) $[FcC_2H]^+$, 121(4) $[CpFe]^+$, 56(9) $[Fe]^+$.

Dehydroaromatisation with N-bromo-succinimide: Reaction of **2d** with NBS in carbon tetrachloride, as described at the preparation of **3c** (*Method C*), after chromatography (dichloromethane) and crystallization resulted in **3d** in 8% yield.

*3.8. Reaction of 3-ferrocenyl-1-phenyl-prop-2-en-1-one (**1**) with methylhydrazine; preparation of 5-ferrocenyl-3-phenyl-1-methyl-4,5-dihydro-1H-pyrazole (**2e**); 5-ferrocenyl-3-phenyl-1-methyl-1H-pyrazole (**3e**); 3-ferrocenyl-5-phenyl-1-methyl-4,5-dihydro-1H-pyrazole (**4e**) and 3-ferrocenyl-5-phenyl-1-methyl-1H-pyrazole (**5e**)*

3.8.1. Method A

To a solution of chalcone **1** (1.50 g, 4.74 mmol) in ethanol (40 mL) was added methylhydrazine (1.418 g, 30.8 mmol) and the mixture was heated under reflux for 1 h, by that time TLC (solvent *B*) indicated complete conversion. Formation of four main products and several by-products was observed. Separation of the components was made by repeated column chromatography (*n*-hexane–ethyl-acetate 3:1) under nitrogen. The fast moving product was crystallized from ethyl-acetate to give pure pyrazoline (**2e,** 0.37 g, 23%), in the form of yellow crystals, m.p. 114–115 °C; R_f 0.86 (solvent *B*). Anal. Calcd for $C_{20}H_{20}FeN_2$ (344.24): C, 69.78; H, 5.86; N, 8.14. Found: C, 69.29; H, 5.83; N, 8.22%. MS: 344(76) M^+, 342(20) $[M-H_2]^+$, 314(5) $[M-R'NH]^+$, 277(3) $[M-H_2-C_5H_5]^+$, 249(5) $[M-C_5H_5-R'N]^+$, 212(33) $[FcC_2H_3]^+$, 186(100) $[FcH]^+$, 121(72) $[CpFe]^+$, 56(16) $[Fe]^+$.

The second moving material after separation and crystallization from ethyl-acetate–petroleum ether gave yellowish-orange crystals of the regioisomeric pyrazoline (**4e**, 0.021 g, 1.3%), m.p. 126–127 °C; R_f 0.81 (solvent *B*). Anal. Calcd for $C_{20}H_{20}FeN_2$ (344.24): C, 69.78; H, 5.86; N, 8.14. Found: C, 69.89; H, 5.63; N, 8.18%. MS: 344(41) M^+, 342(50) $[M-H_2]^+$, 277(8) $[M-H_2-C_5H_5]^+$, 267(100) $[M-RC_6H_4]^+$, 221(3) $[M-H_2-FeCp]^+$, 211(6) $[FcCN]^+$, 210(2) $[FcC_2H]^+$, 186(6) $[FcH]^+$, 121(26) $[CpFe]^+$, 56(13) $[Fe]^+$.

The third component was crystallized from *n*-hexane to give **3e** pyrazole (0.07 g, 4%), yellow crystals, m.p. 90–91 °C; R_f 0.71 (solvent *B*). Anal. Calcd. for $C_{20}H_{18}FeN_2$ (342.22): C, 70.19; H, 5.30; N, 8.19. Found: C, 69.92; H, 5.42; N, 8.12%. MS: 342(100) M^+, 277(3) $[M-C_5H_5]^+$, 221(3) $[M-FeCp]^+$, 210(4) $[FcC_2H]^+$, 121(31) $[CpFe]^+$, 56(15) $[Fe]^+$.

The most slowly moving main product was crystallized from *n*-hexane (or from ethyl-acetate) resulting in orange crystals of the regioisomeric pyrazole (**5e**, 0.70 g, 43%), m.p. 139–140 °C; R_f 0.57 (solvent *B*). Anal. Calcd. for $C_{20}H_{18}FeN_2$ (342.22): C, 70.19; H, 5.30; N, 8.19. Found: C, 70.01; H, 5.39; N, 8.03%. MS: 342(100) M^+, 277(5) $[M-C_5H_5]^+$, 221(12) $[M-FeCp]^+$, 121(38) $[CpFe]^+$, 56(10) $[Fe]^+$.

