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New ferrocenyl-substituted heterocycles. Formation under Biginelli conditions, DFT modelling, and structure determination

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ABSTRACT

A series of novel ferrocene-containing-dihydropyrimidines (DHPs) were prepared by three-component Biginelli reactions of formylferrocene, 1,3-dioxo-components and thiourea catalyzed by boric acid and ytterbium triflate, respectively. When cyclic-1,3-diones were employed as dioxo component in the reactions promoted by boric acid, besides one expected 4-ferrocenyl-2-thioxoquinazoline, 9-ferrocenyl-2*H*-xanthene-1,8-dione and 9-ferrocenylcyclopenta[*b*]chromen-8-ones could also be isolated as products. By means of control reactions and B3LYP/6-31 G(d) modelling the formation of the chromenone was interpreted by hetero-Diels–Alder addition involving the Knoevenagel intermediate and the cyclopentadiene resulted *in situ* from acid-catalyzed decomposition of formylferrocene. The enhanced tendency of the acyclic dioxo components to undergo Biginelli reaction avoiding cycloaddition was reasoned by the formation of Knoevenagel intermediates capable of chelating proton or Lewis acids. The structures of the new compounds were established by IR and NMR spectroscopy, including HMQC, HMBC, DEPT and DNOE measurements. Some structural characteristics were disclosed by B3LYP/6-31 G(d) method.

1. Introduction

There is considerable current interest in the Biginelli reaction, because 3,4-dihydropyrimidin-2(1*H*)-ones (DHP's) and their derivatives have attracted great attention recently in synthetic organic chemistry due to their valuable pharmacological and therapeutic potential [1]. For a characteristic example, dihydropyrimidinone C-5 amides were prepared and assayed as potent and selective α1A receptor antagonists for the treatment of benign prostatic hyperplasia [1d]. Biginelli reactions are simple one-pot condensations of β-dicarbonyl compounds with aldehydes and urea or thiourea most commonly catalyzed by mineral acid, but many synthetic modifications have been reported including a variety of Lewis and protic acids [2]. In spite of the relative simplicity of the available methodologies and a wide range of promising biological effects detected for simple ferrocene derivatives [3], there are only a few examples of ferrocenyl-substituted DHPs of which first representatives have been prepared by Fu et al. [4] using indium(III)-halides as catalyst. In our previous work we reported on facile synthetic routes to further ferrocene-containing Biginelli products [5] exploring H_3BO_3/AcOH and $FeCl_3$/TMSCl/MeCN systems introduced by Tu et al. [6] and Wang et al. [7], respectively. As a continuation of our ongoing research aiming at the extension of ferrocene-containing heterocycles to be tested in biological assays we attempted the preparation of a group of novel 4-ferrocenyl-DHP's and quinoxalines with variably transformable 2-thioxo substituent allowing to obtain further biologically relevant scaffolds or bioconjugates.

2. Results and discussion

Two catalytic systems, namely H_3BO_3/AcOH (Method A) and Yb(OTf)$_3$/MeCN (Method B), respectively (Scheme 1), were evaluated in comparative manner. According to the first protocol employed for the first time to targeting 2-thioxo-DHPs, the mixture of formylferrocene (**1**, 1 equiv.), the corresponding 1,3-dioxo component (**2a**–**i** 1 equiv.), thiourea (1.2 equiv.) and boric acid (0.2 equiv.) were heated in acetic acid for 5 h at 100 °C [6] affording 4-ferrocenyl DHP's (**3a**–**i**) in mediocre yields (21–55%, see Section 4).

The cyclizations were also carried out in refluxing acetonitrile by Method B employing the reagents in the same ratio and ytterbium triflate (0.05 equiv.) as catalyst, but **3a**–**i** could be isolated in lower yields (3–53%, see Section 4). The most significant differences in the yields (53/4% for **3f** and 36/10% for **3g** by Methods A/B) were

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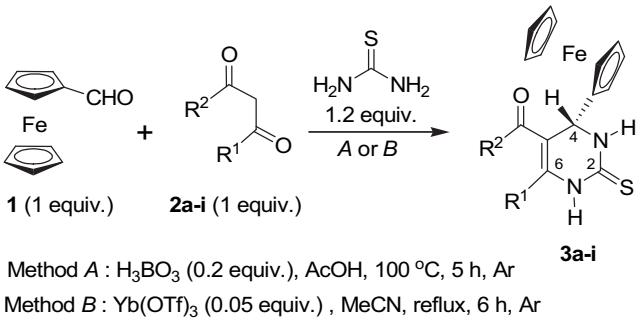


