ISSN 1070-3632, Russian Journal of General Chemistry, 2011, Vol. 81, No. 3, pp. 529–534. © Pleiades Publishing, Ltd., 2011.
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A Feature of Reaction of 1,1'-Diacetylferrocene with Dimethylformamide Dimethyl Acetal Leading to a New Strategy of the Synthesis of Asymmetrical 1,1'-Disubstituted Ferrocene

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Received March 23, 2010

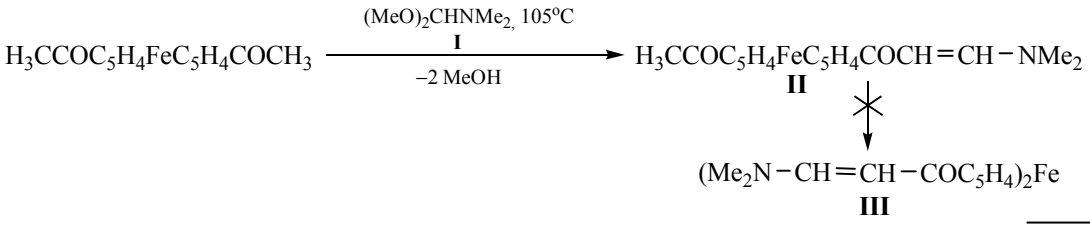
Abstract—The reaction of 1,1'-diacetylferrocene with the dimethylformamide dimethyl acetal proceeds regioselectively to afford [1-acetyl-1'-(1-dimethylamino-3-oxoprop-1-en-3-yl)]ferrocene, based on which new approaches to the synthesis of 1,1'-disubstituted unsymmetrical ferrocene derivatives via the reaction with nucleophilic reagents hydrazine hydrate, hydroxylamine, and amidines were developed.

DOI: 10.1134/S1070363211030145

Ferrocene derivatives possessing several unique and unusual properties [1, 2] attracted attention of researchers in many countries [3]. Recently the biological effects of substituted ferrocenes were extensively studied [4–6], which largely depend on the number and nature of functional groups in their molecules. This stimulates further research in view of new methods for synthesizing compounds of the ferrocene series.

In this paper we first examined the reaction of 1,1'-diacetylferrocene with the dimethylformamide dimethyl acetal **I**, which is known [7–11] to be able to react with compounds containing labile hydrogen atoms to form the corresponding enamines, the highly reactive chemicals in organic synthesis [12–14].

In 1,1'-diacetylferrocene the labile hydrogen atoms belong to two methyl sustituents of acetyl groups, which in principle could react with the acetal **I**. However, we found that under prolonged reflux (30 h) of 1,1'-diacetylferrocene in a large excess of **I** the reaction occurs only with the participation of one acetyl group to form enamine **II** in a yield of 74%. The further refluxing of the reaction mixture led only to the decomposition of the ferrocene-containing components, while no formation of the expected bis-enamine **III** was detected by TLC.



The high regioselectivity of this process is apparently due to the insufficiently strong electron-withdrawing effect of enaminocarbonyl group of the intermediate **II**, which contributes to the lability of the hydrogen atoms in acetyl group of **II**. It is known [9–11] that the higher lability of the hydrogen atoms in the substrate the more readily proceeds its condensation with the acetal **I**.

The composition and the structure of compound **II** are confirmed by elemental analysis, gas chromatography-mass spectrometry (Table 1), IR and ^{1}H NMR

Table 1. Yields, melting points, TLC, elemental analysis, and chromato-mass-spectral data of compounds **II**, **IV–XIV**

