3-Alkenyl-5-ferrocenyl-2-pyrazolines in reactions with azodicarboxylic acid *N*-phenylimide

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Azodicarboxylic acid *N*-phenylimide reacts with 1-acetyl-3-(2-ferrocenylethenyl)-5-ferrocenyl-2-pyrazoline according to the [4+2]-cycloaddition mechanism to form a Diels—Alder adduct. Under analogous conditions, 1-acetyl-5-ferrocenyl-3-(1-cyclohexenyl)-substituted 2-pyrazolines containing allylic hydrogen atoms give monoene addition products.

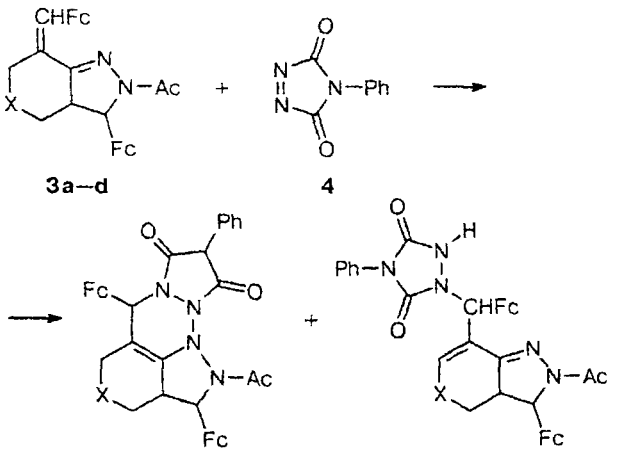
Key words: pyrazoline, hetero-1,3-diene, cycloaddition, ene addition, diene adduct.

It is known that the introduction of ferrocene substituents into molecules of organic compounds leads to an enhancement (or to the appearance) of biological activity of the resulting compounds and to a decrease in their toxicity compared to the initial compounds.[1] Thus tetrahydrophthalates,[2] cyclohexenes,[3] and cyclopropanes[4] containing ferrocene fragments are characterized by analgesic and antiinflammatory activities. Ferrocenyl-substituted 2-pyrazolines also belong to pharmacologically active compounds. In particular, 4-acetyl-3-ferrocenyl-2,4,5-triazatricyclo[5.2.2.0^{2,6}]undec-5-ene exhibits high antiviral activity. One would expect that the introduction of additional nitrogen-containing fragments into heterocyclic compounds of this class will afford products possessing a broader spectrum of useful biological characteristics.

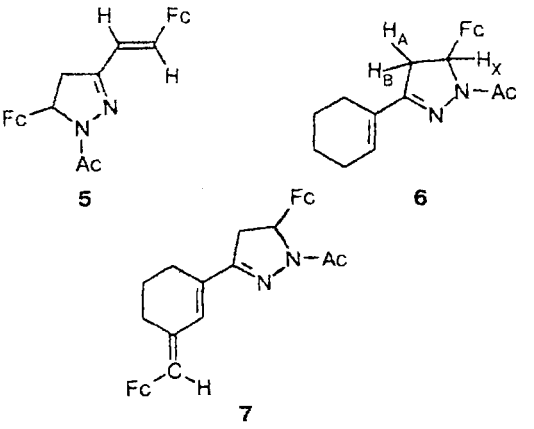
In this respect, adducts of diene condensation (**1**) and monoene condensation (**2**) of bicyclic 2-pyrazolines (**3**) with azodicarboxylic acid *N*-phenylimide (**4**), which have been synthesized recently (Scheme 1),[5,6] are of particular interest. Pyrazolines **3** contain the ferrocenylmethylene fragment conjugated with the C=N fragment of the heterocycle, and hence, these compounds exhibit the properties of hetero-1,3-dienes. The presence of allylic hydrogen atoms in molecules **3** provides conditions for the competitive monoene addition of azo compound **4**. Products **1** and **2** are organic compounds containing several nitrogen atoms, and they exhibit antiviral activity. In this connection, it is of interest to develop procedures for the synthesis of compounds with such structures and to study their chemical and pharmacological properties.