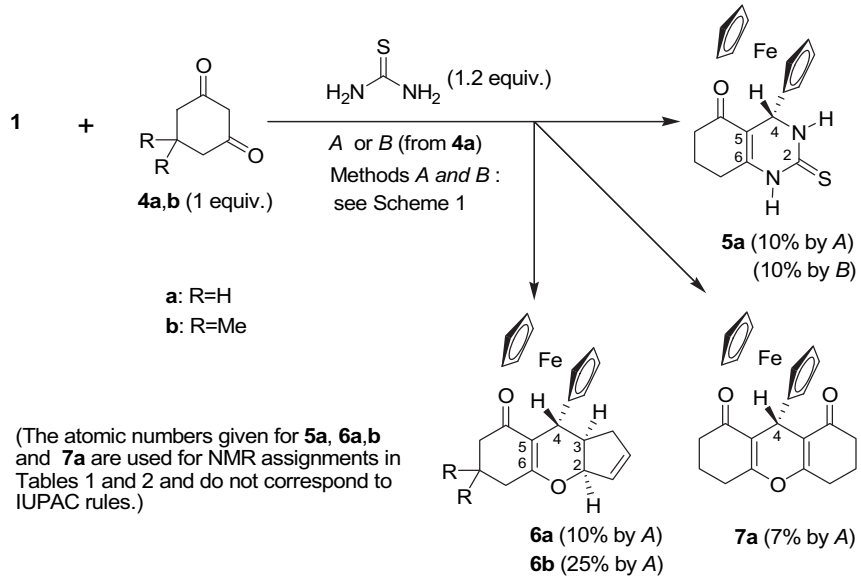
2, 3	R^1	R^2
a	Me	Me
b	Me	OMe
c	Me	OEt
d	Me	O^{t}Bu
e	Me	NEt_2
f	Me	Ph
g	Ph	OEt
h	CH_2CO_2Me	OMe
i	CH_2CO_2Et	OEt

Scheme 1.

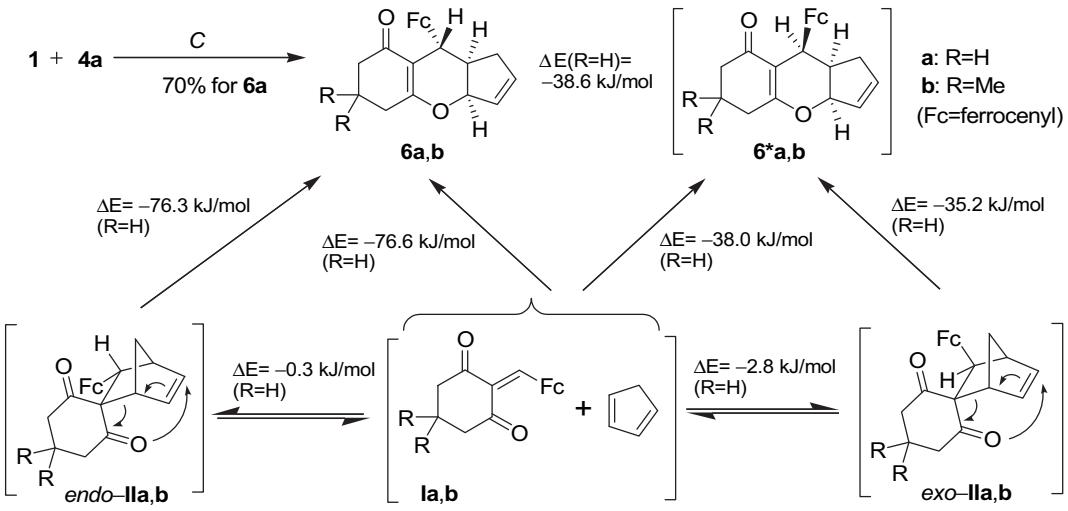
detected for the reactions involving aromatic derivatives **2f**, **g** potentially capable of bonding to the Yb(III) species by η^6-complexation with the participation of the phenyl substituent [8]. The low yields of the reactions with diesters **2h**, **i** performed by either procedures (21/3% for **3h** and 21/7% for **3i** by Methods A/B) can probably be ascribed to uncontrolled condensations involving two highly activated methylene groups. It is also worth to point out that the reaction of **2f** by Method A proved to be regioselective affording 5-benzoyl-6-methyl-substituted DHP **3f**, but the product with alternative substitution pattern could not be isolated in accord with the expected enhanced reactivity of the aliphatic ketone relative to that of the aromatic one.