Comp. no.	Yield, %	mp, °C	R_f (system)	Mass-spectrum, m/z $[M+1]^+$	Found, %				Formula	Calculated, %				M_{calc}
					C	H	Fe	N		C	H	Fe	N	
II	74	136–137	0.42 (**A**)	326	62.56	5.73	17.19	4.26	$C_{17}H_{19}FeNO_2$	62.77	5.85	17.23	4.31	325
IV	58	172–173	0.68 (**B**)	309	58.27	5.06	17.93	18.31	$C_{15}H_{16}FeN_4$	58.44	5.19	18.18	18.18	308
V	69	168–169	0.31 (**A**)	311	57.81	4.39	18.24	8.85	$C_{15}H_{14}FeN_2O_2$	58.06	4.52	18.06	9.03	310
VI	76	198–200	0.54 (**C**)	442	59.67	4.25	12.83	15.43	$C_{22}H_{19}FeN_5O_2$	59.86	4.31	12.70	15.87	441
VII	77	176–177	0.48 (**A**)	311	58.11	4.63	17.97	9.16	$C_{15}H_{14}FeN_2O_2$	58.06	4.52	18.06	9.03	310
VIII	48	156–157	0.30 (**A**)	322	59.75	4.28	17.26	12.87	$C_{16}H_{15}FeN_3O$	59.81	4.67	17.45	13.08	321
IX	50	161–162	0.58 (**A**)	392	61.24	5.32	14.16	10.53	$C_{20}H_{21}FeN_3O_2$	61.38	5.37	14.32	10.74	391
X	68	184–186	0.71 (**C**)	410	67.24	4.67	13.21	10.15	$C_{23}H_{19}FeN_3O$	67.48	4.65	13.69	10.27	409
XI	76	202–205	0.56 (**C**)	455	60.71	4.08	12.57	12.09	$C_{23}H_{18}FeN_4O_3$	60.79	3.96	12.33	12.33	454
XII	84	184–185	0.52 (**B**)	337	57.35	4.63	16.48	16.30	$C_{16}H_{16}FeN_4O$	57.14	4.76	16.67	16.67	336
XIII	91	210–212	0.61 (**C**)	395	51.58	4.41	14.16	20.82	$C_{17}H_{18}FeN_6S$	51.78	4.57	14.21	21.32	394
XIV	65	205–206	0.38 (**B**)	337	56.94	4.53	16.78	16.75	$C_{16}H_{16}FeN_4O$	57.14	4.76	16.67	16.67	336