As part of continuing studies of the chemistry of 2-pyrazolines, in this work we studied 3-alkenyl-5-ferrocenyl-substituted 2-pyrazolines **5**—**7** as diene or

Scheme 1



Fc = $C_5H_5FeC_5H_4$;
X = CH_2 (**a**), $(CH_2)_2$ (**b**); NMe (**c**); NPh (**d**)



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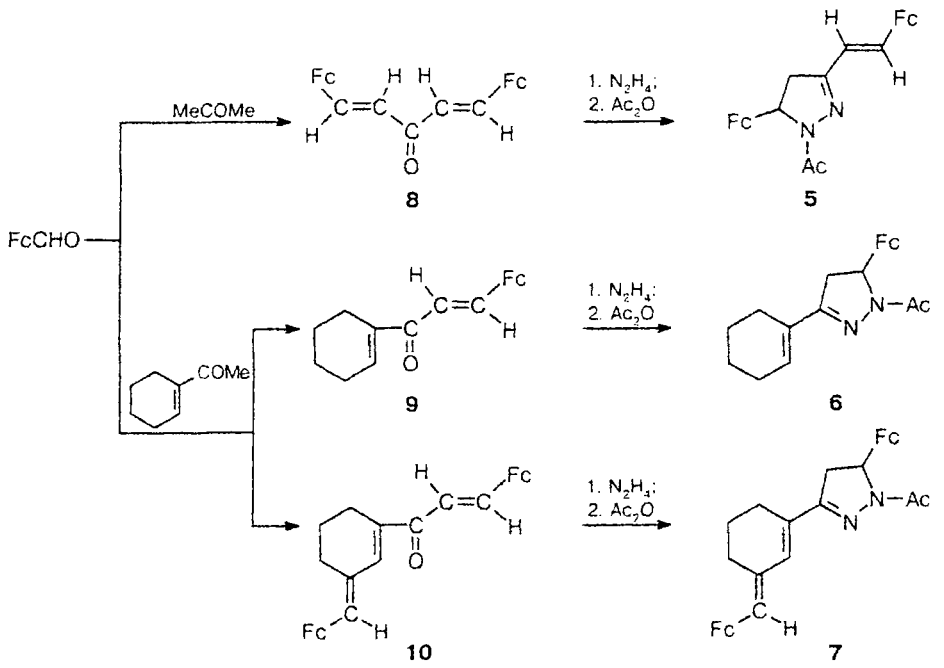
Scheme 2



monoene components in condensation with azo compound **4**.

Ferrocenyl-substituted α,β-unsaturated ketones **8**—**10**, which were prepared by condensation of ferrocenecarbaldehyde with acetone and 1-acetylcyclohexene in aqueous-alcoholic alkali, served as the starting compounds in the synthesis of pyrazolines.

Ketones **8**—**10** were isolated exclusively as one isomeric form with the COCH=CHFc fragments adopting *trans* configurations as evidenced by the spin-spin coupling constants of the protons of the above-mentioned fragments in the ^{1}H NMR spectra (J = 15.6 (**8**), 15.6 (**9**), and 15.3 Hz (**10**)), which is consistent with the published data.[9] We assigned the *E* configuration to the ferrocenylethenyl fragment in compound **10** by analogy with the configurations of the analogous fragments in 2,6-diferrocenylmethylenecycloakanones and ferrocenylmethylene-substituted bicyclic pyrazolines.[8]

1-Acetyl-3-alkenyl-5-ferrocenyl-2-pyrazolines **5**—**7** were synthesized by adding hydrazine[5—8] to ketones **8**—**10**, respectively, followed by acylation of unstable 1-unsubstituted products (Scheme 2).