The *N*-methyl-pyrazolines (**2e** and **4e**) during chromatography, or standing in solution even at RT, spontaneously were partly transformed to the corresponding pyrazoles **3e** and **5e**, respectively, and reconversion of chalcone **1** was also observed at purification of the yellow crude product mixture. A further by-product was isolated in traces during chromatography and was supposed to be 5-ferrocenyl-3-phenyl-*1-H*-pyrazole (see at **3e**, but R = H, R′ = H), on the basis of the MS spectrum, $m/z = 328$ (M^+).

3.8.2. Method B

To the boiling solution of **1** (0.25 g, 0.79 mmol) in toluene (8 mL) was added a solution of methylhydrazine (0.10 g, 2.17 mmol) in toluene (2 mL) and the reaction mixture was refluxed under nitrogen. After 1 h, methylhydrazine (0.10) was added again to the hot solution and refluxing was continued for further 1.5 h. TLC (solvent *B*) revealed the formation of a mixture with the predominance of **4e** and **5e**. Repeated chromatography (*n*-hexane–ethyl-acetate 7:3) under nitrogen resulted in **4e** pyrazoline as orange crystals from petroleum ether (0.021 g, 8%) and **5e** as dark-orange crystals (0.158 g, 58%) from hexane, identical with the corresponding products described in Section 3.8.1. A significant transformation of **4e**–**5e** was observed during chromatography. Pyrazoline **2e** (29.7 mg, 11%) and pyrazole **3e** (8.1 mg, 3%), respectively, were also isolated from the mixture.

*3.9. Reaction of 1-ferrocenyl-3-(p-hydroxyphenyl)-prop-2-en-1-one (**6**) with phenylhydrazine; preparation of 5-ferrocenyl-3-(4-hydroxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**7a**) and 5-ferrocenyl-3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazole (**8a**)*

To a solution of compound **6** (0.35 g, 1.05 mmol) in a mixture of ethanol (10 mL), acetic acid (3.75 mL) and water (3.75 mL) was added phenylhydrazine and the reaction mixture was heated under reflux in nitrogen atmosphere for 3 h, by which time the colour of the solution became yellow and TLC (solvent *B*) indicated complete reaction. After standing in refrigerator for 5 h, the mixture was evaporated to give a dark-brown syrup. It was dissolved in ethyl-acetate and extracted with water. The organic phase was dried and evaporated to give oily-solid crude product, which was purified by repeated column chromatography using *n*-hexane–ethyl-acetate (7:3 → 1:9) as eluent. The faster moving yellow product was crystallized from ethyl-acetate–*n*-hexane (**7a**, 0.26 g, 58%) m.p. 110–111 °C; R_f 0.71 (solvent *C*). Anal. Calcd. for $C_{25}H_{22}FeN_2O$ (422.31): C, 71.10; H, 5.25; N, 6.63. Found: C, 70.87; H, 5.44; N, 6.26%. MS: 422(69) M^+, 420(82) $[M-H_2]^+$, 357(3) $[M-C_5H_5]^+$, 355(8) $[M-H_2-C_5H_5]^+$, 330(19) $[M-R'NH]^+$, 303(5) $[M-RPhCN]^+$, 301(8) $[M-FeCp]^+$, 299(4) $[M-H_2-FeCp]^+$, 266(20) $[M-C_5H_5-R'N]^+$,

212(69) $[FcC_2H_3]^+$, 210(31) $[FcC_2H]^+$, 186(79) $[FcH]^+$, 121(100) $[CpFe]^+$, 56(38) $[Fe]^+$.

The second moving product gave orange crystals (**8a**, 0.028 g, 6.3%) from *n*-hexane, m.p. 225–226 °C; R_f 0.28 (solvent *C*). Anal. Calcd for $C_{25}H_{20}FeN_2O$ (420.29): C, 71.44; H, 4.80; N, 6.67. Found: C, 71.15; H, 5.02; N, 6.45%. MS: 420(100) M^+, 355(6) $[M–C_5H_5]^+$, 299(3) $[M–FeCp]^+$, 210(39) $[FcC_2H]^+$, 186(11) $[M–C_5H_5–R'N]^+$, 121(31) $[CpFe]^+$, 56(14) $[Fe]^+$.