1,3-Cyclohexane-dione and dimedone (**4a**, **b)** were additional choices to target the preparation of 4-ferrocenyl-2-thioxoquinoxalines employing the conditions of Method A which produced higher yields in the reactions of acyclic dioxo components **2a**–**i** (Scheme 2). Under these conditions **4a** got partially converted into the mixture of the expected bicyclic product **5a** (10%), 9-ferrocenylcyclopenta[*b*]chromenone **6a** (10%) and 9-ferrocenylxanthene-dione **7a** (7%), but **4b** afforded cyclopenta[*b*]chromenone **6b** (25%) as exclusively isolable product. Although these reactions were conducted under argon, rather low yields could be achieved due to the formation of substantial amount of tarry materials. In order to increase the yield of quinoxaline **5a**, we attempted to carry out the reaction of **4a** and thiourea by Method B (Scheme 2). Under these conditions **5a** was formed again in low yield (10%) and a considerable amount of **1** could also be recovered by column chromatography from the reaction mixture contaminated by tarry substances. Conversion of **4b** attempted by Method B gave only undefined decomposition products.

The formation of **6a**, **b** can be interpreted by formal [4 + 2] cycloaddition of Knoevenagel-intermediates **Ia**, **b** and cyclopentadiene (Cp) resulted from the acid-catalyzed decomposition of **1** (Scheme 3). This view gains support from the following experimental observations and theoretical considerations: (i) the green colour of the hydrated iron(II) ions was observable on aqueous workup of the reaction mixtures, while the formation of tarry substances under protic conditions can at least partly be attributed to the polymerization of hydroxyfulvene, the other possible decomposition product of **1**; (ii) on treatment of **1** (1 equiv.) with **4a** (1.5 equiv.), boric acid (0.2 equiv.) and Cp (2 equiv.) in acetic acid at 100 °C for 5 h (Method C) **6a** was obtained in good yield (70%, Scheme 3). According to general expectations the overall [4 + 2] cycloadditions might competitively proceed *via* two pathways involving inverse electron-demand hetero Diels–Alder (DA) reaction with **Ia**,**b** as oxadiene component (Scheme 3) and by "normal" DA reaction with Cp as diene component followed by [3,3′] *oxa*-Cope rearrangement (**Ia**, **b** + Cp → *endo*-**IIa**,**b** → **6a**, **b**), respectively. Taking into account the elementary steps which in principle might also afford diastereomeric products **6*a**, **b** (Scheme 3), the energetics of the two possible pathways were disclosed by DFT calculations [9] carried out at B3LYP level of theory [10] using 6-31



Scheme 2.



Method *C*: **1** (1 equiv.), **4a** (1.5 equiv.), H_3BO_3 (0.2 equiv.), AcOH, 100 °C, 1 h, then Cp (2 equiv.) 7 h, Ar

Scheme 3.

G(d) basis set [11] on the optimized structures of the reactants and the potential spirocyclic intermediates *endo*-**IIa** and *exo*-**IIa** unsubstituted on the cyclohexanone unit (R = H). The changes in energy represented on Scheme 3 show that both studied hetero-DA reactions are highly exothermic and, in accord with the preparative results, **6a** carrying the bulky ferrocenyl group in *exo*-position is more stable by 38.6 kJ/mol than **6a*** with *endo*-positioned ferrocenyl substituent. The contribution of the alternative pathway can practically be ruled out by the similar slightly exothermic energetics obtained for the DA additions affording in preequilibrium diastereomeric spirocycles of which *oxa*-Cope rearrangements – contrary to the observed diastereoselectivity – would afford **6a** and **6*a** in comparable yields as suggested by their similar activation barriers ($\Delta E^{\ddagger} = 63.2$ kJ/mol for *endo*-**IIa** → **6a** and 68.2 kJ/mol for *exo*-**IIa** → **6*a**, respectively). The transition states of these intramolecular processes were located by using QST2 calculations [12] at B3LYP/6-31 G(d) level of DFT.

