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Study on ferrocenes, part 9 [1] substrate selective transformations of some ferrocenylhydrazones

Á. Abrán, A. Csámpai[a], A. Kotschy, O. Barabás, P. Sohár*

Department of General and Inorganic Chemistry, Research Group for Structural Chemistry and Spect., Hungarian Academy of Sciences — Eötvös Lóránd University, P.O. Box 32, H-1518 Budapest 112, Hungary

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Abstract

Different ferrocenyl-substituted hydrazones of heteroaryl/arylhydrazines (**1a–e**, **3** and **10**) were reacted with dimethyl fumarate and gave two epimeric pairs of pyrazolidines (*t*,*c*-**2a** and *t*,*c*-**2c**), pyrazolines (**5a**,**c**, **6**, **11**), pyrazoles (**8**, **12**) and condensed triazoles (**4a**, **7**). On treatment with dicyanodichloroquinone (DDQ) the pyrido[2,3-*d*]pyridazinyl-substituted hydrazones (**1b**,**e**) were cyclized to condensed triazoles **4b**,**e**. The reactivity of **1a–e** in the cycloaddition process and oxidation level of the products were found to be highly dependent on the temperature and on the heteroaryl/aryl group. The significant difference was explained by theoretical calculations. The structures of products were determined by IR, 1D and 2D NMR methods (including HMQC, HMBC and DNOE) and single crystal X-ray analysis.

Keywords: Ferrocenylhydrazones; Dipolar cycloaddition; Stereoselectivity; Semi-empirical calculations; Structure determination

1. Introduction

In our previous paper [2] we reported on the 1,3-dipolar cycloaddition reactions of ferrocenyl-hydrazones of 2-hydrazinopyridine and 4-hydrazinophthalazinones with some dipolarophilic reagents. The reactivity of the substrates in these reactions proceeding by proton shift followed by the actual cycloaddition was found to be dependent on the heterocyclic moiety. In order to get more information about the mechanism and to extend the group of 3-ferrocenyl-1-heteroaryl/arylpyrazole- and polycondensed 1,2,4-triazole derivatives, which may be of pharmaceutical interest, we investigated the analogous cycloaddition and oxidative cyclization reactions of the ferrocenylhydrazones of pyrido[2,3-*d*]- and pyrido[3,4-*d*]pyridazinylhydrazines (**1b–e**), thieno[3,2-*c*]pyridylhydrazine (**3**) and 4-bromophenylhydrazine (**10**) as shown on Scheme 1.

2. Experimental

Melting points (uncorrected) were determined with a Boetius apparatus. The IR spectra were recorded in KBr pellets with a BRUKER IFS 55 FT-spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or $[D_6]$DMSO solution in 5 mm tubes at RT, on a Bruker DRX 500 spectrometer at 500 (^{1}H) and 125 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal reference. The standard

* Corresponding author. Tel.: +36-1-209-0599; fax: +36-1-209-0602.

E-mail address: sohar@para.chem.elte.hu (P. Sohár).

[a] Corresponding author.

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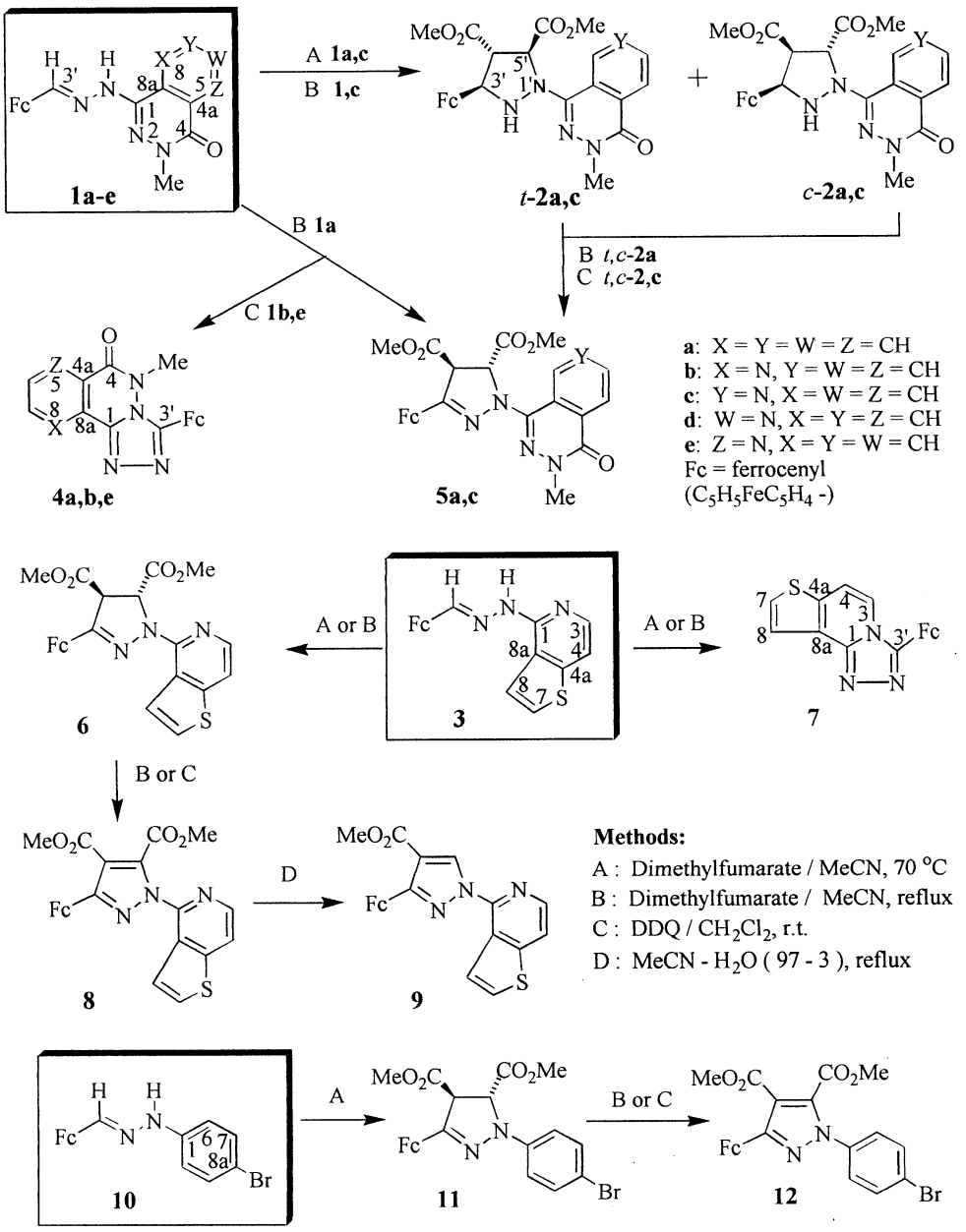