Pyrazolines were obtained in virtually quantitative yields. The data of elemental analysis of these compounds and their physicochemical characteristics are given in Tables 1—3. In our opinion, compounds **5** and **7**, like the initial α,β-unsaturated ketones **8** and **10**, retain the *trans* and *E* configurations of the CH=CH and FcC=CCH fragments, respectively.

All the synthesized 1-acetylpyrazolines **5**—**7** are characterized by the presence of the double C=C bond conjugated with the C=N bond of the heterocycle due to which these compounds can react as hetero-1,3-dienes with active dienophiles. Apparently, dienes **6** and **7** containing allylic hydrogen atoms can also form monoene addition products.

Actually, we found that pyrazoline **5** reacted with dienophile **4** upon boiling in toluene to form Diels—Alder adduct **11** (Scheme 3).

Adduct **11** occurs as a stable crystalline compound, which decomposes at temperatures higher than 300 °C. Condensation proceeded stereospecifically. Compound **11** was obtained exclusively as one diastereomeric form, which is evident from the ^{1}H and ^{13}C NMR spectra (see Tables 2 and 3). However, the configuration of adduct **11** (the relative orientation of two Fc substituents at the C(4) and C(8) atoms) remains to be established.

Scheme 3

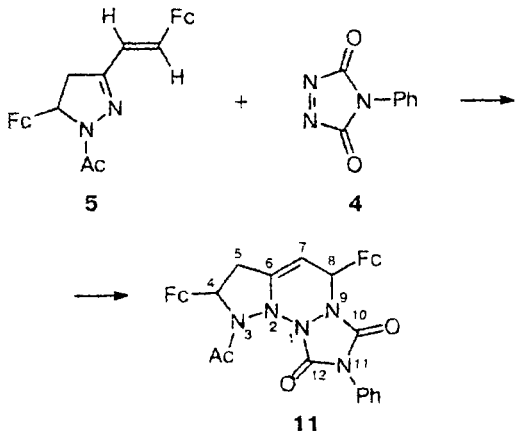


Table 1. Data of elemental analysis of the synthesized compounds

Compound	Yield (%)	M.p./°C (solvent for crystallization)	Found / Calculated (%) C	H	Fe	N	Molecular formula
5	73.5	178—179 (ethanol)	63.82 / 64.06	5.29 / 5.18	21.94 / 22.07	5.40 / 5.53	$C_{27}H_{26}FeN_2O$
6	73	154—155 (ethanol)	67.24 / 67.03	6.21 / 6.43	14.99 / 14.84	7.31 / 7.45	$C_{21}H_{24}FeN_2O$
7	69	203—204 (ethanol)	67.32 / 67.15	5.48 / 5.64	19.71 / 19.53	4.73 / 4.89	$C_{32}H_{32}Fe_2N_2O$
8	76	196—197 (ethanol)	66.87 / 66.70	4.72 / 4.92	25.04 / 24.82	—	$C_{25}H_{22}Fe_2O$
9	36	124—125 (ethanol)	71.18 / 71.26	6.47 / 6.30	17.19 / 17.44	—	$C_{19}H_{20}FeO$
10	42	145—146 (benzene)	69.99 / 69.80	5.31 / 5.46	21.74 / 21.64	—	$C_{30}H_{28}Fe_2O$
11	72	312*	61.57 / 61.70	4.75 / 4.59	16.58 / 16.40	10.50 / 10.27	$C_{35}H_{31}Fe_2N_5O_3$
12	76	288—289 (benzene)	63.41 / 63.17	5.11 / 5.30	10.32 / 10.13	12.60 / 12.70	$C_{29}H_{29}FeN_5O_3$
14	68	334*	64.06 / 64.28	4.73 / 5.00	15.06 / 14.94	9.45 / 9.36	$C_{40}H_{37}Fe_2N_5O_3$

