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Indium(III) halides-catalyzed preparation of ferrocene-dihydropyrimidinones

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Abstract

Indium(III) halides (chloride and bromide) catalyse the three-component Biginelli coupling of ferrocenyl-1,3-diketones, aldehydes and urea (or thiourea) to give 5-ferrocenoyl-3,4-dihydropyrimidinones. 4-Ferrocenyl-3,4-dihydropyrimidinones were obtained from alkyl-acetoacetates, formylferrocene and urea. The tricyclic compound, 13-ferrocenecarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.$0^{2,7}$]trideca-2,4-6-triene, was synthesized from 1-ferrocenyl-1,3-butanedione, salicilaldehyde and urea.

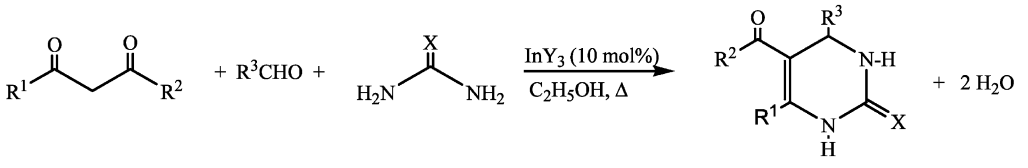
Keywords: Indium(III) halides; Biginelli coupling; Ferrocene-dihydropyrimidinones

1. Introduction

The use of ferrocene as an equivalent to phenyl groups in organic synthesis is employed when is desired a low toxic and stable three-dimensional bulky metal containing substituent capable of acting as an electrochemical probe for electron transfer processes [1,2]. Recently, there is a growing interest in the preparation of ferrocene-substituted heterocycles to use them as functionalised ligands and for biological purposes [3–11]. In fact, some of these compounds have been employed as electrochemical sensors to study redox processes through DNA structures [12–14].

Dihydropyrimidinones (DHPMs) are substances derived from the condensation of β-keto-esters, aldehydes and urea (Eq. (1)). They were firstly prepared by Biginelli more than one century ago [15]. Recently, the DHPMs have attracted considerable attention, mainly because of their use as calcium channel modulators, anti-cancer and anti-HIV activity [16]. The original protocol for the DHPMs synthesis consisted of heating the three-component mixture in ethanol containing HCl as catalyst. The efficiency of the synthesis was improved by several Lewis acid catalysts, such as $BF_3 \cdot OEt_2$, $FeCl_3$ and HCl, $LaCl_3 \cdot 7H_2O$, ytterbium triflate.

Recently, we have demonstrated that indium trihalides, InY_3 (Y = Cl, Br) are superior catalysts for the Biginelli reaction (Eq. (1)) [17], and as a consequence of this finding, we describe here the preparation of some



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ferrocene-dihydropyrimidinones catalyzed by indium trihalides.

2. Experimental

2.1. General

Indium(III) bromide was prepared by passing a flow of bromine gas through melted indium. Formylferrocene [18], 1-ferroceny-1,3-butanedione [19] and 1-ferrocenyl-3-phenyl-1,3-propanedione [20] were prepared according to literature. $InCl_3 \cdot 4H_2O$, urea, thiourea and aldehydes were commercial products. All liquid reagents were distilled and all solid reagents were recrystalized before use. Melting points were determined on a glass disk and are uncorrected. ^{1}H-NMR spectra were recorded in DMSO-d_6 solutions on a BRUKER AC-P-200 spectrometer with TMS as internal standard. IR spectra (KBr plates) were obtained on a Bio-Rad FTS-135 spectrometer. Mass spectra were determined under EI (70 eV) on a VG-ZAB-HS spectrometer. Elemental analyses were carried out on a CHN-CORDERM 7-3 automated analyser.