Scheme 1.

Bruker microprogram NOEMULT.AU to generate NOE was used with a selective preirradiation 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 and 2D HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND, respectively.

*Hydrazones **1a–e**, **3** and **10**.* Preparation and characterization of **1a**,**b**,**e** are reported in Ref. [3].

Table 1
The calculated heats of formation (kJ/mol)/HOMO energies (eV) for the neutral (**1*****a–e** and **3***) and relative heats of formation (kJ/mol) for the dipolar forms (**I–III**) (AM1, MOPAC 6.0)

	ΔH_f (**1***, **3*** in row **f**)	$\Delta\Delta H_f$ (**I–1***, **3*** in row **f**)	$\Delta\Delta H_f$ (**II–1***)	$\Delta\Delta H_f$ (**III–1***, **3*** in row **f**)
a	338.53/−8.87	62.26/−7.77	–	19.33/−8.85
b	389.40/−8.55	69.08/−7.77	158.57/−6.70	28.66/−8.92
c	385.39/−9.03	60.04/−7.93	182.13/−6.64	19.20/−9.02
d	382.88/−9.16	60.96/−7.94	177.40/−6.44	20.58/−9.07
e	399.82/−9.03	62.34/−7.87	163.72/−6.69	21.59/−8.96
f	399.22/−8.35	56.76/−7.58	–	−4.62/−7.88

According to the described procedure formyl-ferrocene and the appropriate hydrazine component (8-hydrazino-6-methylpyrido[3,4-*d*]pyridazin-5(6*H*)-one (**Ac**) for **1c**, 5-hydrazino-7-methylpyrido[3,4-*d*]pyridazin-8(7*H*)-one (**Ad**) for **1d**, 4-hydrazinothieno[3,2-*c*]pyridine [7] for **3** and 4-bromo-phenylhydrazine for **10**) were condensed to give novel hydrazones: 8-[(*E*)-ferrocenylmethylidene-hydrazino]-6-methylpyrido [3,4-*d*]pyridazin-5(6*H*)-one (**1c**) (89%); 5-[(*E*)-ferrocenylmethylidene-hydrazino]-7-methylpyrido [3,4-*d*]pyridazin-8(7*H*)-one (**1d**) (76%); 4-[(*E*)-ferrocenylmethylidene-hydrazino]thieno[3,2-*c*]pyridine (**3**) (92%); *N*-(4-bromophenyl)-*N'*-ferrocenylmethylidene-hydrazine (**10**) (91%). The two-step preparation of **Ac**,**d** via the appropriate chloro compound (**Bc**,**d**) is described below.

*Preparation of 8-chloro-6-methylpyrido[3,4-d]pyridazin-5(6H)-one (**Bc**) and 5-chloro-7-methylpyrido[3,4-d]pyridazin-8(7H)-one (**Bd**).* Sodium (1.38 g, 0.06 mol) and, subsequently, 8-chloropyrido[3,4-*d*]pyridazin-5(6*H*)-one [8]/5-chloropyrido [3,4-*d*]pyridazin-8(7*H*)-one [8] were dissolved in methanol (200 ml) with moderate heating. The mixture was stirred at 35–40°C until a clear solution was obtained (20–25 min). Following the addition of CH_3I (8.52 g, 0.06 mol) the solution was refluxed for 1 h then cooled, filtered and evaporated. The solid residue was extracted with CH_2Cl_2 (100 ml). The solution was washed with water (2 × 50 ml), dried ($MgSO_4$) and evaporated to obtain the pure product. **Bc** Yield 67%; mp 153–55°C; IR (cm^{-1}) 1674, 1595, 1573; ^{1}H NMR ($CDCl_3$) 9.12 (1H, s), 8.95 (1H, d, $J = 5.4$), 8.22 (1H, d, $J = 5.4$), 3.76 (3H, s); ^{13}C NMR ($CDCl_3$) 159.1, 152.8, 150.6, 134.7, 133.7, 121.4, 119.4, 40.2; **Bd** Yield 71%; mp 162–64°C; IR (cm^{-1}) 1670, 1596, 1569; ^{1}H NMR ($CDCl_3$) 9.62 (1H, s), 9.01 (1H, d, $J = 5.4$), 7.68 (1H, d, $J = 5.4$), 3.77 (3H, s); ^{13}C NMR ($CDCl_3$) 158.3, 153.7, 151.3, 135.9, 134.4, 122.4, 117.6, 40.0; Anal. of **Bc**,**d** calcd. for $C_8H_6ClN_3O$ (195.6) C 49.12, H 3.09, Cl 18.12, N 21.48; Found for **Bc/Bd** C 49.10/49.21, H 3.12/3.12, Cl 18.08/18.12, N 21.50/21.43.