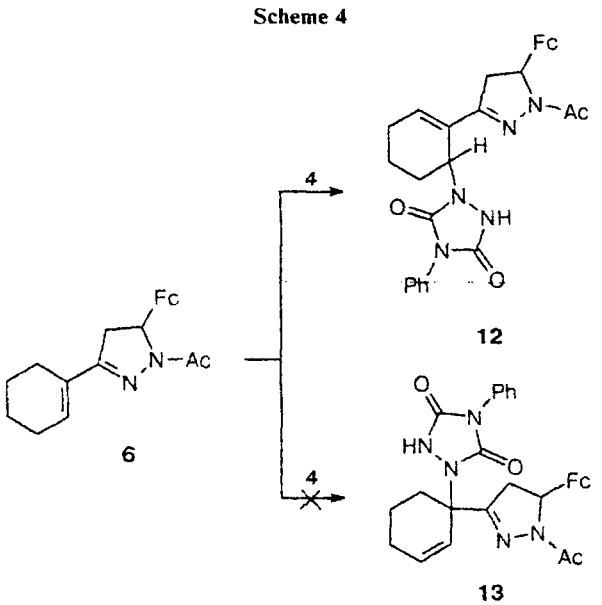
* The decomposition temperature.

We also found that dienes **6** and **7**, unlike pyrazoline **5**, did not react with azo compound **4** to form [4+2]-cycloaddition adducts, and the reactions proceeded exclusively according to the scheme of monoene addition.[10—12] In all cases, only one of two possible directions of the ene addition was realized, which indicates that the process is highly regioselective. Thus, the reaction of pyrazoline **6** with enophile **4** afforded an adduct with structure **12** rather than **13** (Scheme 4).

Under analogous conditions, pyrazoline **7** also gave exclusively one of two possible adducts (**14** and **15**) to which structure **14** was assigned (Scheme 5).

The structures of compounds **12** and **14** were established based on the ^{1}H NMR spectra, which have one broad singlet for the protons of the NH group (at δ 9.65 and 9.53, respectively), and on the ^{13}C NMR spectra (see Tables 2 and 3). The structure of adduct **12** was assigned based on the facts that the ^{1}H NMR spectrum has a triplet for one olefin proton (at δ 6.54, J = 8.4 Hz) and the ^{13}C NMR spectrum has signals for two olefin carbon atoms ($\delta_{CH=}$ 119.79 and $\delta_{C=}$ 125.35). The evidence for the structure of adduct **14** is circumstantial for

Scheme 4



Scheme 5

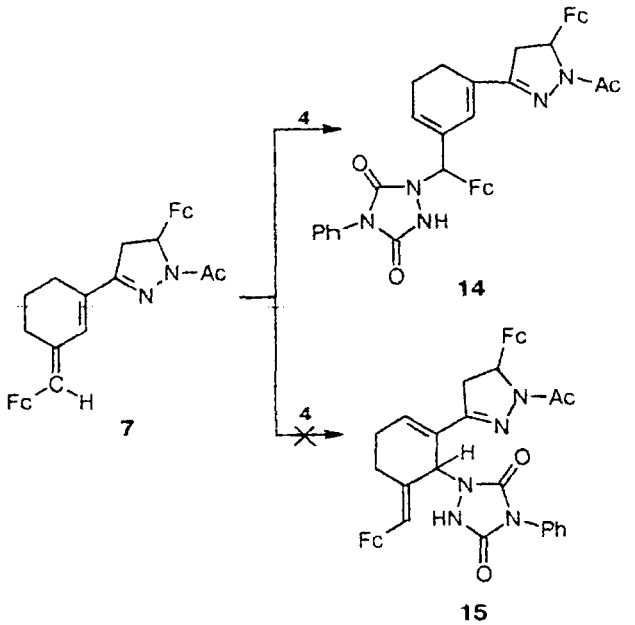


Table 2. ^{1}H NMR spectra of the resulting compounds (δ, *J*/Hz)