2.2. Electrochemical measurements

Cyclic voltammograms were obtained from a BAS-100 B electrochemical analyzer (Purdue Research Park, West Lafayette, IN) equipped with a three-electrode assembly. The solutions were 0.1 mol l^{-1}, in DMF containing n-Bu_4NPF_4 as supporting electrolyte. Amine free DMF was obtained by drying an analytical grade sample over Linde type 4-Å molecular sieves for 72 h and distilled at reduced pressure under N_2, minutes before use. The working electrode was a platinum disk of $\Phi = 200$ μm in diameter embedded in a cobalt glass seal and it was polished consecutively with polishing alumina and diamond suspensions (supplied by BAS as a kit), rinsed with ethanol and dried in air before each run. The reference electrode was a KCl saturated calomel electrode (SCE). A platinum wire (BAS) was used as a counter electrode. The solutions were saturated and blanketed with N_2 before the first scan. Measurements were made at 20 °C. The voltammograms were scanned over the potential range 0–1.0 V (positive potential direction in forward mode) at 200 mV s^{-1}. The redox potentials ($E_{1/2}$ values) were reproducible to ± 10 mV, ≥ 5 mV for consecutive scans suggesting an inherent error of 5–10 mV.

2.3. General experimental procedure for preparation of ferrocene-dihydropyrimidinones (**1**–**9**) and the diazatricyclic compound (**10**) (see Table 1)

A solution of 2 mmol of the diketone (or alkyl acetoacetate), 2 mmol of the aldehyde, 2.6 mmol of urea (or thiourea) and 0.2 mmol (10 mol%) of $InBr_3$ (or $InCl_3 \cdot 4H_2O$) in ethanol-95% (10 ml) was stirred at room temperature (r.t.) for 4 h, then heated under reflux for the required time (Table 1). On cooling, the product spontaneously crystallises from the solution. The solid was filtered, washed with ethanol and dried under vacuo. The yields in Table 1 refer to isolated analytically pure compounds. Purity criteria were melting temperatures, molecular formulae are based on microanalysis and mass spectrometry and structural assignments based on ^{1}H-NMR spectroscopy and cyclic voltammetry. Analytical and spectroscopic data for compounds **1**–**10** are as follow:

2.3.1. 5-Ferrocenylcarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**1**)

M.p. 262–268 °C (dec.); ^{1}H-NMR: $\delta = 8.86$ (s, 1H, N*H*), 7.64 (s, 1H, N*H*), 7.38–7.28 (m, 5H, C_6H_5), 5.41 (s, 1H, C*H*), 4.75–4.52 (m, 4H, Fc–*H*), 3.79 (s, 5H, Fc–*H*), 1.83 (s, 3H, CH_3); IR (KBr): 3200, 3010, 1674, 1642, 1599 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 400 (M, 12), 44 (100). Anal. Calc. for $C_{22}H_{20}O_2N_2Fe$: C, 66.03, H, 5.04, N, 7.00. Found: C, 66.13, H, 4.99, N, 7.05%.

2.3.2. 5-Ferrocenylcarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (**2**)

M.p. 157–160 °C (dec.); ^{1}H-NMR: $\delta = 8.79$ (s, 1H, N*H*), 7.57 (s, 1H, N*H*), 7.22–7.16 (m, 4H, C_6H_4), 5.38 (s, 1H, C*H*), 4.74–4.40 (m, 4H, Fc–*H*), 3.83 (s, 5H, Fc–*H*), 2.26 (s, 3H, Ph–CH_3), 1.83 (s, 3H, CH_3); IR (KBr): 3435, 3238, 3111, 1697, 1657, 1613 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 414 (M, 100), 330 (74). Anal. Calc. for $C_{23}H_{22}O_2N_2Fe$: C, 66.69, H, 5.35, N, 6.76. Found: C, 66.41, H, 5.27, N, 6.89%.

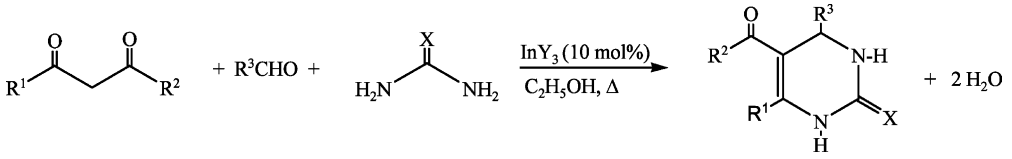
2.3.3. 4-(4-Chlorophenyl)-5-ferrocenylcarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**3**)

M.p. 242–245 °C (dec.); ^{1}H-NMR: $\delta = 8.85$ (s, 1H, N*H*), 7.66 (s, 1H, N*H*), 7.43–7.33 (m, 4H, C_6H_4), 5.40 (s, 1H, C*H*), 4.74–4.42 (m, 4H, Fc–*H*), 3.84 (s, 5H, Fc–*H*), 1.82 (s, 3H, CH_3); IR (KBr): 3434, 3240, 3111, 1694, 1657, 1613 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 434 (M, 67), 350 (10), 28 (100). Anal. Calc. for $C_{22}H_{19}O_2N_2ClFe$: C, 60.79, H, 4.41, N, 6.44. Found: C, 60.91, H, 4.26, N, 6.58%.