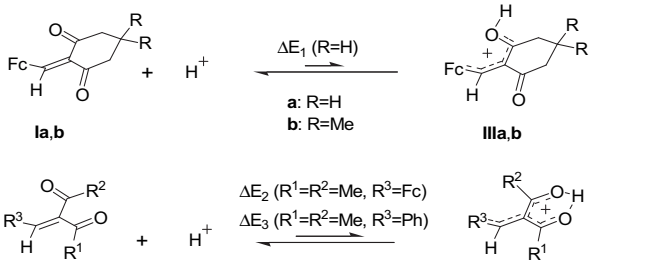
Since the formation of pyran scaffold was not observed in the boric acid-mediated reactions of acyclic 1,3-dioxo components **2a**–i it is plausible to assume that their Knoevenagel intermediates **IVa**–**i** readily undergo protonation to give chelate-stabilized cations **Va**–**i** (Scheme 4) preventing to adopt single-*cis* conformation, the prerequisite of the inverse electron-demand hetero DA reaction. On the other hand, it seems that the acid-mediated decomposition of **1** resulting in Cp may be supressed by **IVa**–**i** having significantly increased basicity relative to that of cyclic dioxo compounds **Ia**, **b**. This view was also supported by B3LYP/6-31 G(d) calculations on equilibrium-protonation reactions of two selected simple models [**Ia** + H^+ ↔ **IIIa** (1, R = H) and **IVa** + H^+ ↔ **Va** (2, $R^1 = R^2 =$ Me), respectively, Scheme 4] affording a considerable difference in the energetics [ΔE_1(**IIIa** – **Ia**)–ΔE_2(**Va** – **IVa**) = + 41.8 kJ/mol] irrespectively of the acid component. Besides chelation it is the highly electron-donating ferrocenyl group [13] located at the terminal of the push-pull system which significantly stabilizes cations **Va**-**i** as evidenced by the difference in the calculated energetics of the equilibrium-protonation of **IVa** and its phenyl analogue **VIa** [ΔE_3(**VIIa** – **VIa**)–ΔE_2(**Va** – **IVa**) = +25.3 kJ/mol, Scheme 4]. Finally, on the basis of the previous considerations it is reasonable to assume that **IVa**-**i** show increased affinity to Lewis acids, too, including boron and Yb(III) capable of replacing proton in the chelated structures. It must also be pointed out that presumably these are the cationic chelated intermediates which undergo conjugate addition with thiourea followed by cyclization affording DHP ring.

The spectral data (^{1}H and ^{13}C NMR and IR) given in Tables 1–3 unambiguously confirm the supposed structures. Only the following additional remarks are necessary.

Because of asymmetric structures (chiral C-4 atom), the atom pairs H/C-2,5 and H/C-3,4 in the substituted Cp rings are chemically non-equivalent and they give separated signals in the spectra of **3a**–**i**, **5a** and also of **6a**, **b** (having two further chiral centra). In case of the symmetric **7a**, of course, common signals were observed for these atom pairs.

In case of compounds **6a**, **b** the position of the C=C double bond in the cyclopentene ring with its *cis* or *trans* annelation and the relative orientation of H-2 to H-3 and H-4, respectively, were to be elucidated.

The position of the double bond in **6a**, **b** follows straightforwardly from the multiplicity of the H-2 signals at 5.12 ppm (for **6a**) and 5.16 ppm (for **6b**), respectively, (and also from the HMBC



For any proton source [calculated by B3LYP/6-31 G(d) method] :
ΔE_1(**IIIa**–**Ia**) – ΔE_2(**Va**–**IVa**)= + 41.8 kJ/mol
ΔE_3(**VIIa**–**VIa**) – ΔE_2(**Va**–**IVa**)= + 25.3 kJ/mol

Scheme 4.

Table 1
^{1}H NMR data[a, b] of compounds **3a**–**i**, **5a**, **6a**,**b** and **7a**.[c]

	CH_3 or CH_2 (Pos. 6)[d]	CH_3 (R^2)[e]	CH_2 (R^2 or R^1)	H-4 d[f]	C_5H_5	H-2,5 H-3,4	NH, s, br (Pos. 1)	NH, d, br (Pos. 3)
					c-Pentene rings in ferrocenyl group			
3a	2.23	2.25	–	5.02	4.24	3.91, ~4.8 (4H)	10.26	9.48
3b	2.20	3.66	–	4.92	4.23	3.93, 4.07, 4.09 (2H)	10.34	9.38
3c	2.20	1.22	~4.1[g]	4.92	4.24	3.92 (1H), ~4.09 (3H)[g]	10.32	9.36
3d	2.17	1.44	–	4.88	4.25	3.93 (1H), ~4.09 (3H)	10.22	9.33
3e	1.67	0.98	3.20 broad	4.72	4.25	4.02, 4.10, 4.11, 4.14 (4× 1H)	9.87	8.66
3f	1.74	–	–	5.10	4.08[g]	4.02, 4.05, 4.08,[g] 4.13 (4×1H)	10.29	9.47
3g	–	0.82	3.83 qa	5.04	4.27	4.10 (1H), 4.16 (2H), 4.19 (1H)	10.45	9.53
3h	3.64[g]	3.64 [g]	3.72 s (R^1)	4.94	4.22	4.00, 4.11, 4.12, 4.18 (4× 1H)	10.40	9.48
3i	1.18[h]	1.19[h]	~4.08 (R^1, R^2)[g]	4.94	4.24	4.00 (1H), ~4.08 (2H),[g] 4.18 (1H)	10.36	9.44
5a	~2.48	~2.28	1.79,[i] 1.94[i]	4.94	4.21	3.89 (1H), ~4.07 (3H)	10.58	9.44
6a	~2.35	~2.32, ~2.43	1.87,[i] 1.94[i]	3.95	4.14[g]	4.04, 4.05, 4.13,[g] 4.20 (4×1H)	–	–
6b	2.18	0.91, 0.96	2.11, 2.17[j]	3.75	4.13	4.02, 4.06 (2H), 4.21	–	–
7a	~2.65	~2.35, ~2.48	~2.00 m (4H)	4.38	4.03	3.99 (2H), 3.75 (2H)	–	–