*Preparation of **Ac**,**d**.* A mixture of hydrazine hydrate (98%, 22 ml), EtOH (3 ml) and the corresponding chloro compound (**Bc**,**d**) (3.91 g, 0.02 mol) was refluxed for 1 h then diluted with water (100 ml). The precipitated product was recrystallized from water. **Ac** Yield 75%; mp 214–17°C; IR (cm^{-1}) 3330, 3281, 1658, 1609; ^{1}H NMR ([D_6]DMSO) 9.52 (1H, s), 8.90 (1H, d, $J = 5.5$), 8.29 (1H, d, $J = 5.5$), 8.21 (1H, s), 4.14 (2H, br s), 3.65 (3H, s); ^{13}C NMR ([D_6]DMSO) 157.6, 151.8, 148.1, 144.4 132.1 120.6, 119.0, 39.6. **Ad** Yield 88%; mp 227–29°C; IR (cm^{-1}) 3322, 3283, 1650, 1611; ^{1}H NMR ([D_6]DMSO) 9.43 (1H, s), 9.00 (1H, d, $J = 5.5$), 8.27 (1H, s), 7.96 (1H, d, $J = 5.5$), 4.14 (2H, br s), 3.62 (3H, s); ^{13}C NMR ([D_6]DMSO) 156.8, 153.0, 150.6, 146.2, 130.0, 122.4, 116.2, 39.2; Anal. of **Ac**,**d** calcd. for $C_8H_9N_5O$ (191.2) C 50.26, H 4.75, N 36.63; Found for **Ac/Ad** C 50.32/50.44, H, 4.73/4.77, N 36.61/36.70.

*Reactions of hydrazones **1a–e**, **3** and **10** with DMFM, (general procedure for Methods A and B).* A reaction mixture containing the hydrazone (2.5 mmol) and DMFM (0.86 g, 6 mmol) was stirred and heated at 70°C (*Method A*) or refluxed (*Method B*) in 30 ml of freshly distilled MeCN in the presence of 0.5 g of molecular sieves (3 Å) under argon atmosphere. The TLC-monitored reactions were conducted for the following periods of time: 8 h (*Method A*) and 15 h (*Method B*) for **1a**; 40 h (*Methods A* and *B*) for **1b–e**; 30 min (*Method A*) and 2 h (*Method B*) for **3**; 3 h (*Method A*) and 6 h (*Method B*) for **10**. The solvent

Table 2
IR (cm^{-1}, in KBr discs) and ^{1}HNMR{In ppm (chemical shifts, $\delta_{TMS} = 0$ ppm) and Hz (coupling constants) at 500 MHz. Solvent: $CDCl_3$ (**1c**, **4e**, **6**–**12**) and/or [D_6]DMSO (*t*-**2a**, **10/1d**, *c*-**2a**, *t*- and *c*-**2c**, **3** and **5c**), for **4b** 10:1 mixture of $CDCl_3$: [D_6]DMSO.} for compounds **1**–**12**. [Assignments were supported by 2D HMQC (except for **4b**,**e** and **11**) and in case of **1d**, *t*- and *c*-**2a**,**c**, **3**, **6**, **7**, and **12** also by DNOE measurements. For the numbering of the ring atoms see Scheme 1.]

	νC=O amide	νC=O ester	νNH band	NMe *s*(3H)	OMe 2/1 × *s*[a] (2 × 3H)	Ferrocenyl group (Fc)			Pyrazol/id/in/e ring			Hetero ring (HC)[b]			
						H-1″-5″	H-2,5[c]	H-3,4[c]	H-3′[d]	H-4′[e]	H-5′[f]	H-5/3	H-6/4	H-7	H-8
1c	1660	1580[g]	3240	3.74	–	4.20	4.59	4.36	7.78			8.24	8.97	–	9.95
1d	1632	1579[g]	~3160	3.61	–	4.21	4.61	4.28	8.08			9.46	–	9.04	8.20
t-**2a**	1647	1734	3465	3.69	3.83	4.17[h]	4.20, 4.23	4.17[I]	4.35	3.50	5.48	8.40	7.71	7.75	8.47
c-**2a**	1642	1731	3455	3.67	3.37, 3.72	4.16	4.09, 4.19	3.99, 4.11	4.71	3.60	5.03	8.43	7.73	7.78	8.89
t-**2c**				3.59	3.715, 3.720	4.11[h]	4.11[h], 4.33	4.13[I], 4.18	4.11[i]	3.46	5.46	8.05	8.93	–	9.90
c-**2c**	1653	1745	~3500	3.57	3.36, 3.64	3.97[h]	3.97[h], 4.11	3.97[i], 4.02	3.72	4.65	4.98	8.12	8.98	–	10.26
3	–	1579	3180	–	–	4.17	4.62	4.36	7.93	–	7.90	7.35	8.20	7.65	–
4b	1679	–	–	3.42	–	4.36	4.63	4.41	–	–	–	8.54	7.59	9.03	–
4e	1698	–	–	3.46	–	4.38	4.61	4.40	–	–	–	–	8.98	7.70	8.72
5c	1656	1749	–	3.56	3.74, 3.79	4.21	4.63, 4.78	4.48, 4.50	–	4.68	5.24	8.14	9.02	–	10.10
6	–	1739		–	3.78, 3.82	4.18	4.68, 4.89	4.38, 4.44	–	4.22	5.56	7.95	7.25	8.35	7.35
7	–	–	–	–	–	4.21	4.91	4.50	–	–	–	8.38	7.32	8.06	7.65
8	–	1723	–	–	3.91, 3.97	4.15	5.11	4.39	–	–	–	8.22	7.79	8.35	7.62
9	–	1720	–	–	3.91	4.13	5.28	4.40	–	–	9.19	8.28	7.78	8.66	7.60
10	–	1590	3305	–	–	4.14	4.56	4.31	7.65	–	–	–	6.88	7.29	–
11	–	1739	–	–	3.72	4.09	4.57, 4.77	4.29, 4.33	–	4.30	4.92	–	6.89	7.29	–
12	–	1728	–	–	3.84, 3.93	4.13	4.91	4.34	–	–	–	–	7.38	7.60	–