2.3.4. 5-Ferrocenylcarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4**)

M.p. 238–242 °C (dec.); ^{1}H-NMR: $\delta = 9.07$ (s, 1H, N*H*), 7.84 (s, 1H, N*H*), 8.30–7.61 (m, 4H, C_6H_4), 5.53 (s, 1H, C*H*), 4.77–4.46 (m, 4H, Fc–*H*), 3.87 (s, 5H, Fc–

Table 1
Indium(III) halides-catalyzed preparation of ferrocene-dihydropyrimidinones



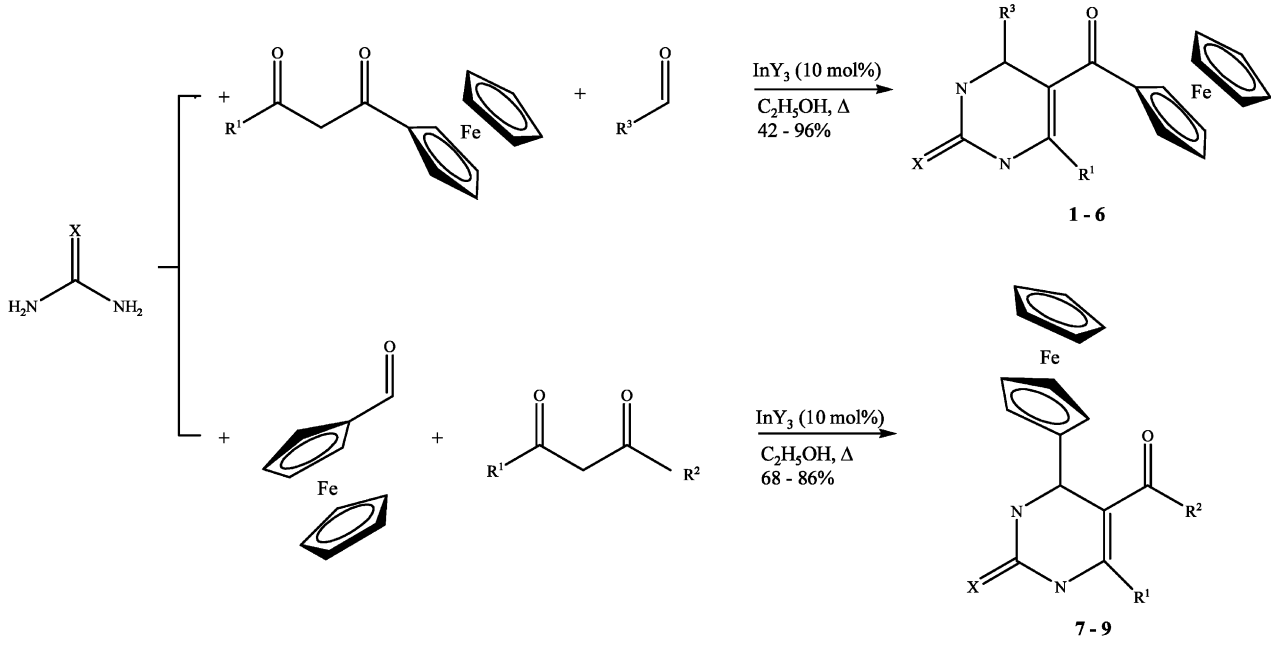
DHPM	R^1	R^2	R^3	X	Time (h)	Yield [a] (%)
1	Me	Fc [b]	Ph	O	14	86[c]
2	Me	Fc	*p*-CH_3–C_6H_4	O	36, 14	73 [c], 82 [d]
3	Me	Fc	*p*-Cl–C_6H_4	O	36	62 [c]
4	Me	Fc	*p*-NO_2–C_6H_4	O	36	70 [d]
5	Me	Fc	Ph	S	12	96 [c]
6	Ph	Fc	Ph	O	36	42 [c]
7	Me	OEt	Fc	O	7, 7	86 [c], 69 [d]
8	Me	OMe	Fc	O	6	68 [d]
9	Me	OEt	Fc	S	10	79 [d]

[a] Isolated yield.
[b] $C_5H_4FeC_5H_5$.
[c] 10 mol% of $InBr_3$.
[d] 10 mol% of $InCl_3 \cdot 4\ H_2O$ under N_2 atmosphere.