3.10. 3-(4-Acetoxyphenyl)-5-ferrocenyl-1-phenyl-4,5-dihydro-1H-pyrazole (**7b**)

Compound **7a** (0.300 g, 0.71 mmol) was acetylated with dist. acetic anhydride (1 mL) in dry pyridine (1.7 mL) for 48 h at 0 °C and then at RT for 2 h, by which time TLC (solvent *A*) indicated complete reaction. The mixture was poured into ice–water and the solidified material was filtered and washed several times with cold water to give 0.30 g crude product. Purification by column chromatography (dichloromethane) resulted in yellow crystals of **7b** (0.226 g, 68.5%), m.p. 193–194 °C; R_f 0.74 (solvent *A*). Anal. Calc. for $C_{27}H_{24}FeN_2O_2$ (464.35): C, 69.84; H, 5.21; N, 6.03. Found: C, 69.98; H, 5.47; N, 6.18%. MS: 464(72) M^+, 462(21) $[M–H_2]^+$, 422(7) $[M–42]^+$, 420(9) $[M–42–H_2]^+$, 330(34) $[M–42–R'NH]^+$, 212(85) $[FcC_2H_3]^+$, 186(97) $[FcH]^+$, 121(100) $[CpFe]^+$, 56(24) $[Fe]^+$.

3.11. 3-(4-Acetoxyphenyl)-5-ferrocenyl-1-phenyl-1H-pyrazole (**8b**)

To a stirred solution of 3-(p-acetoxyphenyl)-5-ferrocenyl-1-phenyl-4,5-dihydro-*1H*-pyrazole (**7b**, 70 mg, 0.151 mmol) in benzene (10 mL) was dropped a solution of DDQ (61 mg, 0.269 mmol) in benzene (5 mL) and the mixture was refluxed for 2 h, by which time TLC (solvent *A*) indicated complete reaction. The suspension was filtered through Silica gel and washed with dichloromethane and subsequently dichloromethane–ethyl-acetate (95:5). The filtrates were evaporated and purified by repeated column chromatography using dichloromethane and then dichloromethane–ethyl-acetate (98:2). Crystallization from dichloromethane by adding a few petroleum ether resulted in pure **8b** (50 mg, 72%) as orange crystals, m.p. 187–188 °C; R_f 0.27 (solvent *A*). Anal. Calc. for $C_{27}H_{22}FeN_2O_2$ (462.33): C, 70.14; H, 4.80; N, 6.06. Found: C, 69.78; H, 5.01; N, 6.36. MS: 462(64) M^+, 420(24) $[M–42]^+$, 397(2) $[M–C_5H_5]^+$, 210(2) $[FcC_2H]^+$, 121(32) $[CpFe]^+$, 56(9) $[Fe]^+$, 43(100) Ac^+.

3.12. 3-(4-Acetoxyphenyl)-5-ferrocenyl-1-(2-pyridyl)-4,5-dihydro-1H-pyrazole (**9b**)

To the solution of compound **6** (0.50 g, 1.5 mmol) in a mixture of ethanol (6 mL), acetic acid (3 mL) and water (3 mL) was added 2-hydrazinopyridine (0.343 g, 3.14 mmol) and the solution was heated under reflux in nitrogen atmosphere for 5 h and then allowed to stand at RT for 20 h. As TLC (solvent *D*) showed incomplete reaction, further amount of 2-hydrazinopyridine (0.21 g, 1.9 mmol), ethanol (3 mL), acetic acid (1.5 mL) and water (1.0 mL) was added to the mixture and heating was continued for further 7 h. On cooling yellow crystals separated, which were filtered and washed with cold methanol–water (1:1) to give 0.373 g (58.6%) of the 3-(*p*-hydroxy-phenyl)-5-ferrocenyl-pyrazoline derivative (**12**, see at **9b**, but R = *p*-OH, R′ = α-Py). Acetylation of crude **12** was made by stirring in a mixture of acetic anhydride (1.3 mL) and pyridine (2.2 mL) for 4 h at RT and then storing the reaction at 0 °C for 20 h. The separated yellow crystals were filtered, washed with methanol–water (1:1) and recrystallized from ethyl-acetate–*n*-hexane to give pure **9b** (0.349 g, 50%, yield calculated for chalcone **6**), m.p. 199–200 °C; R_f 0.34 (solvent *C*). Anal. Calc. for $C_{26}H_{23}FeN_3O_2$ (465.33): C, 67.11; H, 4.98; N, 9.03. Found: C, 66.83; H, 5.16; N, 9.29%. MS: 465(10) M^+, 463(2) $[M–H_2]^+$, 400(3) $[M–C_5H_5]^+$, 304(25) $[M–RPhCN]^+$, 212(16) $[FcC_2H_3]^+$, 210(5) $[FcC_2H]^+$, 186(3) $[FcH]^+$, 121(48) $[CpFe]^+$, 56(17) $[Fe]^+$, 43(100) Ac^+.