Table 2. IR and ^{1}H NMR spectral data for compounds **II**, **IV–XIV**

Comp. no.	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm
	Ferrocene core	Aromatic system	Functional groups	
II	3110, 2998, 1601, 1461, 1336, 809		1682, 1668 (C=O), 1626 (C=C)	2.38 s (3H, $COCH_3$), 2.98 s (6H, $2CH_3$), 4.37 m (4H, C_5H_4), 4.76 m (4H, C_5H_4), 5.38 d (1H, C=CH, *J* 16.5 Hz), 7.70 d (1H, C=CH–N, *J* 16.5 Hz)
IV	3101, 2997, 1597, 1462, 1332, 812	1601, 1505, 1430	3448, 3398 (N–H), 1618 (C=N)	2.05 s (3H, CH_3), 4.28 m (4H, C_5H_4), 4.72 m (4H, C_5H_4), 6.45 d (1H, Het), 7.56 d (1H, Het)
V	3100, 2998, 1600, 1460, 1334, 810	1593, 1506, 1431	3426 (OH), 1621 (C=N)	2.12 s (3H, CH_3), 4.28 m (4H, C_5H_4), 4.75 m (4H, C_5H_4), 6.12 d (1H, Het), 7.96 d (1H, Het), 12.04 s (1H, OH)
VI	3101, 2998, 1598, 1462, 1332, 811	1602, 1564, 1510, 1500, 1430	3428, 3386 (NH), 1624, 1614 (C=N), 1340 (NO_2)	2.08 s (3H, CH_3), 4.29 m (4H, C_5H_4), 4.72 m (4H, C_5H_4), 6.46 d (1H, Het), 7.58 d (1H, Het), 7.83 d (2H, C_6H_2), 8.61 d (2H, C_6H_2), 9.93 s (1H, CH)
VII	3100, 2997, 1601, 1460, 1332, 810	1594, 1506, 1430	3442 (NH), 1658 (C=O)	2.81 d (3H, CH_3N), 4.36 m (4H, C_5H_4), 4.76 m (4H, C_5H_4), 6.14 d (1H, Het), 7.94 d (1H, Het), 9.86 br.s (1H, NH)
VIII	3110, 2998, 1600, 1462, 1337, 812	1594, 1543, 1504, 1435	3446, 3391, 3374 (NH), 1678 (C=O)	2.36 s (3H, CH_3), 4.32 m (4H, C_5H_4), 4.60-4.78 m (6H, C_5H_4, NH_2), 6.10 d (1H, Het), 8.44 d (1H, Het)
IX	3106, 2997, 1598, 1462, 1338, 812	1588, 1541, 1506, 1434	1678 (C=O)	2.36 s (3H, CH_3), 3.24–3.46 m (4H, $2NCH_2$), 3.75–3.97 m (2H, $2OCH_2$), 4.38 m (4H, C_5H_4), 4.78 m (4H, C_5H_4), 6.19 d (1H, Het), 8.45 d (1H, Het)
X	3110, 2996, 1600, 1460, 1337, 810	1590, 1563, 1512, 1500, 1431	3448, 3394, 3380 (NH), 1662 (C=O), 1622 (C=C)	4.34 m (4H, C_5H_4), 4.61–4.75 m (6H, C_5H_4, NH_2), 5.42 d (1H, =CH, *J* 17.4 Hz), 5.96 d (1H, CO–CH=, *J* 17.4 Hz), 6.12 d (1H, Het), 7.44–7.58 m (5H, C_6H_5), 8.45 d (1H, Het)
XI	3110, 2997, 1597, 1461, 1337, 810	1605, 1562, 1512, 1500, 1431	3448, 3390 (NH), 1667 (C=O), 1631 (C=C), 1332 (NO_2)	4.36 m (4H, C_5H_4), 4.66–4.83 m (6H, C_5H_4, NH_2), 5.68 d (1H, =CH, *J* 17.6 Hz), 5.98 d (1H, CO–CH=, *J* 17.6 Hz), 6.14 d (1H, Het), 7.68 d (2H, C_6H_2), 8.45 d (1H, Het), 8.60 d (2H, C_6H_2)
XII	3112, 2996, 1600, 1463, 1334, 809	1594, 1542, 1506	3448, 3389, 3328 (NH, OH), 1621 (C=N)	2.10 s (3H, CH_3), 4.37 m (4H, C_5H_4), 4.64–4.81 m (6H, C_5H_4, NH_2), 6.14 d (1H, Het), 8.46 d (1H, Het), 12.03 s (1H, OH)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}			^1H NMR spectrum, δ, ppm
	Ferrocene core	Aromatic system	Functional groups	
XIII	3110, 2997, 1600, 1462, 1335, 812	1594, 1544, 1508	3464–3285 (NH), 1618 (C=N)	2.08 s (3H, CH_3), 4.36 m (4H, C_5H_4), 4.65–4.78 m (6H, C_5H_4, NH_2), 6.14 d (1H, Het), 8.48 d (1H, Het), 9.96 s (2H, NH_2C=S), 10.84 br.s (1H, NH)
XIV	3109, 2998, 1598, 1458, 1336, 810	1592, 1543, 1508	3445–3326 (NH), 1660 (C=O)	2.83 d (3H, CH_3N), 4.35 m (4H, C_5H_4), 4.65–4.79 m (6H, C_5H_4, NH_2), 6.15 d (1H, Het), 8.47 d (1H, Het), 9.87 br.s (1H, NH)