H), 1.86 (s, 3H, C*H*$_3$); IR (KBr): 3396, 3237, 3109, 1699, 1652, 1609 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 445 (M, 8), 121 (57), 28 (100). Anal. Calc. for $C_{22}H_{19}O_4N_3Fe$: C, 59.35, H, 4.30, N, 9.43. Found: C, 59.47, H, 4.41, N, 9.35%.

2.3.5. 5-Ferrocenylcarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (**5**)

M.p. 233–237 °C (dec.); ^{1}H-NMR: $\delta = 9.48$ (s, 1H, N*H*), 7.46 (s, 1H, N*H*), 7.38–7.35 (m, 5H, C_6H_5), 5.49 (s, 1H, C*H*), 4.80–4.48 (m, 4H, Fc–*H*), 3.84 (s, 5H, Fc–



DHPM	1	2	3	4	5	6	7	8	9
R^1	Me	Me	Me	Me	Me	Ph	Me	Me	Me
R^2	-	-	-	-	-	-	OEt	OMe	OEt
R^3	Ph	*p*-CH_3-C_6H_4	*p*-Cl-C_6H_4	*p*-NO_2-C_6H_4	Ph	Ph	-	-	-
X	O	O	O	O	S	O	O	O	S
Y	Br	Cl, Br	Br	Cl	Br	Br	Cl, Br	Cl	Cl

Scheme 1.

H), 1.89 (s, 3H, C*H*$_3$); IR (KBr): 3298, 3182, 3111, 3014, 1657, 1614, 1579, 1473, 1449 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 416 (M, 44), 352 (5), 317 (9), 213 (7), 121 (13), 31 (100). Anal. Calc. for $C_{22}H_{20}ON_2FeS$: C, 63.49, H, 4.84, N, 6.73. Found: C, 63.21, H, 4.77, N, 6.65%.

2.3.6. 5-Ferrocenylcarbonyl-4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one (**6**)

M.p. 217–223 °C (dec.); ^{1}H-NMR: $\delta = 9.07$ (s, 1H, N*H*), 7.80 (s, 1H, N*H*), 7.49–7.18 (s, 10H, two C$_6$*H*$_5$), 5.34 (s, 1H, C*H*), 4.31–4.09 (m, 4H, Fc–*H*), 3.72 (s, 5H, Fc–*H*); IR (KBr): 3436, 3211, 3103, 1932, 1681, 1640, 1611, 1444 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 462 (M, 100), 396 (21), 332 (12), 247 (19), 186 (12), 121 (22). Anal. Calc. for $C_{27}H_{22}O_2N_2Fe$: C, 70.15, H, 4.80, N, 6.06. Found: C, 70.32, H, 4.89, N, 6.11%.

2.3.7. 5-Ethoxycarbonyl-4-ferrocenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7)

M.p. 229–233 °C (dec.); ^{1}H-NMR: $\delta = 9.11$ (s, 1H, N*H*), 7.49 (s, 1H, N*H*), 4.94 (s, 1H, C*H*), 4.18 (s, 5H, Fc–*H*), 4.12–3.94 (m, 6H, Fc–*H*, OC*H*$_2$CH$_3$), 2.15 (s, 3H, C*H*$_3$), 1.23 (t, J = 7.1Hz, 3H, OCH$_2$C*H*$_3$); IR (KBr): 3365, 3252, 3117, 1704, 1647, 1457 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 368 (M, 100), 258 (52), 186 (38), 121 (22). Anal. Calc. for $C_{18}H_{20}O_3N_2Fe$: C, 58.72, H, 5.48, N, 7.61. Found: C, 58.53, H, 5.25, N, 7.81%.