[a] One *s*(6H) for *t*-**2a**, **9**, and **11**.
[b] Hetero ring: phthalazine (**1**, **2**, **4**, **5**), pyridothiophene (**3**, **6**–**9**), *p*-bromo-phenyl (**10**–**12**).
[c] Two signals due to hindered rotation of the Fc-group.
[d] Azomethine (N=CH) group for **1c**,**d**. Singlet (1H) for **1c**,**d**, **3** and **10**, *d*for *t*- and *c*-**2a**,**c** (*J*: 7.5, 8.2, (and 7.8).
[e] Multiplicity: dd (1H) for *t*- and *c*-**2a**, *t* for *t*- and *c*-**2c**, *d* for **5c**,**6** and **11** ($J = 5.2$, 4.8 and 4.5 Hz).
[f] Doublet (1H) for *t*- and *c*-**2a**,**c**, **5c**, **6** and **11**, s(1H) for **9**.
[g] νC=N band for **1c**, **d 3** and 10.
[h] Overlapping signals.
[i] In [D_6]DMSO. Broad for *c*-**2a**,**c**, *d* ($J = 12$ Hz) for *t*-**2a**,**c**.

Table 3
^{13}C NMR chemical shifts {In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz. Solvent: $CDCl_3$ (**1c**, *t*-**2a, 4e, 6–12**) or [D_6]DMSO (**1d**, *c*-**2a**, *t*-**2c**, *c*-**2c**, **3** and **5c**), for **4b** 10:1 mixture of $CDCl_3$-[D_6]DMSO; OMe lines: 52.5 (*t*-**2a**, two overlapping lines), 52.0 and 52.3 (*c*-**2a**), 53,3 and 53,4 (*t*-**2c**), 52.5 and 53.1 (*c*-**2c**), 53,4 and 54,1 (**5c**), 53,1 and 53,5 (**6**), 52.4 and 53.4 (**8**), 51.8 (**9**, two overlapping lines), 53.4 and 53.5 (**11**), 52.6 and 53.4 (**12**).} for compounds **1–12** [Assignments were supported by DEPT, 2D HMQC (except for **4b**,**e** and **11**) and 2D HMBC measurements (except for **4b**).]

	NMe	Ferrocenyl group (Fc)				Pyrazol/ine/idin/e ring[a]			Phthalazine/Pyridothiophene/*p*-Bromo-pheny/ring[b] (HC)							
		C-1″-5″	C-1	C-2,5	C-3,4	C-3′	C-4′	C-5′	C-1	C-4	C-4a	C-5/3	C-6	C-7	C-8	C-8a
1c	39.0	69.2	78.8	67.4	70.1	143.8	–	–	150.8	157.3	134.3	119. 2	150.8	–	149.9	120.0
1d	39.2	69.8	80.9	68.0	70.5	145.8	–	–	141.5	157.0	123.0	150.6	–	512.9	117.5	130.4
t-**2a**	38.9	68.7	84.5	66.7, 67.3	68.1, 68.4	61.5	57.4	65.6	145.1	159.1	129.0	126.7	131.3	131.9	126.8	126.6
c-**2a**	38.8	69.0	81.8	68.2, 69.0	65.3, 67.7	62.6	55.2	65.4	144.1	158.9	129.0	126.9	131.3	131.8	127.2	126.9
t-**2c**	39.7	69.5	84.5	67.2, 68.3	68.4, 69.0	63.0	57.7	65.7	145.3	157.4	134.4	119.2	151.5	–	151.5	121.2
c-**2c**	39.6	69.4	~84[c]	68.0, 69.5	66.5, 68.6	62.2	56.1	63.5	145.1	157.0	134.1	119.4	151.7	–	151.7	120.7
3	–	69.7	81.7	67.6	70.3	141.2	–	–	152.5	109.4	150.1	142.0	–	125.1	125.1	121.6
4b	36.7	70.3	72.4	69.1	71.2	146.9	–	–	143.1	159.7	119.9	136.6	125.0	155.5	–	142.1
4e	37.0	70.6	72.6	69.4	71.7	141.9	–	–	139.6	158.4	146.9	–	153.0	128.1	131.6	121.8
5c	39.5	70.5	75.1	67.7, 68.6	71.2, 71.3	151.5	54.9	66.0	140.7	156.6	134.7	119.8	152.0	–	150.8	119.8
6	–	70.0	75.8	67.5, 67.8	70.5, 70.7	147.9	55.7	65.4	150.0	109.8	149.7	140.9	–	126.2	123.5	123.0
7	–	69.9	71.4	68.4	70.3	147.3	–	–	147.9	109.7	137.0	119.6	–	123.3	128.9	126.6
8	–	70.4	76.5	70.0	70.1	152.9	113.3	138.9	151.4	117.5	145.3	140.2	–	124.5	128.2	127.5
9	–	70.2	76.9	69.8	70.0	154.1	113.3	134.6	145.6	116.8	151.7	140.8	–	125.4	127.5	126.3
10	–	69.6	82.1	67.3	70.0	138.7	–	–	145.8	–	–	–	114.4	132.5	–	109.5
11	–	70.0	74.4	67.4, 67.9	70.4, 70.6	146.3	57.6	66.0	143.7	–	–	–	115.2	132.3	–	112.3
12	–	70.1	75.9	69.0	69.6	151.5	115.3	137.0	138.6	–	–	–	126.7	132.6	–	123.2