3.13. 3.3.6. 3-(4-Acetoxyphenyl)-5-ferrocenyl-1-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (**10b**)

Compound **6** (0.50 g, 1.5 mmol) was dissolved in a mixture of ethanol (9 mL), acetic acid (3 mL) and water (0.75 mL), *p*-nitrophenylhydrazine (0.482 g, 3.15 mmol) was added and the suspension was refluxed under nitrogen for 6 h and then it was allowed to stand at RT for 20 h. On the basis of TLC analysis (solvent *D*), further amount of *p*-nitrophenylhydrazine (0.06 g, 0.39 mmol), ethanol (3 mL), acetic acid (1.5 mL) and water (1.0 mL) was added to the mixture and heating was continued for further 7 h. On cooling orange crystals separated, which were filtered and washed with cold methanol–water (1:1) to give 0.57 g (81%) 3-(*p*-hydroxyphenyl)-5-ferrocenyl-pyrazoline derivative (**14**, see at **10b**, but R = *p*-OH, R′ = *p*-NO_2Ph). Crude **14** was acetylated with acetic anhydride (2 mL) and pyridine (3.25 mL) by stirring for 4 h at RT and then storing the reaction mixture at 0 °C for 20 h. The separated red crystals were filtered, washed with methanol–water (1:1) and recrystallized from ethyl-acetate–*n*-hexane to give pure **10b** (0.388 g, 51%, yield calculated for chalcone **6**), m.p. 236–237 °C; R_f 0.57 (solvent *A*). Anal. Calc. for $C_{27}H_{23}FeN_3O_4$ (509.34): C, 63.67; H, 4.55; N, 8.25. Found: C, 63.96; H, 4.46; N, 8.49%. MS: 509(6) M^+, 479(15) $[M–30]^+$, 477(5) $[M–30–2]^+$, 330(9) $[M–42–R'NH]^+$, 212(23) $[FcC_2H_3]^+$, 210(4) $[FcC_2H]^+$, 186(18) $[FcH]^+$, 121(43) $[CpFe]^+$, 56(17) $[Fe]^+$, 43(100) Ac^+.

3.14. 5-Ferrocenyl-3-phenyl-1-(2-pyridyl)-4,5-dihydro-1H-pyrazole (**13a**)

Preparation of this compound was described earlier [7].

MS: 407(56) M^+, 405(16) $[M–H_2]^+$, 340(33) $[M–H_2–C_5H_5]^+$, 342(19) $[M–C_5H_5]^+$, 314(11) $[M–R'NH]^+$, 304(100) $[M–RPhCN]^+$, 286(4) $[M–FeCp]^+$, 212(21) $[FcC_2H_3]^+$, 121(90) $[CpFe]^+$, 56(34) $[Fe]^+$.

3.15. 3-Ferrocenyl-5-phenyl-1-(2-pyridyl)-4,5-dihydro-1H-pyrazole (**13b**)

Preparation of this compound was described earlier [7].

MS: 407(100) M^+, 405(18) $[M–H_2]^+$, 342(37) $[M–C_5H_5]^+$, 314(5) $[M–R'NH]^+$, 304(7) $[M–RPhCN]^+$, 250(7) $[M–C_5H_5–R'N]^+$, 211(23) $[FcCN]^+$, 121(49) $[CpFe]^+$, 56(25) $[Fe]^+$.

4. Supplementary data

CCDC 735603 and 735604 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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