Compound	C_5H_5 (s, 5 H)	C_5H_4 (m)	ABX system	Me (s, 3 H)	CH	CH_2 (m)	Ph, NH
5	4.167, 4.169	4.0 (1 H); 4.12 (2 H); 4.40 (2 H); 4.46 (1 H); 4.51 (1 H); 4.54 (1 H)	3.46 (H_A), 3.34 (H_B), 5.41 (H_X) (J_{AB} = 16.9, J_{AX} = 10.8, J_{BX} = 4.2)	2.26	6.70 (d, 1 H, *J* = 16.5); 6.78 (d, 1 H, *J* = 16.5)	—	—
6	4.13	3.99 (1 H); 4.10 (1 H); 4.13 (1 H); 4.45 (1 H)	3.37 (H_A), 3.26 (H_B), 5.35 (H_X) (J_{AB} = 17.0, J_{AX} = 10.5, J_{BX} = 4.5)	2.23	6.23 (t, 1 H, *J* = 4.20)	1.70 (4 H); 2.28 (2 H, *J* = 4.20); 2.41 (2 H)	—
7	4.16, 4.17	4.02 (1 H); 4.12 (1 H); 4.32 (2 H); 4.34 (1 H); 4.40 (2 H); 4.86 (1 H)	3.44 (H_A), 3.34 (H_B), 5.41 (H_X) (J_{AB} = 16.8, J_{AX} = 10.5, J_{BX} = 4.2)	2.25	6.29 (s, 1 H); 6.52 (s, 1 H)	1.84 (2 H); 2.53 (2 H); 2.60 (2 H)	—
8	4.18 (10 H)	4.46 (4 H); 4.57 (4 H)	—	—	6.61 (d, 2 H, *J* = 15.6); 7.63 (d, 2 H, *J* = 15.6)	—	—
9	4.15	4.41 (2 H); 4.52 (2 H)	—	—	6.89 (d, 1 H, *J* = 15.6); 6.93 (t, 1 H, *J* = 5.4); 7.54 (d, 1 H, *J* = 15.6)	1.62—1.77 (4 H); 2.27 (2 H); 2.36 (2 H)	—
10	4.15, 4.18	4.34 (2 H); 4.44 (2 H); 4.47 (2 H); 4.57 (2 H)	—	—	6.45 (s, 1 H); 7.02 (d, 1 H, *J* = 15.3); 7.19 (s, 1 H); 7.61 (d, 1 H, *J* = 15.3)	1.79 (2 H); 2.46 (2 H); 2.56 (2 H, *J* = 6.1)	—
11	4.18, 4.24	4.05 (1 H); 4.08 (1 H); 4.10 (1 H); 4.12 (1 H); 4.29 (1 H); 4.35 (1 H); 4.42 (1 H); 4.54 (1 H)	3.61 (H_A), 3.38 (H_B), 5.37 (H_X) (J_{AB} = 18.0, J_{AX} = 10.8, J_{BX} = 4.5)	2.17	4.26 (d, 1 H, *J* = 9.13); 5.82 (d, 1 H, *J* = 9.13)	—	6.95—7.73 (m, 5 H)
12	4.18	3.98 (1 H); 4.31 (1 H); 4.49 (2 H)	3.31 (H_A), 3.20 (H_B), 5.21 (H_X) (J_{AB} = 17.2, J_{AX} = 11.0, J_{BX} = 4.3)	2.05	5.33 (t, 1 H, *J* = 5.9); 6.54 (t, 1 H, *J* = 8.4)	1.81 (2 H); 2.15 (2 H); 2.34 (2 H)	7.22—7.54 (m, 5 H); 9.65 (br.s, 1 H)
14	4.11, 4.15	3.94 (1 H); 3.99 (1 H); 4.04 (2 H); 4.16 (2 H); 4.19 (1 H); 4.23 (1 H)	3.26 (H_A), 3.00 (H_B), 5.31 (H_X) (J_{AB} = 18.0, J_{AX} = 9.9, J_{BX} = 4.2)	2.05	6.08 (s, 1 H); 6.55 (t, *J* = 6.7); 7.08 (s, 1 H)	2.20—2.67 (4 H)	7.19—7.53 (m, 5 H)