[a] CH(Fc)=N group for **1c**,**d**, **3** and **10**, triazole ring for **4b**,**e** and **7**.
[b] For the numbering see Scheme 1.
[c] Detected indirectly only by 2D HMBC measurement.

Table 4
Results of DNOE experiments with compounds **1–3**, **6**, **7** and **12** (Interacting pairs showing only trivial effects (NOE between geminal or vicinal hydrogens) are not included in this Table. Responses relevant for stereostructures are exclusively given.)

	Responding signals						
Saturated signal	H-8	H-4′	H-2,5[a]	H-3′	H-3	OMe	H-6
NH	**1d**, *t*-**2c**		*t*-**2c**	**3**			
H-2,5[b]		*t*-**2a**,**c**, **6**		**3**	**7**	*c*-**2a**	
OMe		*t*-**2a**	*c*-**2a**				**12**
H-5				*t*-**2a**		*c*-**2a**	

[a] Substituted cyclopentadiene ring (Fc).

was evaporated in vacuo to dryness. The residue was contaminated by paramagnetic substances in each case. The separation by chromatography on silica (Kieselgel type 9385; eluent: $CHCl_3$) and subsequent recrystallization from ethanol gave the pure products (see Tables 2–5): 4-[(3R*,4S*,5S*)-4,5-*bis*-carbomethoxy-3-ferrocenyl-2,3,4,5-tetrahydropyrazol-1-yl]-2-methylphthalazin-1(2H)-one (*t*-**2a**) (40% by *Method A*); 4-[(3R*,4R*,5R*)-4,5-*bis*-carbo-methoxy-3-ferrocenyl-2,3,4,5-tetrahydropyrazol-1-yl]-2-methylphthalazin-1(2*H*)-one (*c*-**2a**) (33% by *Method A*); 8-[(3R*,4S*,5S*)-4,5-*bis*-carbomethoxy-3-ferrocenyl-2,3,4,5-tetrahydropyrazol-1-yl]-6-methylpyrido[3,4-*d*]pyridazin-5(6*H*)-one (*t*-**2c**) (38% by *Method A* and 44% by *Method B*); 8-[(3R*,4R*,5R*)-4,5-*bis*-carbomethoxy-3-ferrocenyl-2,3,4,5-tetrahydropyrazol-1-yl]-6-methylpyrido[3,4-*d*]pyridazin-5(6*H*)-one (*c*-**2c**) (4% by *Method A* and 10% by *Method B*); 4-[(3R*p*,4R*,5S*)-4,5-*bis*-carbomethoxy-3-ferrocenyl-4,5-dihydropyrazol-1-yl]thieno[3,2-*c*]pyridine (**6**) (75% by *Method A*); 3-ferrocenyl-[1,2,4]-triazolo[4,3-*a*]thieno[3,2-*c*]pyridine (**7**); (14% by *Method A* and 69% by *Method B*) 4-(4,5-*bis*-carbomethoxy-3-ferrocenylpyrazol-1-yl)-thieno[3,2-*c*] pyridine (**8**) (22% by *Method B*); (3R*p*,4R*,5S*)-1-(4-bromophenyl)-4,5-*bis*-carbomethoxy-3-ferrocenyl-4,5-dihydropyrazole (11) (82% by *Method A*); 1-(4-bromophenyl)-4,5-*bis*-carbomethoxy-3-ferrocenyl-pyrazole (**12**) (69% by *Method B*). Hydrazones **1b**,**d**,**e** were recovered unchanged in good yields (93, 88 and 95%) by chromatography.

*Oxidation of pyrazolidines t,c-**2a** and pyrazolines **6** and **11*** carried out under the conditions of *Method B* (reaction time 6 h) followed by the purification described above yielded 76–88% of **5a** (from *t*,*c*-**2a**), **8** (from **6**) and **12** (from **11**).

*Oxidation of hydrazones **1b**,**e**, pyrazolidines t,c-**2c** and pyrazolines **6** and **11** by Method C.* The mixture of the substrate (1 mmol) and DDQ (0.227 g; 1 mmol) was dissolved in CH_2Cl_2 (5 ml). The reaction mixture was stirred at RT for 6 h then evaporated to dryness. The solid residue was recrystallized from ethanol (5–10 ml) to obtain the corresponding product (see Tables 2–5): 3-ferrocenyl-5-methyl-[1,2,4]-triazolo[4,3-*b*]pyrido[2,3-*d*]pyridazin-6(5H)-one (**4b**) (67%); 3-ferrocenyl-5-methyl-[1,2,4]-triazolo[4,3-*b*]-pyrido[3,2-*d*]pyridazin-6(5H)-one (**4e**) (71%); **5c** (83% from *t*-2c and 62% from *c*-**2c**); **8** (77%); **12** (85%). Employing the same procedure for hydrazones **1a**,**c**,**d** and pyrazolidines *t*,*c*-**2a** in each case a deep dark solution with unidentifyable paramagnetic substances was formed.

