Journal of Organometallic Chemistry 694 (2009) 3667–3673

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Application of Biginelli reaction to the synthesis of ferrocenylpyrimidones and [3]-ferrocenophane-containing pyrimido[4,5-*d*]pyrimidinediones

A. Csámpai [a], A.Z. Györfi [b], Gy.I. Túrós [c], P. Sohár [a,c,*]

[a] Institute of Chemistry, Eötvös Loránd University, H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary
[b] Department of Organic Chemistry, Babeş-Bolyai University, RO-40028 Cluj-Napoca, Str. Arany János 11, Romania
[c] Research Group for Structural Chemistry and Spectroscopy, Hungarian Academy of Sciences – Eötvös Loránd University, H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary

ARTICLE INFO

Article history:
Received 17 April 2009
Accepted 15 June 2009
Available online 18 June 2009

Keywords:
Ferrocene
Dihydropyrimidine
Biginelli reaction
[3]-Ferrocenophane
NMR spectroscopy

ABSTRACT

A series of ferrocene-containing *mono*- and *bis*-dihydropyrimidines (DHP's) were prepared by boric acid mediated three-component Biginelli reactions of formyl- and 1,1′-diformylferrocene, 1,3-dioxo-components and urea. A few further transformations including hydrogenolysis of a benzyl 4-ferrocenyl-DHP-5-carboxylate were also performed. Novel *cis*-fused saturated pyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones incorporating [3]-ferrocenophane moiety were constructed by means of iron(III)-catalyzed Biginelli-like condensations of 1,1′-diformylferrocene with urea and *in situ* generated methyl ketone-derived silyl enol ethers. The structures of the new compounds were established by IR and NMR spectroscopy, including HMQC, HMBC and DEPT measurements.

1. Introduction

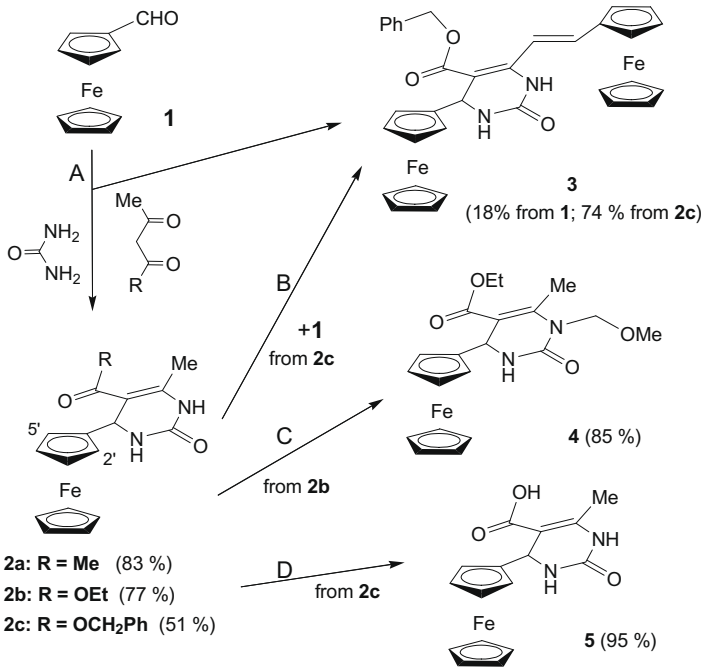
3,4-Dihydropyrimidin-2(1*H*)-ones and their derivatives (DHP's) have attracted great attention recently due to their pharmacological and therapeutic properties such as antibacterial–antihypertensive and calcium channel blocker activity as well as behaving as neuropeptide antagonists [1]. Biginelli reaction is a simple one-pot method for the synthesis of DHP's. The low-yielding condensations of β-dicarbonyl compounds with aldehydes and urea or thiourea can be improved using Lewis acids such as $BF_3{\cdot}OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, InX_3 (X = Cl, Br), $ZrCl_4$, $BiCl_3$, $LiClO_4$ as catalyst [2]. Microwave technique [3] and ultrasound irradiation [4] were also applied to increase the yields. In spite of the relative simplicity of the available methodologies and a wide range of biological effects found for simple ferrocene derivatives [5], only a few ferrocenyl-substituted DHPs including ethyl ester **2b** (Scheme 1) have been prepared by indium(III)-mediated synthesis [6]. Encouraged by their promising pharmaceutical properties we started to search for expedient synthetic routes to a variety of further DHP's containing ferrocenes.

2. Results and discussion

First, we applied boric acid as catalyst (0.2 equiv.) in acetic acid solution containing 1,3-dioxo components (1 equiv.) and urea (1.2 equiv.) [7] to convert formylferrocene (**1**) at 100 °C (Method A) into the corresponding 4-ferrocenyl DHP (**2a**–**c**, Scheme 1). Within a relatively short reaction time (1 h) good yields were achieved for **2a** and **2b** (83% and 77%, respectively), but a mediocre yield (51%) was obtained for benzyl ester **2c** contaminated by a substantial amount of ferrocenylvinyl derivative **3** (18%) which was formed by aldol condensation of the activated 6-methyl group with unreacted **1**. When **2c** was condensed with **1** under the conditions of Method B employing 0.2 equiv. of boric acid and prolonged reaction time (4 h) (Scheme 1) **3** formed in higher yield (74%). The exclusive formation of C=C double bond with "*E*"-configuration in **3** can be attributed to the much higher degree of steric crowding which would be accumulated in the "*Z*"-isomer. In order to get carboxylic acid **5**, suitable to coupling with a variety of biomolecules, a mild hydrolysis of **2b** was attempted under PTC conditions using Bu_4NOH in a 20:1 mixture of DCM–MeOH (Method C). Instead of esther-hydrolysis consuming the whole amount of the applied base (1 equiv.) methoxymethylation on the more acidic 1-NH group took place with the participation of both components of the solvent mixture selectively resulting DHP **4** in good yield (85%). Finally, facile debenzylation of **2c** was carried out by catalytic hydrogenation over Pd(C) in EtOAc–AcOH (3:1) solution to give carboxylic acid **5** in almost quantitative yield (Scheme 1). Combination of these two supplementary reactions of these two

* Corresponding author. Address: Research Group for Structural Chemistry and Spectroscopy, Hungarian Academy of Sciences – Eötvös Loránd University, H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary. Tel.: +36 1 209 0555 1900; fax: +36 1 209 0602.
E-mail address: sohar@chem.elte.hu (P. Sohár).