a number of reasons. Thus, the ^{1}H NMR spectra of compounds **14** and **15** should have two signals for the olefin protons with equal multiplicities and one singlet for the methine protons of the N—CH—Fc and CH—N groups, while the characteristics of their ^{13}C NMR spectra are virtually identical, which hinders the establishment of the structure of the product. However, structure **14** was assigned to the resulting adduct based on a comparison of the chemical shifts of the protons of the N—CH—Fc and CH—N fragments in the ^{1}H NMR spectra of compounds **12** and **14** (5.33 and 6.08 ppm, respectively) with the chemical shifts of the protons of the N—CH—Fc groups in adducts **2a—d** (6.16, 6.21, 6.08, and 6.03 ppm, respectively).[7]

Apparently, the absence of noticeable amounts of [4+2]-cycloaddition products in the reactions of pyrazolines **6** and **7** with azo compound **4** is due to steric hindrances, which prevent dienes **6** and **7** from adopting an *s-cis* conformation necessary for diene condensation. In the case of hetero-1,3-dienes **3a,b** with the fixed *cis*-arrangement of the double bonds[7,8] or in the absence of steric hindrances to the *s-cis* conformation (as, for example, in pyrazoline **5**), the reactions with dienophile **4** afforded Diels—Alder adducts.

Table 3. ^{13}C NMR spectra of compounds **5**—**7**, **9**—**12**, and **14** (δ)

Compound	C_5H_5	C_5H_4	CH_2	CH	C	Fc_{ipso}	C=O	HC=	C=N	Me	Ph
5	68.57, 69.54	65.66, 67.30, 67.98, 68.15, 68.31, 69.97, 70.16, 70.23	38.30	54.98	—	80.93, 87.55	168.44	118.25, 136.97	155.53	22.01	—
6	68.51	65.61, 68.03, 68.20, 70.11	21.83, 22.03, 24.44, 26.04, 38.62	54.77	132.07	87.58	168.68	133.22	156.23	22.08	—
7	68.56, 69.21	68.09, 69.28, 69.31, 69.56, 69.67, 69.77, 69.97, 70.28	22.06, 24.41, 26.66, 38.31	55.16	134.09, 136.02	81.02, 87.91	168.45	129.26, 130.06	156.12	21.91	—
9	69.60	68.62, 70.78	21.63, 22.04, 23.62, 26.13	—	143.76	79.65	190.46	118.43, 138.78, 140.15	—	—	—
10	69.31, 69.64	68.66, 69.76, 69.98, 70.80	20.07, 23.62, 27.57	—	140.49, 143.38	79.95, 81.15	189.41	118.38, 133.62, 134.01, 137.61	—	—	—
11	68.62, 68.99	68.16, 68.25, 68.37, 68.55, 68.81, 69.20, 70.90, 71.17	31.55	52.11, 55.34	123.59, 138.42	84.41, 87.15	172.39, 173.39, 174.82	120.40	—	22.10	128.78, 129.15, 130.14
12	69.36	67.50, 69.63, 70.81, 71.28	25.58, 28.56, 29.64, 38.64	49.36, 54.96	125.35, 140.17	91.27	153.35, 153.59, 168.82	119.79	150.68	21.78	124.97, 127.93, 128.98, 131.47
14	68.67, 68.93	67.93, 68.12, 68.40, 68.87, 69.04, 69.19, 70.12, 70.39	27.31, 29.57, 38.29	55.22, 59.84	124.18, 126.21, 139.56	88.93, 90.56	156.73, 158.92, 166.99	120.11, 121.35	152.18	22.04	127.15, 129.10, 130.05, 132.18

Experimental

The ^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on a Unity Inova Varian spectrometer (operating at 300 and 75 MHz, respectively) with Me_4Si as the internal standard.