*Partial hydrolysis and decarboxylation of pyrazole **8** by Method D.* The substrate (0.501 g; 1 mmol) was dissolved in 100 ml of MeCN–H_2O (97-3). The solution was boiled for 15 min then evaporated in vacuo. The solid residue was recrystallized from EtOH (4 ml) to obtain 4-(4-carbomethoxy-3-ferrocenylpyrazol-1-yl)-thieno[3,2-*c*]pyridine (**9**) (0.332 g; 75%) as yellow needles (see Tables 2–5).

3. Results and discussion

The reaction of **1a** with dimethylfumarate (DMFM) in boiling MeCN (*Method B*), which resulted in the mixture of condensed triazole **4a** and pyrazoline **5a**, has been reported [2]. When the conversion was conducted at lower temperature (70°C, *Method A*), a 5.5:4.5 mixture of epimeric pyrazolidines (*t*-**2a** and *c*-**2a**) could be isolated in good yield (73%). Neither **4a** nor **5a** were isolated after this reaction. Now, we

Table 5
Physical and analytical data of compounds 1**c**,**d**, *t*-**2a**,**c**, *c*-**2a**,**c** **3**, **4b**,**e**, **5c** and **6**–**12**

	Appearance	Mp °C	Formula	Calcd%/Found% C	H	N	S/Br[a]
1c	Orange powder	194–197	$C_{19}H_{17}FeN_5O$	58.93/59.00	4.42/4.39	18,09/18.14	–
1d	Orange powder	203–205	$C_{19}H_{17}FeN_5O$	58.93/58.95	4.42/4.37	18,09/18.10	–
t–**2a**	Yellow needles	135–137	$C_{26}H_{26}FeN_4O_5$	58.88/58.79	4.94/4.98	10.56/10.56	–
c–**2a**	Yellow needles	140–143	$C_{25}H_{25}FeN_5O_5$	56.51/56.57	4.74/4.71	13.18/13.20	–
t–**2c**	Yellow powder	139–141	$C_{26}H_{26}FeN_4O_5$	58.88/58.89	4.94/4.88	10.56/10.58	–
c–**2c**	Yellow powder	134–137	$C_{25}H_{25}FeN_5O_5$	56.51/56.60	4.74/4.70	13.18/13.21	–
3	Brown powder	204–206	$C_{18}H_{15}FeN_3S$	59.85/59.78	4.19/4.18	11.63/11.68	8.86/8.90
4b	Red powder	168–170	$C_{19}H_{15}FeN_5O$	59.24/59.29	3.92/3.90	18.18/18.11	–
4e	Red powder	176–177	$C_{19}H_{15}FeN_5O$	59.24/59.20	3.92/3.96	18.18/18.17	–
5c	Orange powder	170–171	$C_{25}H_{23}FeN_5O_5$	56.73/56.81	4.38/4.40	13.23/13.19	–
6	Orange needles	160–162	$C_{24}H_{21}FeN_3O_4S$	57.27/57.28	4.21/4.16	8.35/8.36	6.37/6.40
7	Orange powder	150–152	$C_{18}H_{13}FeN_3S$	60.18/60.14	3.65/3.69	11.70/11.73	8.93/8.92
8	Orange powder	153–154	$C_{24}H_{19}FeN_3O_4S$	57.50/57.49	3.82/3.75	8.38/8.40	6.40/6.41
9	Orange powder	179–180	$C_{22}H_{17}FeN_3O_2S$	59.61/59.56	3.87/3.87	9.48/9.55	7.23/7.20
10	Red needles	157–160	$C_{17}H_{15}BrFeN_2$	53.30/53.33	3.94/3.88	7.31/7.38	20.86/20.91
11	Orange needles	131–133	$C_{23}H_{21}BrFeN_2O_4$	52.60/52.49	4.03/4.11	5.33/5.35	15.21/15.19
12	Orange cubes	120–121	$C_{23}H_{19}BrFeN_2O_4$	52.80/52.77	3.66/3.58	5.35/5.34	15.27/15.22

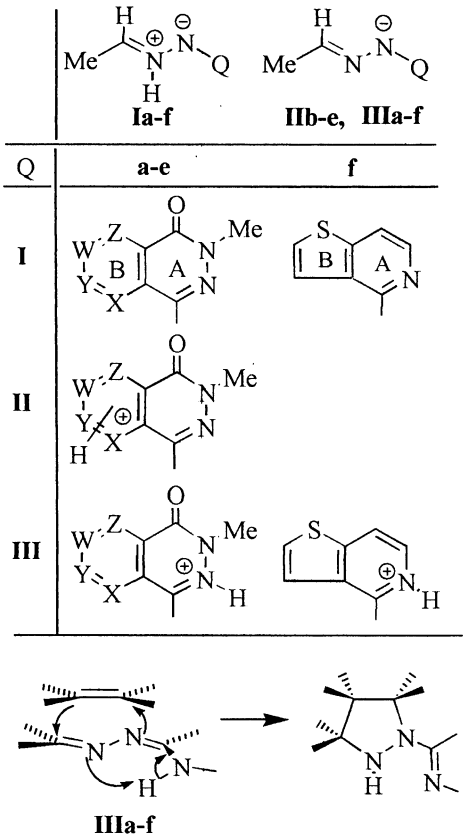
[a] S% for compounds **3**, **6**, **7**, **8** and **9** and Br% for compounds **10**, **11** and **12**.

intended to compare the reactivity of **1b**–**e** [3] with that of **1a** towards DMFM.