0022-328X/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2009.06.017

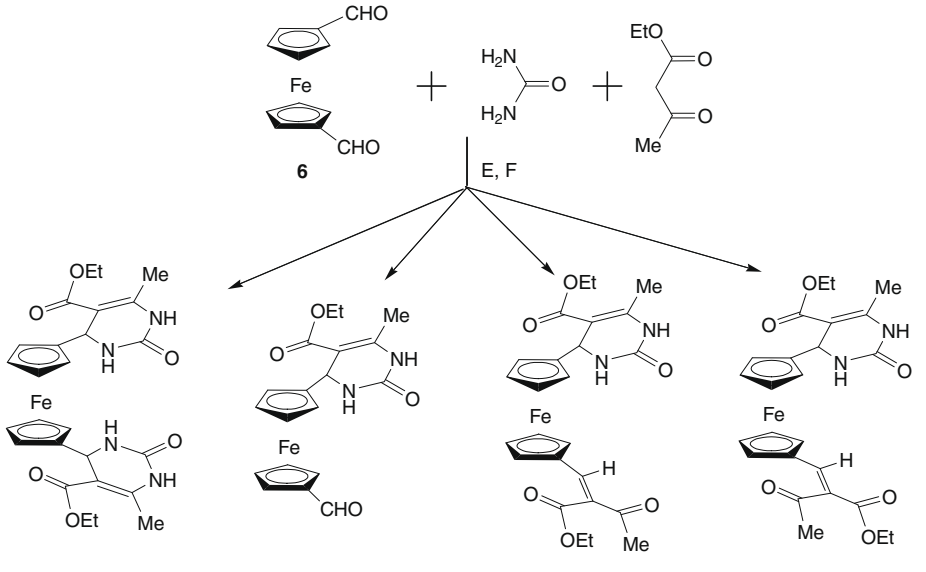


A: H_3BO_3 (0.2 equiv.), 1,3-dicarbonyl component (1 equiv.), urea (1.2 equiv.), AcOH, 100 °C, 1 h
B: H_3BO_3 (0.2 equiv), AcOH,100 °C: 4 h;
C: Bu_4NOH, DCM-MeOH (20:1), rt, 5 h;
D: H_2/Pd(C) EtOAc-AcOH (3-1), 1h

Scheme 1.

esters may open up ways to a number of selectively polyfunctionalized DHP's.

Using 0.4 equiv. of boric acid, an analogous cyclization reaction of 1,1′-diformyl-ferrocene (**6**) was also attempted with ethyl acetoacetate (2 equiv.) and 2.4 equiv. of urea (Method E). The reaction afforded *bis*-DHP **7** as a single diastereomer (Scheme 2) in moderate yield (42%) along with *mono*-DHP's [**8** (10%), (*Z*)-**9** (18%) and (*E*)-**9** (12%)] derived from incomplete reactions on one of the Cp rings. In an attempt to increase the ratio of the target compound we employed four equivalents of urea with 6 h reaction time (Method F, Scheme 2) and **7** could be isolated in 70% yield with decreased amount of *mono*-DHP's **8**, (*Z*)-**9** and (*E*)-**9** (4%, 10% and 7%). The comparable yields of the latter two products can be reasoned by the similar size of the acetyl- and ethoxycarbonyl groups. It is worth



7 [42% (E); 70% (F)] **8** [10% (E); 4% (F)] (*Z*)-**9** [18% (E);10% (F)] (*E*)-**9** [12% (E); 7% (F)]

E: H_3BO_3 (0.4 equiv.), 1,3-dicarbonyl component (2 equiv.), urea (2.4 equiv.), AcOH, 100 °C, 4 h

F: H_3BO_3 (0.4 equiv.), 1,3-dicarbonyl component (2 equiv.), urea (4 equiv.), AcOH, 100 °C, 6 h

Scheme 2.

to point out that the formation of the alternative diastereomer of **7** was not observed at all. So far we have failed to grow crystals suitable for X-ray analysis and the relative configuration could not be determined on the basis of NMR data.

In order to get 2,4-diferrocenyl-DHP without substituent at position 5 we resorted to a Biginelli-like protocol developed by Wang et al. [8] reacting formylferrocene (**1**) with acetylferrocene (**10**) and urea in the presence of catalytic amount of $FeCl_3{\cdot}6H_2O$ (0.1 equiv.) and TMSCl (1 equiv.) in refluxing MeCN (Method G, Scheme 3). Although the reaction was conducted under argon, we could isolate only 2,4-diferrocenyl-2-hydroxypyrimidine (**11**) in moderate yield (38%). We assume that in the course of work-up the primarily formed target compound underwent facile aromatization promoted by two ferrocenyl groups.

An interesting bridging reaction associated with the formation of *cis*-anellated hexahydropyrimido[4,5-*d*]pyrimidine ring system (**12a–d**, Scheme 4) took place when the reaction of 1,1′-diformylferrocene (**6**) was conducted in the presence of doubled amount of the keton component (2 equiv.), urea (3 equiv.), $FeCl_3{\cdot}6H_2O$ (0.2 equiv.) and TMSCl (2 equiv.) (Method H). The facile formation of this ring system incorporating [3]-ferrocenophane unit can be rationalized by two subsequent aldol reactions followed by condensation with two molecules of urea. The new tetraazadecalines of type **12** accessible by our reactions can be explored as precursors for the synthesis of a wide variety of new saturated heterocycle-bridged ferrocene derivatives due to the presence of four non-equivalent NH groups.

3. Structure

The spectral data proving the postulated structures of the new compounds are given in Tables 1A, B, 2A, B and 3. Only the following additional remarks are necessary.