[a] In DMSO-d_6 or $CDCl_3$ (**3a**, **6a**) solution at 500 MHz. Chemical shifts in ppm ($\delta_{TMS} = 0$ ppm), coupling constants in Hz.
[b] Further ^{1}H NMR signals: CH_2 (Pos. 6, **3i**): 3.69, CH_2 (c-pentene ring): 2.14 and 2.55, 2× qadd (*J*: 17.7, 7.8 and 2.3 and 17.7, 8.0 and 1.7, resp., **6a**), 1.96 and 2.60, ddd and dd (*J*: 15.7, 7.5 and 1.4 and 16.6 and 8.0, resp., **6b**); H-2,6 (Ph), ~d (2H): 7.64 (**3f**), 7.24 (**3g**); H-3,5 (Ph), ~t (2H): 7.51 (**3f**), 7.38 (**3g**); H-4 (Ph), ~t (1H): 7.59 (**3f**), 7.41 (3g); =CH(CH), m (1H): 5.91(**6a**, **b**); =CH(CH_2), td (1H): 6.10 (**6a**, *J*: 5.5, 2.3), m (**6b**); H-2, dt (1H): 5.12 (**6a**, *J*: 7.2 and 2.0), ~d (1H): 5.16 (**6b**, *J*: 7.1).
[c] Assignments were supported by HMQC and H,C-HMBC (except for **3b**), for **6a**, **b** also by 2D-COSY and DIFFNOE measurements.
[d] s (3/2H) for **3a**–**f**/**3h**, **i**, **6b**, m (2H, **5a**, **6a**) (4H, **7a**).
[e] s (3H) for **3a**, **b**, **d**, **h**, ***t*** [*J*: 7.1 (**3c**, **g**), 6.7 (**3e**)], *m* (2H) for 5a or 2× m (2× 1H, **6a**, 2× 2H, **7a**), 2× s (2× 3H, **6b**).
[f] *J*: 4.4 ± 0.2 (**3a**–**d**, **g**), 3.4 ± 0.1 (**3e**, **h**), 4.0 ± 0.1(**3f**, **5a**), 3.7 (**3i**), s (**6a**,**b**, **7a**).
[g] Overlapping signals.
[h] Interchangeable assignments.
[i] $CH_2CH_2CH_2$.
[j] 2× d (*J*: 16.0): AB-type spectrum (**6b**).

spectrum), which are triple doublets split by ca. 7, 2 and 2 Hz, originating from one vicinal and two allylic-type couplings.

The relative position of the three methine hydrogens in **6a**, **b** were determined by DIFFNOE measurements. Irradiating the H-2,5 signal of the substituted cyclopentene ring both H-2 and H-3 signals gave responses. This means that the two latter H's lie on the same side of the molecular skeleton, thus they are in *cis* position, on the same side with the ferrocenyl moiety and, consequently, *trans* to H-4.

The structures of four representative 4-ferrocenyl-DHP's (**3a**, **b**, **e**, **f**) were also analyzed by B3LYP/6-31 G(d) method. Geometry optimization carried out for **3a**, **b** disclosed nearly coplanar C-5,C-6 bond and C=O group at Pos. 5 (interplanar angles: 0.9° for **3a** and 10.0° for **3b**) allowing efficient enone conjugation. In **3e** and **3f** the bulky COR^2 substituents at pos. 5 were found to turn out of the plane of C-5,C-6 bond (interplanar angles: 51.2° for **3e** and 40.6° for **3b**) separating ferrocenyl- and R^2 groups on the opposite sides of the DHP ring.