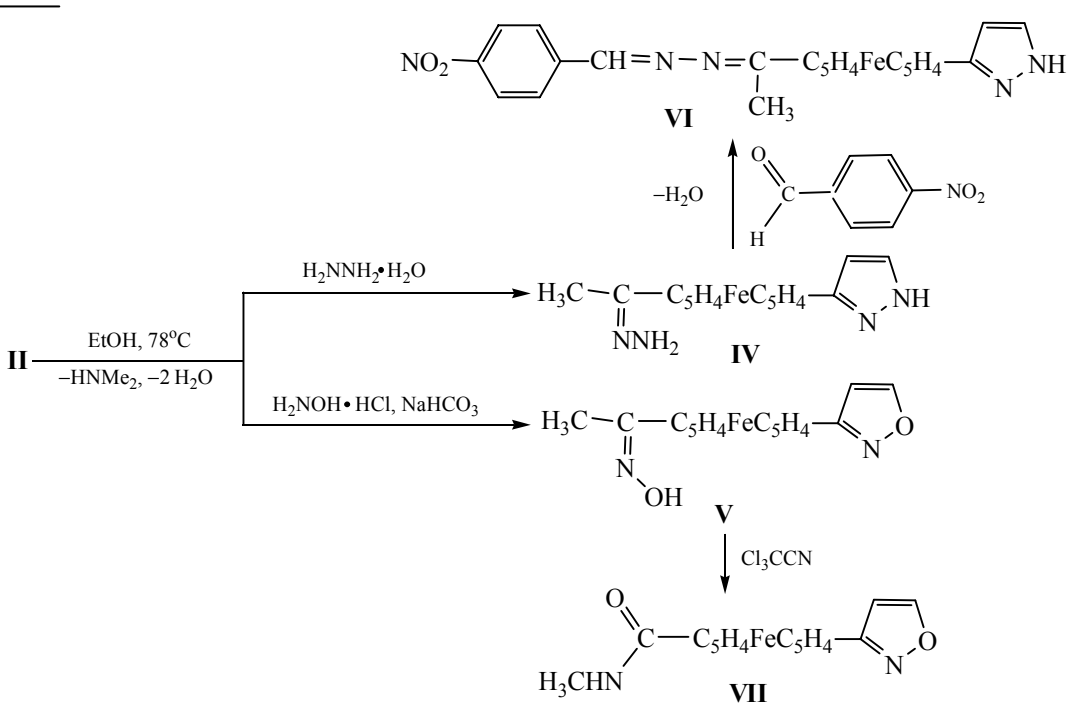
spectroscopy (Table 2), as well as by chemical transformations.

The IR spectrum of compound **II** contains the absorption bands characterizing the stretching vibrations of C–H bond of the cyclopentadienyl rings at 3110–2998 cm^{-1}, the carbonyl groups at 1682 and 1668 cm^{-1}, and the double C=C bond at 1626 cm^{-1}.

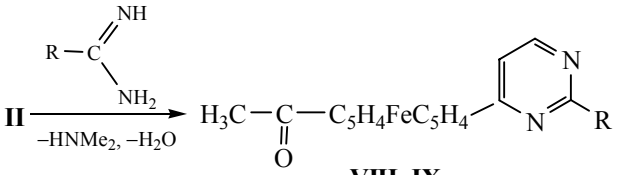
In the ^1H NMR spectrum of compound **II** the signals of HC=CH groups appear as doublets at 5.38 and 7.70 ppm with coupling constants 16.5 Hz, indicating *trans*-arrangement of substituents at the carbon atoms relative to the double bond. Methyl protons of $COCH_3$ and $N(CH_3)_2$ resonate as singlets at 2.38 and 2.98 ppm, respectively. The spectrum also contains the multiplets at 4.37 and 4.76 ppm originating from the protons (8H) of the substituted cyclopentadienyl rings of the ferrocene core.

The presence of different functionalities in compound **II** allows to develop a new strategy for the synthesis of a number of asymmetric 1,1'-disubstituted ferrocene derivatives.

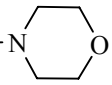
In particular, refluxing enamine **II** with an excess of hydrazine hydrate in ethanol or reacting it with hydroxylamine in aqueous ethanol afford heterocyclic compounds **IV** (58%) and **V** (69%) containing functional groups also capable of further chemical transformations. Thus, compound **IV** containing hydrazone group readily reacts with 4-nitrobenzaldehyde to give the mixed azine **VI**. Oxime **V** undergoes Beckmann rearrangement under the trichloroacetonitrile action [15] to provid the corresponding N-methylamide **VII**.