The formation of the dihydropyrimidone ring (Biginelli-product) follows straightforwardly from the presence of a carbonyl line in the ^{13}C NMR spectra of compounds **2**–**5** and **7**–**9**, from the chemical shifts characteristic [9] for urethanes (153.9–154.9 ppm) and from the two NH-signals in ^1H NMR between 6.3 and 7.6 ppm (NH-3) and 7.6 and 9.2 ppm (NH-1), respectively, removable by adding heavy water.

Due to smaller α-effect of a C(sp^2) atom as compared to that of C(sp^3) (by >10 ppm) [9] the C-1′ signal of the Fc moiety attached to the vinyl group in **3** appears at 82.1 ppm, while this line falls in the interval of 92.7–95.2 ppm for compounds **2a–c**, **4**,**5**, **7** and **8**.

The OCH_2 signal is downfield shifted (66.0 and 66.5 ppm) both in ^1H and ^{13}C NMR spectra of **2c** and **3** (for the $PhCH_2O$ groups) relative to the ethyl esters **2b**, **4**, **7**, **8** and **9** (*E* and *Z*) (60.2–62.4 ppm).

The N(1)-substitution in **4** is revealed by the upfield shift of NH(3) signal (to 5.74 ppm), probably due to the absence of H-bonds which reduces the electron attracting property of the neighbouring carbonyl group forming dimeric cyclic association with the NH(1) group in the other compounds.

The symmetric (aromatic iminohydrine) form of **11** follows from the identical shifts of C-4 and C-6 as well as of the C-1′ (and all further) lines of both Fc substituents.

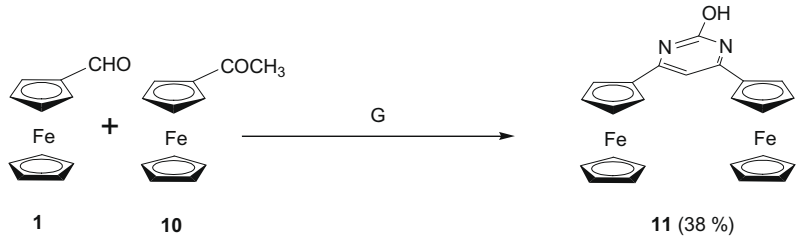
Similarly, the identical shifts of all H/C-signals of the two pyrimidone moieties and Cp rings, respectively, in **7** confirm the symmetric structure of this compound.

The structure of **8** is evidenced by the presence of the formyl H/C signals in both the ^1H and ^{13}C NMR spectra (10.03 and 195.0 ppm).

The *E* and *Z* configurations, resp., of the isomers **9** are unambiguous because of the field effects [10] on C=O and CH_3 lines of the acetyl group in *E* and on ester C=O in *Z* isomer: 194.2 and 27.0 ppm for (*E*)-**9**, while 205.5 and 31.5 ppm for (*Z*)-**9** and 164.9 ppm for (*Z*)-**9**, while 170.0 for (E)-**9**, respectively.

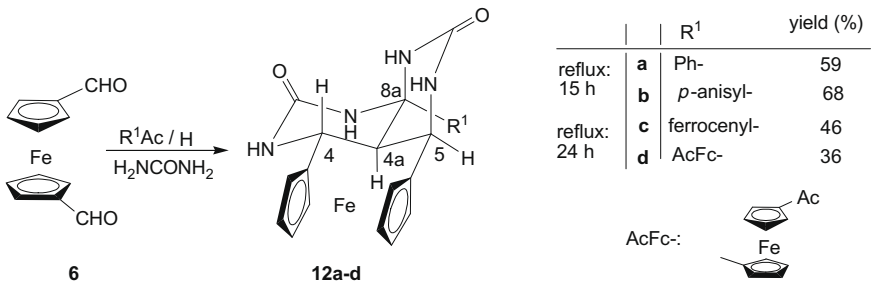
The structures of **12a–d** are supported by the following facts:

(1) The signals of R^1 group (e.g., the H/C signals of the phenyl substituent in case of **12a**, the OCH_3 and CH_3(Ac) signals for **12b** and **12d**, respectively, and the signals of a second ferrocenyl moiety for **12c** and **12d**) are present in the ^1H and ^{13}C NMR spectra.



G: urea (1.5 equiv.), $FeCl_3{\cdot}6H_2O$ (0.1 equiv.), TMSCl (1 equiv.), MeCN, reflux: Ar, 24 h

Scheme 3.



H: R^1Ac (2 equiv.), urea (3 equiv.), $FeCl_3{\cdot}6H_2O$ (0.2 equiv.), TMSCl (2 equiv.), MeCN, reflux

Scheme 4.

Table 1A
The most important ^{1}H NMR data[a] of compounds **2a–c**, **3–5**, **7**, **8**, (*E*)-**9**, (*Z*)-**9** and **11**.[b]

Compound	CH_3 (Pos 6) *s* (3H)	CH_3[c] *t* (3H)	CH_2[d] *qa*[e] (2H)	H4[e] *d* (1H)	H-2,5 (2H or 2 × 1H) Substituted *c*-pentane ring	H-3,4 (2H or 2 × 1H)	CH[f] *s* (5H)	NH-1 br (1H)	NH-3 br (1H)
2a[g]	2.19	–		5.05	3.92, 4.10	4.05	4.18	9.10	7.58
2b	2.15	1.23	4.10	4.95	3.94, 4.09	4.07, 4.08	4.18	9.10	7.47
2c[g]	2.25	–	~5.15[h]	~5.15[h]	4.08, 4.14	4.05	4.17	8.46	6.45
3	–	–	5.21	5.07	4.35 (4H)	4.00, 4.07 (2H), 4.09	4.14, 4.17	9.17	7.57
4	2.45	1.34	4.22	5.16[i]	4.09, 4.24	4.10 4.13	4.20		5.74
5	2.13	–	–	4.92	3.95[j], 4.10	4.05 (4H)[j]	4.17	9.00	~ 7.4
7	2.16	1.23	~4.1[h]	4.95	~4.1[h]	~4.1[h]	–	9.09	7.49
8	2.26	1.32	4.19	5.11	4.30, 4.47, 4.80, 4.95	4.16, 4.21, 4.67 (2H)	–	8.29	6.34
(*E*)-**9**	2.22	1.34, 1.37	4.21[h], 4.40	5.17	4.22[h], 4.36, 4.58 (2H)[k]	4.15, 4.16, 4.56 (2H)[k]	–	7.68	6.74
(*Z*)-**9**	2.23	1.33, 1.35	4.21, 4.28	5.18	4.23, 4.37, 4.49[k], 4.54[k]	4.13, 4.14, 4.52 (2H)[k]	–	7.66	6.81
11	–	–	–	–	5.03 (4H)	4.63 (4H)	4.20	–	–