3. Conclusion

The Biginelli reactions of formylferrocene, thiourea and a variety of 1,3-dioxo components performed in comparative manner under two conditions point to the preference of the method employing the cheaper and more efficient H_3BO_3/AcOH system. However, the extension of this simple protocol seems to be limited to the synthesis of monocyclic 4-ferrocenyl-DHP's of which formation presumably proceeds *via* ferrocenyl-stabilized Knoevenagel intermediates of chelated structure. On the other hand, on the use of cyclic 1,3-dioxo components partial acid-catalyzed degradation of formylferrocene followed by inverse electron-demand DA reaction of the resulted cyclopentadiene with the Knoevenagel intermediates must also be taken into account. From the aspect of synthetic utilization, the extension of this transformation to other electron-donor dienophilic components may serve as an easy access to a series of novel tricyclic ferrocenyl-substituted pyrane derivatives of potential biological interest.

4. Experimental

Melting points were determined with a Boethius microstage and are uncorrected. All calculations were performed by the Gaussian03 suite of programs [14]. The structures of the located stationary points are available from the authors on request. The IR spectra were run in KBr disks on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. DEPT spectra were run in a standard manner, using only a $\Theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased "up"

Table 2
^{13}C NMR chemical shifts[a] of compounds **3a**–**i**, **5a**, **6a**, **b** and **7a**.[b, c]

	CH_3 (R^1)	CH_3 (R^2)	C=S (C-2)	C=O Pos. 5	C-4	C-5	C-6	CH_2	C-1′	C-2′,5′	C-3′,4′	C_5H_5
									Substituted *Cp* ring (Fc-group)			
3a	19.0	31.4	175.5	195.4	49.7	113.4	144.3	–	93.7	66.2, 67.2	68.0, 68.1	69.5
3b	17.9	52.0	175.7	166.6	49.9	102.8	145.3	–	93.3	66.0, 67.0	68.2, 68.3	69.5
3c	17.9	15.1	175.7	166.1	49.9	103.1	145.1	60.5	93.4	66.0, 67.1, 68.1, 68.2		69.5
3d	18.0	28.8	175.8	165.5	50.0	104.6	144.3	80.8[d]	93.7	66.0, 66.9, 68.0, 68.1		69.5
3e	16.1	14.0	175.4	168.1	52.7	108.8	130.3	40.8	92.7	65.9, 67.6, 68.0, 68.7		69.4
3f	18.3	–	175.5	195.2	51.6	111.9	142.0	–	92.7	66.4, 66.9, 68.2, 68.6		69.5
3g	–	14.4	175.7	165.9	50.4	103.6	146.0	60.4	92.7	66.4, 67.1, 68.3, 68.4		69.6
3h	52.2[e]	52.7[e]	175.4	166.3	50.0	104.1	141.7	36.8	92.7	66.5, 67.1, 68.2, 68.4		69.5
3i	14.9[f]	14.9[f]	175.5	165.8	50.0	104.5	141.4	60.9, 61.3	92.8	66.4, 67.2, 68.2, 68.3		69.5
5a	26.1[g]	37.2[g]	175.8	194.6	47.5	110.8	151.3	21.4 [h]	93.5	66.4, 66.8, 68.0, 68.1		69.5
6a	30.0[g]	37.3[g]	82.6[i]	197.5	29.0	113.7	173.2	20.9[h] 38.3[k]	93.8	66.4, 67.45	67.51, 68.5	69.1
6b	27.8, 29.2	51[g]	82.7	196.5	29.3	112.4	171.5	38.6[k]	93.9	66.6, 67.4, 67.8, 68.4		69.2
7a	27.5[g]	37.4[g]	–	197.5	23.4	117.0	166.6	20.8[h]	95.2	67.1	67.4	69.2

[a] In DMSO-d_6 or $CDCl_3$ (**3a**, **6a**, **b**) solution at 125 MHz. Chemical shifts in ppm ($\delta_{TMS} = 0$ ppm).
[b] Assignments were supported by DEPT, HMQC and H,C-HMBC (except for **3b**) measurements.
[c] Further ^{13}C-NMR signals: =CH(CH): 130.9 (**6a**), 131.7 (**6b**); =CH(CH_2): 138.7 (**6a**), 138.8 (**6b**); C-1 (Ph): 140.5 (**3f**), 134.9 (**3g**); C-2,6 (Ph): 129.1 (**3f**), 129.6 (**3g**); C-3,5 (Ph): 129.6 (**3f**), 128.5 (**3g**); C-4 (Ph): 133.1 (**3f**), 129.9 (3g); C=O (CH_2COOMe, Pos. 6, **3h**): 169.9; $C(sp^3)_{quat.}$: 32.3.
[d] $C_{quat.}$(*t*-Bu).
[e] Interchangeable assignments.
[f] Overlapping lines.
[g] CH_2.
[h] $CH_2CH_2CH_2$.
[i] OCH.
[k] CH_2 in c-pentene ring.