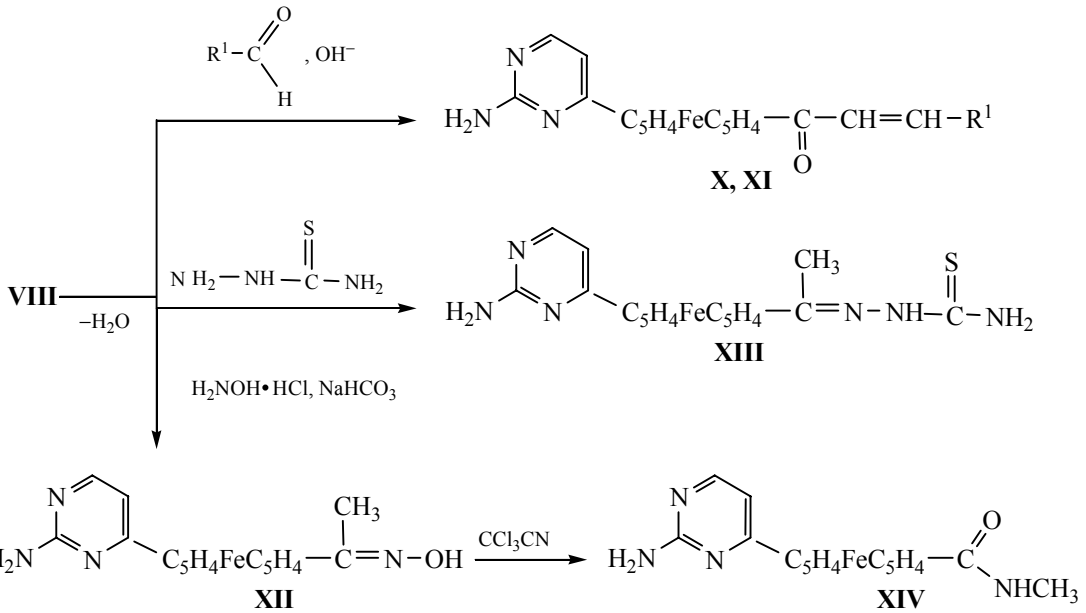
Unlike hydrazine hydrate and hydroxylamine, the amidines (guanidine and morpholino-1-carboxamidine) react with enamine **II** chemoselectively involving enaminocarbonyl moiety. As a result ferrocene-containing pyrimidines **VIII** and **IX** containing an acetyl group were obtained in moderate yields.



VIII, IX

R = H_2N (**VIII**),  (**IX**).

Acetyl derivatives of the ferrocene series can participate in a variety of chemical transformations [1]. Indeed, by an example of compound **VIII** we showed that it can react with aldehydes, hydroxylamine, thiosemicarbazide to form the corresponding condensation products involving methyl (**X**, **XI**) as well as carbonyl (**XII**, **XIII**) group. Oxime **XII** as well as the previously described compound **V** is rearranged into *N*-methylamide **XIV** under the action of trichloroacetonitrile.



X, XI

XIII

XII

XIV

R^1 = Ph (**X**), 4-$NO_2C_6H_4$ (**XI**).

The composition and structure of compounds **IV**–**XIV** were confirmed by analytical and spectroscopic data listed in Tables 1 and 2.

Thus, based on [1-acetyl-1'-(1-dimethylamino-3-oxoprop-1-en-3-yl)]ferrocene **II** we developed new approaches to the synthesis of 1,1'-disubstituted unsymmetrical ferrocene derivatives, which are of scientific and practical interest.

EXPERIMENTAL

Commercial reagents (Acros) were used. The IR spectra were recorded on a UR-20 spectrometer from KBr pellets. The ^{1}H NMR spectra were registered on a Varian Mercury Plus-400 spectrometer (400 MHz) in $CDCl_3$ with internal reference HMDS. The GC–MS spectra were recorded on a Thermo Finnigan Surveyor MSQ (USA) instrument by the method of chemical

ionization at atmospheric pressure. Identity and purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates, eluents ethyl acetate (A), benzene–chloroform, 2:1 (B), ethyl acetate–chloroform, 4:1 (C).