[a] In DMSO-d_6 or $CDCl_3$ (for **4** and **8**) solution, for **11** in $CDCl_3$ + CD_3OD at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz.
[b] Assignments were supported by HMQC and HMBC (except for **2c**, **5**, **7** and **11**), for **2a**, **c**, **d** also by 2D-COSY measurements. Further signals, CH_3(Ac), *s* (3H): 2.23 (**2a**), 2.38 [(***E***)-**9**], 2.42 [(***Z***)-**9**]; OCH_3, *s* (3H): 3.37 (**4**), OH, *br* (1H): 11.95 (**5**), 7.39 (**11**), CHO, *s* (1H): 10.03 (**8**); =CH (α to Cp): 7.20, *d*, *J*: 16.4 (**3**), 7.46 *s* [(***E***)-**9**, (***Z***)-**9**], =CH (β to Cp): 7.35, *d* (**3**); H-5 *s* (1H): 6.53 (**11**).
[c] Ethyl group, *t* (3H), *J*: 7.1, for **7** 6.9 and for (***Z***)-**9** 7.3.
[d] *s* (**2c** and **3**).
[e] *d* (*J*: 4.0 for **2a**,**b**, **3**, **5**, 3.1 for **7** and **8**, 3.6 for (***E***)-**9**, (***Z***)-**9**.
[f] Unsubstituted Cp ring in ferrocene.
[g] Contaminated: 0.5 mol CH_2Cl_2 (**2a**, δ: 5.74 ppm) and H_3BO_3 (**2c**, δ: 4.73 ppm).
[h] Overlapping signals.
[i] In overlap with the NCH_2 signal (3H).
[j] Interchangeable assignments.
[k] With the CH=C(Ac)COOEt group substituted Cp ring.

Table 1B
The most important 1H NMR data[a] of compounds **12a–d**.[b]

Compound	H-4a *d* (1H)	H-5 *s* (1H)	H-4[c] *d* (1H)	H-2,5 (2H) Substituted *c*-pentane ring	H-3,4 (2H)	CH[d] *s* (5H)	NH-1 br (1H)	NH-3 br (1H)
12a	2.77	3.64	4.13	3.90, 4.47, 4.24, 4.60	3.95, 4.03[e], 4.04[e], 4.12		7.00, 6.81	6.28, 6.56
12b	2.74	3.69	4.12[e]	3.92, 4.48, 4.23, 4.59	3.95, 4.03[e], 4.04[e], 4.12[e]		7.04, 6.83	6.25, 6.16
12c	2.34	3.97[f]	4.04	3.91, 4.47, 4.22, 4.44	3.95, 4.03[e], 4.03[e], 4.09	4.41	7.27, 6.95	5.39, 6.50
12d	2.35	3.97	4.03[e]	3.89, 4.47, 4.22, 4.41[fp]	3.95, 4.03 [e], 4.02[e], 4.08		7.22, 6.94	5.38, 6.50

[a] In DMSO-d_6 solution at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz.
[b] Assignments were supported by HMQC and HMBC measurements. Further signals, CH_3(Ac), *s* (3H): 2.38 (**12d**), H(Fc-8a): 4.41[d] (**12c**), H25 (Fc-8a,subst. Cp in **12c**): ~4.3 (2H), 4.33 and 4.07; H(Cp attached to the skeleton in Pos. 8a, **12d**), H2,5: 4.06, 4.30, H3,4: 4.32, 4.40[f], H(Ac-subst.Cp, **12d**): H2,5: 5.02, 5.06, H3,4: 4.80 (2H).
[c] *d* (*J*: 10.7 for **12a**,**c** and 10.4 for **12b**).
[d] Unsubstituted Cp ring in ferrocene.
[e] Overlapping signals.
[f] *d*, *J*: 3.

Table 2A
The most important ^{13}C NMR chemical shifts[a] of compounds **2a–c**, **3–5**, **7**, **8** and (*E*)-**9**, (*Z*)-**9**.[b,c]

Compound	CH_3 (Pos. 6)	CH_3 (Et)	CH_3 (Ac)	CH_2 (R)	C=O(2)	C-4	C-5	C-6	Cp[d] (Fc)	C-1′	C-2′,5′	C-3′,4′	C=O (R)
					Pyrimidone ring					Substituted *c*-pentane ring			
2a	19.7	–	31.3	–	153.9	49.4	112.5	147.7	69.4	95.0	66.3, 66.9	67.6, 68.0	194.9
2b	18.5	15.2	–	60.2	153.9	49.6	101.7	148.3	69.3	94.6	65.9, 66.8	67.8, 68.1	166.4
2c	18.8	–	–	66.0	154.5	50.3	102.0	147.6	68.8	93.6	65.5, 67.4	67.7, 68.0	166.0
3	–	–	–	66.5	154.3	49.8	101.8	137.2	69.4, 70.2	94.1, 82.1	66.1, 66.5, 66.9, 67.8	68.0, 68.1, 68.8, 70.8	166.2
4	15.9	14.8	–	60.8	154.9	50.1	107.2	147.1	69.0	92.7	65.5, 67.8	68.3, 68.5	166.5
5	18.5	–	–	–	154.2	49.9	102.2	147.4	69.4[e]	94.6	66.1, 66.8	68.0, 69.4[e]	168.2[f]
7	18.5	15.1	–	60.2	154.0		101.4	148.5	–	94.8	66.9, 67.4	68.8, 69.2	166.4
8	19.2	14.8	–	60.6	154.7	50.1	120.8	146.7	–	95.2	67.3, 68.8	69.3, 70.1	166.1
(*E*)-**9**[g]	19.3	14.5, 14.9	27.0	60.5, 62.4	154.5	49.7	103.0	146.6	–	94.8, 76.4	67.8, 68.5, 71.4, 71.7	69.1, 70.2, 73.18, 73.21	166.2, 170.0
(*Z*)-**9**[g]	19.3	14.6, 14.8	31.5	60.4, 61.6	154.5	49.7	102.9	146.7	–	94.8, 76.6	67.6, 68.5, 71.1, 72.0	69.0, 70.2, 72.9, 73.0	166.1, 164.9