and "down", respectively. The 2D-COSY, HMQC and HMBC 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), thiourea (0.274 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 5 h. After cooling, water (100 mL) was added to the mixture. The precipitate was filtered and thoroughly washed with water and dried. The crude product was chromatographed on silica gel using DCM–MeOH (100:1) as eluent to obtain the products as yellowish powders which were crystallized with cold EtOH (description of the products: see after the next section).

Table 3
Characteristic IR frequencies [cm^{-1}] of compounds **3a**–**i**, **5a**, **6b** and **7a** (in KBr discs).

	νNH band (broad or diffuse)	νC=O band[a, b]	νC=C band	νC–O ester or ether bands	ν_{as}Cp–Fe–Cp and tilt of Cp
3a	~3270	1610	1572	–	482
3b	3380–2800	1667	1570	1182, 1108	496
3c	3300–2500	1670	1570	1185, 1120	~500
3d	3300–2700	1704	1589	1156, 1095	487
3e	3500–2500	1690	1608	–	482, 501
3f[c]	3406, 3300–2700	1656	1619	–	504, 480, 469
3g[c]	3400–2700	1692	1573	1197, 1138,	494
3h	~3320	1746	1563	1189, 1112	486
3i	3350–2800	1736	1569	1187, 1108	497
5a	~3260, ~3163	1620	1570	–	523, 489
6a	–	1643	1605	1020	509, 495
6b	–	1650	1619	1207, 1086	480
7a	–	1669[d]	1613	1129	486

[a] Ester or ketone (for **3a**, **f**, **5a**, **6a**, **b**, **7a**) group, amide-I band for **3e** (amide-II band: 1655).
[b] CH_2COOMe/Et group for **3h**, i, νC=O conjugated ester: 1682 (**3h**, **i**).
[c] $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ band: 731, 698 (**3f**), 698, 765 (**3g**).
[d] Split band-pair with the second maximum at 1649.

4.2. Three-component condensations of formylferrocene (*1*) by Method B

A mixture of **1** (0.643 g, 3 mmol), 1,3-dioxo reagent (3 mmol), thiourea (0.274 g, 3.6 mmol), and ytterbium-triflate (0.093 g, 0.15 mmol) in acetonitrile (10 mL) was stirred and heated at reflux for 6 h. After cooling, water (100 mL) was added to the mixture. The precipitate was filtered and thoroughly washed with water and dried. The crude product was chromatographed on silica gel using DCM–MeOH (100:1) as eluent to obtain the products as yellowish powders which were crystallized with cold EtOH. Within experimental errors the mps and analytical data of the products were identical to those obtained by Method A.

4.2.1. 5-Acetyl-3,4-dihydro-4-ferrocenyl-6-methylpyrimidin-2(1H)-thione (*3a*)

Yield: 46/31% (A/B); mp 244-245 °C; anal. calcd. for $C_{17}H_{18}FeN_2OS$ (354.25) C 57.64, H 5.12, N 7.91, S 9.05%; found C 57.77, H 5.11, N 7.86, S 9.12%.

4.2.2. Methyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-methyl-2-thioxopyrimidine-5-carboxylate (*3b*)

Yield: 55/53% (A/B); mp 233–235 °C; anal. calcd. for $C_{17}H_{18}FeN_2O_2S$ (370.25) C 55.15, H 4.90, N 7.57, S 8.66%; found C 55.23, H 4.79, N 7.48, S 8.74%.

4.2.3. Ethyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-methyl-2-thioxopyrimidine-5-carboxylate (*3c*)

Yield: 37/30% (A/B); mp 229–231 °C; anal. calcd. for $C_{18}H_{20}FeN_2O_2S$ (384.27) C 56.26, H 5.25, N 7.29, S 8.34%; found C 56.32, H 5.20, N 7.21, S 8.42%.

4.2.4. Tert-butyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-methyl-2-thioxopyrimidine-5-carboxylate (*3d*)

Yield: 36/25% (A/B); mp 239–240 °C; anal. calcd. for $C_{20}H_{24}FeN_2O_2S$ (412.33) C 58.26, H 5.87, N 6.79, S 7.78%; found C 58.37, H 5.79, N 6.70, S 7.73%.