2.3.8. 4-Ferrocenyl-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (8)

M.p. 237–241 °C (dec.); ^{1}H-NMR: $\delta = 9.18$ (s, 1H, N*H*), 7.53 (s, 1H, N*H*), 4.95 (s, 1H, C*H*), 4.18 (s, 5H, Fc–*H*), 4.10–3.94 (m, 4H, Fc–*H*), 3.65 (s, 3H, OC*H*$_3$), 2.16 (s, 3H, C*H*$_3$); IR (KBr): 3416, 3244, 3114, 1704, 1656, 1645 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 354 (M, 100), 256 (28), 186 (45), 121 (33). Anal. Calc. for $C_{17}H_{18}O_3N_2Fe$: C, 57.66, H, 5.12, N, 7.91. Found: C, 57.48, H, 5.11, N, 7.89%.

2.3.9. 5-Ethoxycarbonyl-4-ferrocenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (9)

M.p. 215–219 °C (dec.); ^{1}H-NMR: $\delta = 10.37$ (s, 1H, N*H*), 9.41 (s, 1H, N*H*), 4.92 (s, 1H, C*H*), 4.25 (s, 5H, Fc–*H*), 4.15–3.92 (m, 6H, Fc–*H*, OC*H*$_2$CH$_3$), 2.20 (s, 3H, C*H*$_3$), 1.23 (t, J = 7.1Hz, 3H, OCH$_2$C*H*$_3$); IR (KBr): 3422, 3323, 3161, 3094, 1672, 1570, 1454 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 384 (M, 100), 350 (14), 186 (19), 121 (19). Anal. Calc. for $C_{18}H_{20}O_2N_2FeS$: C, 56.28, H, 5.25, N, 7.29. Found: C, 56.37, H, 5.33, N, 7.18%.

2.3.10. 13-Ferrocenylcarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}] trideca-2,4,6-triene (**10**)

M.p. 250–254 °C; ^{1}H-NMR: $\delta = 7.55$ (s, 1H, N*H*), 7.01 (s, 1H, N*H*), 7.25–6.81 (m, 4H, C$_6$*H*$_4$), 4.90–4.47 (m, 4H, Fc–*H*), 4.32–4.28 (m, 5H, Fc–*H*), 3.74 (s, 1H, C*H*), 3.32 (s, 1H, C*H*), 1.72 (s, 3H, C*H*$_3$); IR (KBr): 3434, 3254, 3090, 1689, 1667, 1588, 1495, 1452 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 416 (M, 100), 308 (7), 229 (14), 213 (68), 121 (34). Anal. Calc. for $C_{22}H_{20}O_3N_2Fe$: C, 63.49; H, 4.84; N, 6.73. Found: C, 63.61; H, 4.77; N, 6.76%.

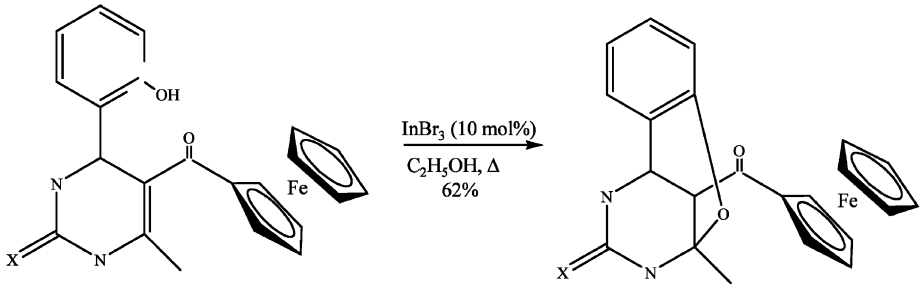
3. Results and discussion

3.1. Preparative, analytical and spectroscopic studies

A variety of ferrocene-containing DHPMs were synthesized in good to excellent yields (Table 1), from a Biginelli reaction catalysed by $InBr_3$ and/or $InCl_3 \cdot 4H_2O$ in aqueous ethanol

5-Ferrocenoyl substituted DHPM, **1**–**6** were prepared from the corresponding 1-ferrocenyl-1,3-propanedione. Formylferrocene leads to the 4-ferrocenyl substituted DHPMs, **7**–**9** (Scheme 1).