[a] In DMSO-d_6 or $CDCl_3$ (for **4** and **8**) solution at 125 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm).
[b] Assignments were suppported by DEPT (except for **2c** and **5**), HMQC (except for **2c**, **5** and **7**) and HMBC (except for **2c**, **3**, **5** and **7**).
[c] Further lines: Olefinic =CH's α and β to Fc: 136.5 and 117.5 (**3**), 142.2 and 129.5 [(***Z***)-**9**], 142.9 and 130.6 [(***E***)-**9**]; NCH_2: 74.0 (**4**); OCH_3: 56.7 (**4**); C=O (formyl, **8**): 195.0; C-1′, C-2′,5′ and C-3′,4′ for formyl substituted Cp: 79.9, 70.2 and 71.5, 74.3 and 74.4 (**8**); C=O(Ac): 194.2 (**9***E*), 205.5 (**9***Z*).
[d] C-1′-5′ (unsubstituted Cp).
[e] Overlapping lines.
[f] Carboxyl group.
[g] The data in the first row refer to the pyrimidone substituted Cp ring, in the second row to the side chain [(***E***)-**9**, (***Z***)-**9**].

Table 2B
The most important ^{13}C NMR chemical shifts [a] of compounds **11** and **12a–d**.[b,c]

Compound	CH_3 (Ac)	CH_2 (R)	C=O(2)	C-4	C-5	C-6	Cp[d] (Fc)	C-1′	C-2′,5′	C-3′,4′
			Pyrimidone ring					Substituted *c*-pentane ring[e]		
11	–	–	159.0	146.2[f]	98.3	146.2[f]	70.8		68.7	72.5
12a	–	–	154.7, 155.7	46.2, 46.3	52.9	71.6	–	86.6, 84.8	66.3, 69.1, 67.9, 72.2	68.1, 70.3, 69.3, 70.8
12b	–	–	154.8, 155.8	46.2, 46.3	53.1	71.2	–	86.6, 84.9	66.3, 69.1, 67.8, 72.2	68.1, 70.3, 69.3, 70.8
12c	–	–	154.0, 155.4	46.4, 46.5	53.9	67.3	69.5	86.8, 84.7	66.3, 69.2, 67.7, 72.2	68.1, 70.4, 69.3, 70.8
12d	28.4	–	154.0, 155.2	46.3, 46.5	53.5	67.3	–	86.6, 84.6	66.3, 69.2, 67.6, 72.2	68.05, 69.4, 67.6, 70.89

[a] In DMSO-d_6 solution, for **11** in $CDCl_3$ + CD_3OD at 125 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm).
[b] Assignments were supported by DEPT (except for **11**), HMQC and HMBC (except for **11**).
[c] Further lines: OCH_3: 56.1 (**12b**); C-1′, C-2′,5′ and C-3′,4′ for Cp in Pos. 8a (**12c**,**d**): 97.9, 68.4 and 68.7, 65.9 and 70.1 (**12c**, Cp attached to the HC), 99.1, 68.11 and 69.6, 70.5 and 72.1 (**12d**, Cp attached to the HC), 80.7, 70.85 and 71.4, 73.8[e] (**12d**, Ac-substituted. Cp).
[d] C-1′-5′ (unsubstituted Cp).
[e] The data in the first row refer to the Cp ring attached to C-4, in the second row to C-5.
[f] Because of molecular symmetry C-4 and C-6 have common lines in **11**.

Table 3
The most important characteristic IR frequencies [cm^{-1}] of compounds **2a–c**, **3–5**, **7**, **8**, (*E*)-**9**, (*Z*)-**9**, **11** and **12a d** (in KBr discs).*

Compound	νNH band broad or diffuse (*df*)	*ν*C=O (ester)	Amide-I band[a]	*ν*C=O ketone or aldehyde	ν_{as}Cp–Fe–Cp and tilt of Cp
2a	3500–2500 *df*	–	1609	1701	497
2b	3500–2500 *df*	1702	1647	–	489
2c	3250, 3110	1710	1685	–	498, 486
3	3419, 3235, 3090	–	1687	–	485
4	3320, 3226	1706	1691	–	504
5	3600–2700 *df*	1684	1656	–	499, 484
7	3240, 3110	1702	1648	–	488
8	3248, 3113	1701	1644	1684	526, 495, 485
(*E*)-**9**	3375, 3235	1699	1653	1688	482
(*Z*)-**9**	3250, 3115	1701[b]	1651	1701[b]	522
11	3350–2600 *df*	–	–	–	502, 483
12a	3405, 3215, 3085	–	1689	–	524, 509
12b	3500–2800 *df*	–	1681	–	522
12c	3415, 3310, 3220		1670	–	523, 513, 489
12d	3500–2700 *df*	–	1670[b]	1670[b]	525

* Further bands, *ν*C=N-type aromtic skeletal band (**11**): 1622, *ν*C=C band: 1645 (**2c**), 1624 (**5**), 1611 (**9***Z*), *ν*C=O: 1–3 bands between 1029 and 1242 cm^{-1}:$\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ bands: 757 and 697 (**2c**), 762 and 700 (**12a**).
[a] Splitted band, with the second maximum at 1662 (**12b**).
[b] Overlapped maxima.