[1-Acetyl-1'-(1-dimethylamino-3-oxoprop-1-en-3-yl)]ferrocene (II). A mixture of 2.7 g of 1,1'-diacetylferrocene and 50 ml of dimethylformamide dimethyl acetal **I** was refluxed under argon for 30 h at stirring. Excess of acetal **I** was removed in a vacuum. The residue was dissolved in ethyl acetate and subjected to chromatography, eluting with ethyl acetate the starting 1,1'-diacetylferrocene (0.24 g), and then with ethyl acetate–methanol mixture (2:1) the target product **II** (2.4 g, 74%).

[1-Acetyl-1'-(pyrazol-3-yl)]ferrocene hydrazone (IV). A mixture of 1.07 g of compound **II**, 0.8 ml of hydrazine hydrate in 20 ml of ethanol was refluxed for 3 h with stirring. The solvent was removed in a vacuum. The residue was dissolved in 30 ml of water and extracted with ethyl acetate (2×50 ml). The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated. The product was purified by chromatography, eluting with system B. Yield 0.59 g (58%).

[1-Acetyl-1'-(oxazol-3-yl)]ferrocene oxime (V). To a solution of 1.07 g of **II** in 15 ml of ethanol was added hydroxylamine solution obtained from 1.26 g of $HONH_2 \cdot HCl$ and 1.68 g of $NaHCO_3$ in 10 ml of water. The mixture was refluxed for 4 h under stirring, then mixed with 50 ml of water and processed as in the previous experiment. Yield 0.71 g (69%).

Compound **XII** was prepared similarly.

4-Nitrobenzaldehyde-[1-acetyl-1'-(pyrazol-3-yl)]-ferrocene azine (VI). A mixture of 0.62 g of compound **IV**, 0.3 g of 4-nitrobenzaldehyde, and 0.1 ml of glacial acetic acid in 8 ml of ethanol was refluxed for 2 h with stirring, then mixed with 30 ml of water and kept for 15 h under cooling at 6–7°C. The reddish orange precipitate was filtered off and recrystallized from ethanol–water mixture (2:1). Yield 0.67 g (76%).

Compound **XIII** was prepared similarly.

[1-(*N*-Methylcarbamido)-1'-(oxazol-3-yl)]ferrocene (VII). A mixture of 0.62 g of compound **V**, 2 ml of trichloroacetonitrile in 8 ml of anhydrous chloroform was refluxed under argon for 6 h at stirring (monitoring with TLC). Then the solvent was removed in a vacuum, and the residue was subjected to chromatography eluting with ethyl acetate. Yield 0.48 g (77%).

Compound **XIV** was prepared similarly.

[1-Acetyl-1'-(2-aminopyrimidin-4-yl)]ferrocene (VIII). A mixture of 1.07 g of compound **II**, 0.96 g of guanidine hydrochloride, and 1.68 g of potassium tert-butoxide in 20 ml of anhydrous ethanol was refluxed for 5 h at stirring. Then the mixture was cooled, mixed with 100 ml of water, and extracted with methylene chloride (2×80 ml). The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was subjected to chromatography eluting with ethyl acetate. Yield 0.51 g (48%). The product was recrystallized from water–methanol mixture (2:1).

Compound **IX** was prepared similarly.

[(1-Phenyl-3-oxoprop-1-en-3-yl)-1'-(2-aminopyrimidin-4-yl)]ferrocene (X). To a solution of 0.32 g of compound **VIII** and 0.11 g of the freshly distilled benzaldehyde was added 0.2 ml of 30% aqueous NaOH. The mixture was kept for 3 days at room temperature. The reddish violet precipitate formed was filtered off, washed with water, and dried. Yield 0.28 g (68%).

Compound **XI** was prepared similarly.

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