*4.2.5. N,N-Diethyl-1,2,3,4-tetrahydro-6-methyl-4-ferrocenyl-2-thioxopyrimidine-5-carboxamide (**3e**)*

Yield: 50/40% (A/B); mp 232–234 °C; anal. calcd. for $C_{20}H_{25}FeN_3OS$ (411.34) C 58.40, H 6.13, N 10.22, S 7.80%; found C 58.50, H 6.15, N 10.30, S 7.91%.

*4.2.6. 5-Benzoyl-3,4-dihydro-4-ferrocenyl-6-methylpyrimidin-2(1H)-thione (**3f**)*

Yield: 53/4% (A/B); mp 251–253 °C; anal. calcd. for $C_{22}H_{20}FeN_2OS$ (416.32) C 63.47, H 4.84, N 6.73, S 7.70%; found C 63.55, H 4.76, N 6.67, S 7.74%.

*4.2.7. Ethyl 1,2,3,4-tetrahydro-4-ferrocenyl-6-phenyl-2-thioxopyrimidine-5-carboxylate (**3g**)*

Yield: 36/10% (A/B); mp 223–225 °C; anal. calcd. for $C_{23}H_{22}FeN_2O_2S$ (446.34) C 61.89, H 4.97, N 6.28, S 7.18%; found C 61.95, H 4.90, N 6.21, S 7.15%.

*4.2.8. Methyl 6-[(methoxycarbonyl)methyl]-1,2,3,4-tetrahydro-4-ferrocenyl-2-thioxopyrimidine-5-carboxylate (**3h**)*

Yield: 21/3% (A/B); mp 194–195 °C; anal. calcd. for $C_{19}H_{20}FeN_2O_4S$ (428.28) C 53.28, H 4.71, N 6.54, S 7.49%; found C 53.32, H 4.66, N 6.50, S 7.40%.

*4.2.9. Ethyl 6-[(ethoxycarbonyl)methyl]-1,2,3,4-tetrahydro-4-ferrocenyl-2-thioxopyrimidine-5-carboxylate (**3i**)*

Yield: 21/7% (A/B); mp 161–163 °C; anal. calcd. for $C_{21}H_{24}FeN_2O_4S$ (456.34) C 55.27, H 5.30, N 6.14, S 7.03%; found C 55.33, H 5.21, N 6.11, S 7.11%.

*4.2.10. 1,2,3,4,7,8-Hexahydro-4-ferrocenyl-2-thioxoquinazolin-5(6H)-one (**5a**)*

Yield: 10/10% (A/B); mp 260–261 °C; anal. calcd. for $C_{18}H_{18}FeN_2OS$ (366.26) C 59.03, H 4.95, N 7.65, S 8.75%; found C 59.10, H 4.88, N 7.62, S 8.68%.

4.2.11. (3aR,9S*,9aR*)-6,7,9,9a-Tetrahydro-9-ferrocenylcyclopenta[b]chromen-8(1H,3aH,5H)-one (**6a**)*

Yield: 10% (A); mp 169–170 °C; anal. calcd. for $C_{22}H_{22}FeO_2$ (374.25) C 70.60, H 5.93%; found C 70.64, H 5.90%.

4.2.12. (3aR,9S*,9aR*)-6,7,9,9a-Tetrahydro-6,6-dimethyl-9-ferrocenylcyclopenta[b]chromen-8(1H,3aH,5H)-one (**6b**)*

Yield: 25% (A); mp 189–190 °C; anal. calcd. for $C_{24}H_{26}FeO_2$ (402.31) C 71.65, H 6.51%; found C 71.70, H 6.47%.

*4.2.13. 3,4,6,7-Tetrahydro-9-ferrocenyl-2H-xanthene-1,8(5H,9H)-dione (**7a**)*

Yield: 7% (A); mp 217–219 °C; anal. calcd. for $C_{23}H_{22}FeO_3$ (402.26) C 68.67, H 5.51%; found C 68.73, H 5.49%.

*4.3. Preparation of **6a** using hetero-DA reaction by Method C*

A solution of **1** (1000 g, 4.67 mmol), **4a** (0.785 g, 7 mmol) and H_3BO_3 (0.058 g, 0.94 mmol) in glacial acetic acid (10 mL) was heated and stirred under Ar at 100 °C for 1 h, then freshly distilled cyclopentadiene (0.647 g, 9.34 mmol) was added to the reaction mixture which was kept at 100 °C. After 7 h water (100 mL) was added to the mixture. The precipitate was thoroughly washed with cold EtOH to obtain **6a** as yellowish powder. Yield: 1.23 g (70%). Within experimental error the mp and analytical data were identical to those of the sample obtained by Method A.

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