(2) The chemically non-equivalent H/C pairs in positions 2,5 and 3,4 in both Cp rings of the skeleton give separated signals in contrast to **7**, where the two not condensed pyrimidone moieties give chemically equivalent signals with doubled intensity.
(3) The H/C signals of three C(sp^3)H groups (in positions 4, 4a and 5) and the signal of a saturated quaternary carbon (C-8a) are observable in the ^1H and ^{13}C NMR spectra.
(4) The high value (>10.5 Hz) of the H-4,H-4a vicinal coupling refers to a *diaxial* interaction [11] and a small H-4a,H-5 coupling proves ca. 60° dihedral angle of the latter H's in accord with their *axial–equatorial* interaction giving unambiguous support to the *cis*-annealation of the two saturated pyrimidine rings.

4. Experimental

Melting points were determined with a Boethius microstage and are uncorrected. The IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 spectrometer at 500.13 (^1H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. DEPT spectra [12] were run in a standard manner [13] using only a Θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-COSY [14a,15a] HMQC [14b,15b] and HMBC [16,17] spectra were obtained by using the standard Bruker pulse programs.

4.1. Three-component condensations of formylferrocene (*1*) by Method A

A solution of **1** (0.642 g, 3 mmol), 1,3-dicarbonyl compound (3 mmol), urea (0.216 g, 3.6 mmol) and H_3BO_3 (0.037 g, 0.6 mmol) in glacial acetic acid (10 mL) was heated under Ar at 100 °C, while stirring for 1 h. After the reaction mixture was cooled to r.t. and was poured into ice-water (50 mL). The precipitated solid was filtered, washed with ice-water, dried and subjected to flash column chromatography on silica using DCM–eOH (80:1) as eluent to obtain the products which were recrystallized from EtOH.

4.2. 5-Acetyl 3,4-dihydro-4-ferrocenyl-6-methylpyrimidin-2(1H)-one (*2a*)

Yellow microcrystals; yield: 0.842 g, 83%; mp 243–245 °C (decomp.); Anal. Calc. for $C_{17}H_{18}FeN_2O_2$ (338.18): C, 60.38; H, 5.36; N, 8.28. Found: C, 60.50; H, 5.54; N, 8.16%.

4.3. Ethyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-methyl-2-oxopyrimidine-5-carboxylate (*2b*)

Yellow powder; yield: 0.850 g, 77%; mp 227–230 °C (decomp.) (229–231 °C [6]); Anal. Calc. for $C_{18}H_{20}FeN_2O_3$ (368.21): C, 58.71; H, 5.47; N, 7.61. Found: C, 58.56; H, 5.54; N, 7.72%.

*4.4. Benzyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-methyl-2-oxopyrimidine-5-carboxylate (**2c**)*

Yellow powder; yield: 0.636 g, 51%; mp 285–288 °C (decomp.); Anal. Calc. for $C_{22}H_{20}FeN_2O_3$ (416.25): C, 63.48; H, 4.84; N, 6.73. Found: C, 63.40; H, 4.91; N, 6.65%.

*4.5. Benzyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-(2-ferrocenylvinyl)-2-oxopyrimidine-5-carboxylate (**3**)*

Orange needles; yield: 0.338 g, 18%; mp 234–238 °C(decomp.); Anal. Calc. for $C_{34}H_{30}Fe_2N_2O_3$ (626.30): C, 65.20; H, 4.83; N, 4.47. Found: C, 65.32; H, 4.95; N, 4.55%.

*4.6. Aldol condensation of **2c** with **1** by Method B*

A solution of **2c** (0.416 g, 1 mmol), **1** (0.214 g, 1 mmol) and H_3BO_3 (0.013 g, 0.2 mmol) in glacial acetic acid (4 mL) was heated under Ar at 100 °C, while stirring for 4 h. The reaction mixture was cooled to r.t. and was poured into ice-water (20 mL). The precipitated yellowish-grey solid was filtered, washed with ice-water, dried and purified by flash column chromatography on silica using DCM–MeOH (80:1) as eluent to separate the tarry substances from **3** which was recrystallized from EtOH. Yield: 0.463 g, 74%. Within experimental error the analytical and spectral data were identical with those listed under Method A.

*4.7. Attempted hydrolysis of **2b**: formation of ethyl 1,2,3,4-tetrahydro-4-ferrocenyl-1-(methoxymethyl)-6-methyl-2-oxopyrimidine-5-carboxylate (**4**) (Method C)*

To the suspension made of **2b** (0.736 g, 2 mmol) and DCM (40 mL) 1 M methanolic solution of Bu_4NOH (2 mL) was added under Ar. The reaction mixture was stirred at r.t. under Ar for 5 h and extracted with water (3 × 50 mL). The organic phase was dried (Na_2SO_4) and evaporated. The solid residue was recrystallized from EtOH to obtain **4** as yellow microcrystals. Yield: 0.700 g, 85%; mp 184–187 °C; Anal. Calc. for $C_{20}H_{24}FeN_2O_4$ (412.26): C, 58.27; H, 5.87; N, 6.80. Found: C, 58.45; H, 5.65; N, 6.64%.

*4.8. 1,2,3,4-Tetrahydro-4-ferrocenyl-6-(2-ferrocenylvinyl)-2-oxopyrimidine-5-carboxylic acid (**5**) (Method D)*

In the solution of **2c** (0.416 g, 1 mmol) in the mixture of EtOAc–AcOH (24–8 mL) Pd/C (0.2 g) was suspended. The mixture was hydrogenated at atmospheric pressure for 1 h and the catalyst was removed by filtration. The yellow solution was evaporated and the residue was recrystallized from EtOH to obtain **5** as yellow powder. Yield: 0.323 g, 95%; mp 295–298 °C (decomp.); Anal. Calc. for $C_{16}H_{16}FeN_2O_3$ (340.15): C, 56.50; H, 4.74; N, 8.24. Found: C, 56.65; H, 4.83; N, 8.27%.