Under the same conditions (*Method A*) the two pyrido[2,3-*d*]pyridazinylhydrazones (**1b**,**e**) and one of the pyrido[3,4-*d*]pyridazinylhydrazone (**1d**) did not react at all. After prolonged treatment (40 h) at reflux temperature (*Method B*) 1**b**,**d**,**e** were recovered unchanged from the reaction mixtures. Pyrido[3,4-*d*]pyridazinylhydrazone (**1c**) was the only isomer which underwent a very slow cycloaddition even at 70°C affording a 9:1 mixture of diastereomeric pyrazolidines *t*-**2c** and *c*-**2c** (reaction time: 40 h; yield: 42%). In accord with our expectations the *t*:*c* ratios for **2a**,**c** (5.5:4.5 and 9:1, respectively) clearly indicate that the cycloaddition involving the intermediate formed by proton shift [2] from **1c** takes place with much higher diastereoselectivity than that involving the dipol formed from **1a** of more pronounced donor character. On the other hand, the importance of the acceptor character of the dipolarophilic component is also indicated by the fact that similar reactions of **1a**–**e** could not be carried out with cinnamic acid ethyl ester containing a less activated C=C double bond than does DMFM.

The electronaffinity of the *N*-substituent has also a significant effect on the redox properties both of the hydrazone and the primarily formed pyrazolidine, as supported by the following observations. While the reaction of **1a** by *Method B* gave directly pyrazoline **5a** and condensed triazole **4a**, [2] under the same conditions **1c** produced again *t*-**2c** and *c*-**2c** with a slightly lower selectivity (8.2:1.8, yield: 54%), but formation neither of pyrazoline **5c** nor a condensed triazole analogous to **4a** was detected even in traces. In control experiments both *t*-**2a** and *c*-**2a** could be oxidized to **5a** in refluxing MeCN in the presence of DMFM under an argon atmosphere (*Method B*). However, in the absence of DMFM no oxidation occurred in the boiling solvent suggesting that the oxidizing agent is the reagent itself. Accordingly, neither *t*-**2c** nor *c*-**2c** could be oxidized to **5c** with DMFM. However, DDQ dissolved in CH_2Cl_2 (*Method C*) proved to be a suitable reagent not only to perform conversions *t*, *c*-**2c** → **5c**, but also oxidative cyclization of pyrido[2,3-*d*]pyridazinylhydrazones (**1b**, **e** → **4b**, **e**) at room temperature. Using this reagent the hydrazones **1a**,**c**,**d** and the epimers *t*,*c*-**2a** underwent decomposition to unidentifyable substances. Pyrazolines **5a**,**c** resisted aromatization by *Method C*.

Reactions of thieno[3,2-*c*]pyridyl- and 4-bromophenylhydrazones (**3** and **10**) also demonstrate the



Scheme 2.

dependence of the reactivity of ferrocenylhydrazones and the oxidation level of products on the *N*-substituent. On treatment by *Method A* both **3** and **10** gave directly pyrazolines (**6** and **11**, respectively). Probably, due to their fast oxidation the primarily formed pyrazolidines could not be isolated in either cases. Besides pyrazoline **6** (75%) some condensed triazole **7** (14%) was also isolated. The reaction of **3** by *Method B* afforded **7** as the major product (69%) and a smaller amount of **8** (22%). Under the same conditions bromophenyl derivative **10** was converted to pyrazole **12**. Aromatization of the isolated pyrazolines (**6** → **8** and **11** → **12**, respectively) could be achieved either by *Method B* or *C*. Finally, the enhanced electron density of the pyridine ring due to the presence of the fused electron-releasing thiophene is reflected by the facile conversion of **8** → **9** probably including hydrolysis assisted by the pyridine-nitrogen and subsequent decarboxylation which was effected by boiling MeCN–H_2O (97-3) (*Method D*). Analogous conversion of pyrazole **12** could not be carried out by *Method D*.

The different reactivity pattern of closely related hydrazones (i.e. only **1a** and **1c** reacted with DMFM) is quite unprecedented in the literature. In order to rationalize this experimental finding we carried out semi-empirical calculations for the possible "active" forms of the hydrazones, using the model systems **1*****a–e** and **3*** (Me–CH=N–NHQ, * indicates that the Fc is replaced by a methyl group as shown on Scheme 2). Earlier results suggest [2] that the generation of the active species proceeds via proton shift inside the hydrazone moiety. However, except for **10**, this proton transfer can lead to more different intermediates (Scheme 2). The proton can move onto the adjacent hydrazone nitrogen (**Ia–f**), in form **II** onto the nitrogen of the distant heterocycle B (unavailable at **1*****a** and **3***), meanwhile in form **III** onto the proximal nitrogen of the pyridazine/pyridine ring A.

In the course of the calculations the geometry of the models **1*** and **3*** and all the isomeric forms **I–III** was optimised on semi-empirical (AM1) level and the heats of formation as well as the relevant frontier orbital (HOMO) energies (with reasonable 2_{pz} atomic orbital coefficients on both the carbon and the distant nitrogen of the hydrazone moiety) were calculated (MOPAC 6.0) and listed in Table 1. The calculated data suggest that the formation of the zwitterionic forms **I** and particularly **II** are unfavorable, and their formation (even in equilibrium) might practically be ruled out.