In our previous paper [17], we have described the synthesis and the complete characterization by X-ray means of diazatricyclic compounds from Biginelli condensations involving salicylaldehyde. As in that case, we have now prepared 13-ferrocenecarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}]trideca-2,4,6-



(2)

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Table 2
Cyclic voltammetric data (in DMF) for DHPMs [a]

Compound	E_{pa} (mV)	E_{pc} (mV)	$E_{1/2} = 1/2(E_{pa} + E_{pc})$ (mV)	$E_{pa} - E_{pc}$ (mV)
Ferrocene	506	394	450	112
FcCHO	764	628	696	136
	488	339	413.5	149
$FcCOCH_2COCH_3$	724	602	663	122
$FcCOCH_2COPh$	705	595	650	110
1	655	553	604	102
5	670	564	617	106
6	602	503	552.5	99
7	497	412	454.5	85
10	755	604	679.5	151

[a] In DMF solutions at 200 mV s^{-1}.

triene (**10**) (62% with $InBr_3$, 58% with $InCl_3 \cdot 4H_2O$) as the result of the cyclization of the DHPM derived from salicylaldehyde and 1-ferrocenyl-1,3-butanedione (Eq. (2)).

Molecular formulae (see Section 2) for **1**–**10** were determined from microanalysis (C, H and N) and confirmed by mass spectrometry. The ^{1}H-NMR spectra of compounds **1**–**9** (except **6**) exhibit two sets of singlets (at 4.9–5.5 and 1.8–2.2 ppm), which are characteristic for the hydrogen and methyl substituents at position 4 and 6 of the DHPM ring, respectively. For compound **10**, the two methyne resonances of the tetrahydropyrimidinone were detected at 3.74 and 3.32 ppm.

3.2. Electrochemical results

Cyclic voltammetry is a useful tool to determine the substitution pattern of ferrocenyl substituents at the DHPM ring. The relevant electrochemical data for ferrocene, the parent ferrocenyl derivatives and products are given at Table 2. The electrochemical studies were carried out in DMF solutions since the DHPMs **1**–**10** are unsoluble in most common organic solvents. It is well documented that DMF reacts slowly with the $FeCp_2^+$ cation leading to its decomposition; accordingly we have observed quasi-reversible electrochemical behaviour of compounds **1**–**10** ($E_{pa} - E_{pc} > 57$ mV; $i_{pa}/i_{pc} \neq 1$) [21]. We focused attention on the Fe^{II}/Fe^{III} oxidation processes, for which the parameter of interest is the formal reduction potentials $E_{1/2}$. The observed $E_{1/2}$ values for all the parent compounds, formylferrocene, 1-ferrocenyl-1,3-butanedione and 1-ferrocenyl-3-phenyl-1,3-propanedione, are anodically shifted (ca. 200–250 mV) with respect to the observed value of ferrocene as the result of the electron-withdrawing effect of the carbonyl group directly attached to the cyclopentadienyl ring of ferrocene. Formylferrocene revealed two redox waves at 696 and 413.5 mV, assigned to redox processes on the ferrocene and the aldehyde groups, respectively. Smaller shifts of 154, 167 and 102 mV towards anode were observed for DHPMs **1**, **5** and **6**, respectively, and this is consistent with a conjugated ferrocenoyl ligand attached to carbon 5 of the DHPM ring. For compound **10**, the observed $E_{1/2}$ (679.5 mV) is very close to the potential measured for its parent 1-ferrocenyl-1,3-butanedione (663 mV); this result is in keeping with a non-conjugated ferrocenoyl substituent as indeed is observed for the proposed tryciclic ring structure. Finally, we notice no appreciable change in the $E_{1/2}$ for **7** (454.5 mV) compared to the value of ferrocene (450 mV), again consistent with the proposed structure containing a non-conjugated ferrocenyl substituent attached to position 4 of the DHPM ring.

4. Conclusion

In summary, we have described the route for introducing ferrocenyl substituents at different positions of the DHPMs ring system. We have also demonstrated how cyclic voltammetry is easily applied for determining the position of the substitution at the DHPM ring. The products comprise a valuable class of compounds especially for those interested on the study of ferrocenyl derivatives as an electrochemical probe in biological systems and those interested in the development of new drugs containing the DHPM ring system.

Acknowledgements

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