*4.9. Three-component condensations of 1,1′-diformylferrocene (**6**) by Methods E and F*

A solution of **6** (0.484 g, 2 mmol), ethyl acetoacetate (0.520 g, 4 mmol), urea (0.290 g, 4.8 mmol by Method E and 0.480 g, 8 mmol by Method F, resp.) and H_3BO_3 (0.025 g, 0.4 mmol) in glacial acetic acid (20 mL) was heated under Ar at 100 °C, while stirring (for 4 h by Method E and for 6 h by Method F, respectively).After the reaction mixture was cooled to r.t. and was poured into ice-water (100 mL). The precipitated solid was filtered, washed with ice-water, dried and subjected to flash column chromatography on silica using DCM–MeOH (50:1) as eluent to obtain the products which were recrystallized from EtOH.

*4.10. 1,1′-Bis-(1,2,3,4-tetrahydro-5-ethoxycarbonyl-6-methyl-2-oxopyrimidine-4-yl)ferrocene (**7**)*

Yellow powder; yield: 0.462 g, 42% (by Method E) and 0.771 g, 70% (by Method F); mp > 310 °C; Anal. Calc. for $C_{26}H_{30}FeN_4O_6$ (550.38): C, 56.74; H, 5.49; N, 10.18. Found: C, 56.62; H, 5.42; N, 10.32%.

*4.11. Ethyl 1,2,3,4-tetrahydro-4-(1′-formylferrocenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (**8**)*

Orange powder; yield: 0.079 g, 10% (by Method E) and 0.032 g, 4% (by Method F); mp 260–264 °C (decomp.); Anal. Calc. for $C_{19}H_{20}FeN_2O_4$ (396.22): C, 57.60; H, 5.09; N, 7.07. Found: C, 57.72; H, 5.12; N, 7.18%.

*4.12. Ethyl 4-(1′-((Z)-2-(ethoxycarbonyl)-3-oxobut-1-enyl)ferrocenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ((Z)-**9**)*

Red powder; yield: 0.183 g, 18% (by Method E) and 0.102 g, 10% (by Method F); mp 252–256 °C (decomp.); Anal. Calc. for $C_{25}H_{28}FeN_2O_6$ (508.34): C, 59.07; H, 5.55; N, 5.51. Found: C, 58.96; H, 5.72; N, 5.59%.

*4.13. Ethyl 4-(1′-((E)-2-(ethoxycarbonyl)-3-oxobut-1-enyl)ferrocenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate ((E)-**9**)*

Red powder; yield: 0.122 g, 12% (by Method E) and 0.071 g, 7% (by Method F); mp 274–278 °C (decomp.); Anal. Calc. for $C_{25}H_{28}FeN_2O_6$ (508.34): C, 59.07; H, 5.55; N, 5.51. Found: C, 59.21; H, 5.60; N, 5.67%.

*4.14. Iron(III)-mediated condensation of formylferrocene (**1**), acetylferrocene (**10**) and urea: preparation of 4,6-diferrocenylpyrimidin-2-ol (**11**) by Method G*

Under Ar urea (0182 g, 3 mmol), **10** (0.456 g, 2 mmol) and TMSCl (0.218 g, 2 mmol) were added successively to a solution of **1** (0.428 g, 2 mmol) and $FeCl_3{\cdot}6H_2O$ (0.054 g, 0.2 mmol) in MeCN (6 mL). The reaction mixture was refluxed for 24 h under Ar then cooled to r.t. and quenched with water (40 mL). The precipitated dark solid was filtered off, dried and purified by flash column chromatography on silica using *n*-hexane–EtOAc (3:1) as eluent to obtain **11** separated from tarry substances. The solid product was recrystallized from EtOH affording deep red microcrystals. Yield: 0.353 g, 38%; mp 297–300 °C (decomp.); Anal. Calc. for $C_{24}H_{20}Fe_2N_2O$ (464.12): C, 62.11; H, 4.34; N, 6.04. Found: C, 62.21; H, 4.21; N, 5.97%.

*4.15. Iron(III)-mediated condensations of 1,1′-diformylferrocene (**6**), methyl-ketones and urea Method H*

Under Ar urea (0364 g, 6 mmol), the corresponding ketone (4 mmol) and TMSCl (0.436 g, 4 mmol) were added successively to a solution of **6** (0.484 g, 2 mmol) and $FeCl_3{\cdot}6H_2O$ (0.108 g, 0.4 mmol) in MeCN (10 mL). The reaction mixture was refluxed for the time given in Scheme 4 then cooled to r.t. and quenched with water (70 mL). The precipitated dark solid was filtered off, dried and purified by flash column chromatography (silica DCM–MeOH (25:1)) and subsequent crystallization from EtOH.

4.16. (4R,4aS*,5R*,8aS*)-Hexahydro-4,5-(ferrocene-1,1′-diyl)-8a-phenylpyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (**12a**)*

Yellow powder; 0.505 g, 59%; mp 299–302 °C (decomp); Anal. Calc. for $C_{22}H_{20}FeN_4O_2$ (428.26): C, 61.70; H, 4.71; N, 13.08. Found: C, 61.79; H, 4.64; N, 13.19%.

4.17. (4R,4aS*,5R*,8aS*)-Hexahydro-4,5-(ferrocene-1,1′-diyl)-8a-(4-methoxy-phenyl)pyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (**12b**)*

Yellow powder; 0.623 g, 68%; mp > 310 °C; Anal. Calc. for $C_{23}H_{22}FeN_4O_2$ (458.29): C, 60.28; H, 4.84; N, 12.23. Found: C, 60.22; H, 4.69; N, 12.16%.

4.18. (4R,4aS*,5R*,8aS*)-Hexahydro-4,5-(ferrocene-1,1′-diyl)-8a-ferrocenylpyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (**12c**)*

Yellow powder; 0.493 g, 46%; mp > 310 °C; Anal. Calc. for $C_{26}H_{24}Fe_2N_4O_2$ (536.18): C, 58.24; H, 4.51; N, 10.45. Found: C, 58.41; H, 4.60; N, 10.37%.

4.19. (4R,4aS*,5R*,8aS*)-Hexahydro-4,5-(ferrocene-1,1′-diyl)-8a-(1′-acetylferro-cenyl)pyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (**12d**)*

Orange powder; 0.416 g, 36%; mp > 310 °C; Anal. Calc. for $C_{28}H_{26}Fe_2N_4O_2$ (578.22): C, 58.16; H, 4.53; N, 9.69. Found: C, 58.02; H, 4.64; N, 9.59%.