On the other hand, formation of the isomers **III** is not only feasible because of their reasonably lower heats of formation, but also reflects the tendency that in case of the reactive condensed pyridazines (**1*****a**,**c**) their formation is more favorable than that of the completely resistant isomers (**1*****b**,**d**,**e**). Our hypothesis is in very good accord with the case of thienopyridyl derivative **3**, the far most reactive investigated substrate, of which conversion by *Method A* was completed within 0.5 h. Calculations on its model analogue (**3***) furnished a strong argument for its high reactivity as the formation of tautomer **IIIf** is particularly favorable and its HOMO energy is also significantly higher than those for **IIIa–e**. Consequently, it seems plausible that the key step in the investigated

reactions of **1a–e** and **3** is the formation of the reactive intermediate **III** which then undergoes a fast cycloaddition associated with 1,4-proton migration (Scheme 2).

The characteristic IR-bands and the ^{1}H and ^{13}C NMR data of the new compounds are given in Tables 2 and 3.

The spectral data confirm the structures unambiguously without any explanation. (The single crystal X-ray analysis of pyrazole **12** was also carried out and provided as supplementary proof.) It is necessary to make the following remarks: In the pyrazolines (**5c**, **6** and **11**) and pyrazolidines (*t*/*c*-**2a**,**c**) the rotation of the ferrocenyl moiety is hindered. As a consequence, the signals of H/C-2,5 and H/C-3,4 of the substituted cylopentadienyl ring are separated due to the chemical non-equivalance of the related atom pairs in contrast to the same signals of the other compounds containing a pyrazole ring, in which these atom pairs have identical shifts and signals.

The possible tautomeric structure of the hydrazones (**1**) containing the NH-group in the ring was excluded for **1d** by DNOE experiment (Table 4) due to the NOE observed between the exocyclic-NH and H-8.

Similarly, the *trans* position of the two carbomethoxy groups was confirmed by mutual NOE's stated for the methoxy hydrogens and the vicinal H-4′ or H-5′ atoms in the pyrazoline/dine ring (e.g. *t*-**2a**, see Table 4).

The *cis* or *trans* orientation of H-3′ and H-4′ (the ferrocenyl moiety and the vicinal carbomethoxy group) follows from the significantly different H-3′ and H-5′ chemical shifts of the isomers. The H-3 atom is more shielded in the *trans* isomers (by 0.36 and 0.54 ppm for the *c*-*t* pairs of **2a**,**c**), due to the anisotropic shielding effect of the ester group. [4] The similar shielding of the Fc-moiety was observed on H-5′ in the *cis*-isomers (0.45 and 0.49 ppm for the *c*-*t* pairs of **2a** and **2c**). The *t*- or *c*-position of H-3′ and H-4′ is also reflected from the chemical shifts of the methoxy–hydrogens: while both signals have similar shifts in the *trans*-isomers (about 3.75 ppm), in their *cis*-counterparts one line is significantly upfield shifted (by ca 0.4 ppm–3.36 ppm) again due to the anisotropic shielding effect of the vicinal Fc-group. The assignment of the upfield shifted OMe-signal to the group in Pos. 4 was proved by DNOE experiment (cf. Table 4) for *c*-**2a**. The more crowded steric structure of the *cis* isomers is manifested in the upfield shift (steric compression shift [5,6]) of the C-4′ and one of C-2,5(Fc) lines by 2.2 and 1.5 ppm for *c*/*t*-**2a** and by 1.6 and 0.8 ppm for the *c*-*t* pair of **2c**. This effect is observable also for C-1(Fc) line of *c*/*t*-**2a** pair (2,7 ppm). Due to bad solubility, the shift of C-1(Fc) signal of *c*-**2c** is detectable only with limited accuracy, thus the similar effect for the pair *c*/*t*-**2c** was not determinable. The anisotropic shielding effect of the ester carbonyl group also results in an upfield shift of the H-2,5 and H-3,4 signals in the *cis*-**2a**,**c** isomers, while the NH-signal shows an opposite and larger downfield shift relative to the *trans*-counterparts (by 0.36 and 0.54 ppm for the *t*-*c* pairs of **2a**,**c**), due to stronger association in accord with the less hindered steric position of the NH-group in *c*-**2a**,**c**.

4. Conclusions

The reactivity of ferrocenylhydrazones of the investigated heteroarylhydrazines (**1a–e**, **3**) in 1,3-dipolar cycloaddition reaction with DMFM in MeCN highly depends on the *N*-heteroaryl group and the employed temperature. Besides the thieno[3,2-*c*]pyrid-4-yl derivative (**3**) of outstanding reactivity only the phthalazon-4-yl- and the pyrido[3,4-*d*]pyridazon-8-yl derivatives (**1a**,**c**) can be converted into the corresponding 3-ferrocenyl-1-heteroaryl-pyrazole with different oxidation levels (*t*-**2a**,**c**, *c*-**2a**,**c**, **5a**,**c**, **6**, **8**). According to comparative semi-empirical calculations (AM1), which give plausible reason for the observed substrate selectivity, the reactive intermediate is formed by a tautomerization step followed by the actual stereoselective cycloaddition (*t*-**2a**/*c*-**2a** and *t*-**2c**/*c*-**2c** $\gg 1$) associated with 1,4-proton migration. The transformation of *N*-(4-bromo-phenyl)hydrazone **10** with DMFM takes place in the expected way resulting in pyrazoline (**11**) and/or pyrazole (**12**) derivatives.

Under the conditions employed for cycloadditions the highly reactive *N*-thienopyridylhydrazone **3** partly undergoes oxidative cyclization in competitive manner to yield condensed 1,2,4-triazole **7**, too. Similar transformation of the pyrido[2,3-*d*]pyridazonylhydrazones **2b**,**e** which are completely resistant to cycloaddition, can be effected by DDQ in CH_2Cl_2 at

room temperature to obtain condensed triazoles **4b**,**e** in good yields.

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