Acknowledgements

This work was supported by the Hungarian Scientific Research Fund (OTKA T-043634). The authors are indebted to Dr. Hedvig Medzihradszky-Schweiger for analyses.

References

[1] (a) P. Biginelli, Gazz. Chim. Ital. 23 (1893) 360–416;
(b) K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg, B.C. O'Reilly, J. Med. Chem. 34 (1991) 806–811;
(c) G.J. Grover, S. Dzwonczyk, D.M. Mcmullen, C.S. Normadinam, P.G. Slenph, S.J. Moreland, J. Cardiovasc. Pharmacol. 26 (1995) 289–294;
(d) E.H. Hu, D.R. Sidler, U.J. Dolling, Org. Chem. 63 (1998) 3454;
(e) Y. Ma, C. Qian, L. Wang, M.J. Yang, Org. Chem. 65 (2000) 3864;
(f) A. Kappe, Acc. Chem. Res. 33 (2000) 879.
[2] (a) J.S. Yadav, B.V.S. Reedy, R. Srinivas, C. Venugopal, T. Ramalingam, Synthesis (2001) 1341;
(b) A.K. Kumar, M. Kasturaiah, S.C. Reedy, C.D. Reddy, Tetrahedron Lett. 42 (2001) 7873;
(c) J. Peng, Y.Q. Deng, Tetrahedron Lett. 42 (2001) 5917;
(d) N. Fu, Y. Yuan, Z. Cao, S. Wang, J. Wang, C. Peppe, Tetrahedron 58 (2002) 4801;
(e) M. Xia, Y. Wang, Tetrahedron Lett. 43 (2002) 7703;
(f) K.R. Reddy, C.V. Reddy, M. Mahesh, P.V.K. Raju, V.V.N. Reddy, Tetrahedron Lett. 44 (2003) 8173;
(g) G. Maiti, P. Kundu, C. Guin, Tetrahedron Lett. 44 (2003) 2757;
(h) R. Varala, M.M. Alam, S.R. Adapa, Synlett (2003) 67;
(i) A. Dondoni, A. Massi, E. Minghini, S. Sabbatini, V. Bertolasi, J. Org. Chem. 68 (2003) 6172.
[3] M.S. Manhas, S.N. Ganguly, S . Mukherjee, A.K. Jain, A.K. Bose, Tetrahedron Lett. 47 (2006) 2423.
[4] H.A. Stefani, C.B. Oliveira, R.B. Almeida, C.M.P. Pereira, R.C. Braga, R. Cella, V.C. Borges, L. Savegnago, C.W. Nogueira, Eur. J. Med. Chem. 41 (2006) 513.
[5] (a) S. Top, A. Vessiéres, C. Cabestaing, I. Laios, G. Leclerq, C. Provot, G. Jaouen, J. Organomet. Chem. 637–639 (2001) 500;
(b) T. Klimova, E.I. Klimova, M. Martinez Garcia, E.A. Vázquez López, C. Alvarez Toledano, A.R. Toscano, L. Ruíz Ramírez, J. Organomet. Chem. 628 (2001) 107;
(c) B. Weber, A. Serafin, J. Michie, C. Van Rensburg, J.C. Swarts, L. Bohm, Anticancer Res. 24 (2B) (2004) 763;
(d) G. Jaouen, S. Top, A. Vessieres, G. Leclercq, M.J. McGlinchey, Curr. Med. Chem. 11 (2004) 2505;
(e) E. Hillard, A. Vessieres, L. Thouin, G. Jaouen, C. Amatore, Angew. Chem., Int. Ed. 45 (2006) 285.
[6] N.-Y. Fu, Y.-F. Yuan, M.-L. Pang, J.-T. Wang, C. Peppe, J. Organomet. Chem. 672 (2003) 52–57.
[7] S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, X. Wang, Tetrahedron Lett. 44 (2003) 6153.
[8] Z.-T. Wang, L.-W. Xu, C.-G. Xia, H.-Q. Wang, Tetrahedron Lett. 45 (2004) 7951.
[9] (a) E. Pretsch, T. Clerc, J. Seibl, N. Simon, Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden, Springer Verlag, Berlin, 1976. p. C 185.
[10] P. Sohár, Nuclear Magnetic Resonance Spectroscopy, vol. 2, CRC Press, Boca Raton, FL, 1983. pp. 164–166.
[11] M. Karplus, J. Chem. Phys. 30 (1959) 11;
M. Karplus, J. Chem. Phys. 33 (1960) 1842.
[12] D.T. Pegg, D.M. Doddrell, M.R. Bendall, J. Chem. Phys. 77 (1982) 2745.
[13] M.R. Bendall, D.M. Doddrell, D.T. Pegg, W.E. Hull, High Resolution Multipulse NMR Spectrum Editing and DEPT, Bruker, Karlsruhe, 1982.
[14] (a) R.R. Ernst, G. Bodenhausen, A. Wokaun, Principles of Nuclear Magnetic Resonance in One and Two Dimensions, Clarendon Press, Oxford, UK, 1987. pp. 400–448;
(b) R.R. Ernst, G. Bodenhausen, A. Wokaun, Principles of Nuclear Magnetic Resonance in One and Two Dimensions, Clarendon Press, Oxford, UK, 1987. pp. 471–479.
[15] (a) J.K.M. Sanders, B.K. Hunter, Modern NMR Spectroscopy. A Guide for Chemists, University Press, Oxford, UK, 1987. pp. 108–113;
(b) J.K.M. Sanders, B.K. Hunter, Modern NMR Spectroscopy. A Guide for Chemists, University Press, Oxford, UK, 1987. pp. 94–97, 100–107.
[16] A. Bax, G. Morris, J. Magn. Res. 42 (1981) 501–505.
[17] H. Kessler, C. Griesinger, J. Zarboch, H. Loosli, J. Magn. Res. 57 (1984) 331–336.