1,5-Diferrocenyl-1(*E*),4(*E*)-pentadien-3-one (8) was synthesized from acetone and ferrocenecarbaldehyde. **(*E*)-1-(Cyclohexen-1-yl)-3-ferrocenylpropen-2-one (9)** and **3(*E*)-ferrocenyl-1(*E*)-(3-ferrocenylmethylenecyclohexen-1-yl)propen-2-one (10)** were synthesized from 1-acetylcyclohexene and ferrocenecarbaldehyde in aqueous-alcoholic alkali.[5] The resulting compounds were purified and separated by chromatography on Al_2O_3 (Brockmann III) with the use of hexane as the eluent. Then the compounds were recrystallized from ethanol.

1-Acetyl-5-ferrocenyl-3-(2-ferrocenylethenyl)-2-pyrazoline (5), 1-acetyl-3-(1-cyclohexenyl)-5-ferrocenyl-2-pyrazoline (6), and **1-acetyl-5-ferrocenyl-3-(3-ferrocenylmethylene-1-cyclohexenyl)-2-pyrazoline (7)** were synthesized according to standard procedures[5,6] from ketones **8**, **9**, and **10**, respectively, and hydrazine hydrate in alcohol. The precipitates of 1-unsubstituted pyrazolines that formed were filtered off, dried *in vacuo* over P_4O_{10}, and treated with acetic anhydride. Compounds **5**—**7** were isolated by column chromatography on Al_2O_3 (Brockmann III) and purified by crystallization from ethanol. Compounds **5** and **6** were obtained as orange crystals. Compound **7** was obtained as a brown powder.

3-Acetyl-4,8-diferrocenyl-10,12-dioxo-11-phenyl-1,2,3,9,11-pentaazatricyclo[7.3.0.0^{2,6}]dodec-6-ene (11). A mixture of acetylpyrazoline **5** (0.5 g, 0.001 mol) and imide **4** (0.175 g, 0.001 mol) in toluene (50 mL) was refluxed with stirring until the color of the solution changed from bright-red to yellow (~3 h). The solvent was evaporated *in vacuo* and the residue was chromatographed on Al_2O_3 (chloroform as the eluent). Adduct **11** was obtained as a yellow powder in a yield of 0.49 g.

Reactions of acetylpyrazolines 6 and 7 with imide 4. Imide **4** (0.175 g) was added with stirring to a solution of pyrazoline **6** or **7** (0.001 mol) in acetone at 20 °C. The reaction mixture was stirred at the same temperature for 1 h. Then the solvent was distilled off *in vacuo* and the residue was chromatographed on Al_2O_3 (benzene as the eluent). **1-Acetyl-3-[1-cyclohexenyl-6-(2,5-dioxo-1-phenyl-2,3,4,5-tetrahydro-1,3,4-triazol-3-yl)]-5-ferrocenyl-2-pyrazoline (12)** was obtained as a yellow powder in a yield of 0.42 g. **1-Acetyl-5-ferrocenyl-3-[3-ferrocenyl-(2,5-dioxo-1-phenyl-2,3,4,5-tetrahdyro-1,3,4-triazol-3-yl)-methylcyclohexa-1,3-dienyl]-2-pyrazoline (14)** was obtained as orange crystals in a yield of 0.51 g.

The characteristics of the resulting compounds are given in Table 1.

References

1. E. G. Perevalova, M. D. Reshetova, and K. I. Grandberg, *Metody elementoorganicheskoi khimii: zhelezoorganicheskie soedineniya. Ferrotsen* [*Methods of Organometallic Chemistry. Organoiron Compounds. Ferrocene*], Nauka, Moscow, 1983, 484 pp. (in Russian).
2. E. I. Klimova, V. N. Postnov, N. N. Meleshonkova, M. Martinez Garcia, and A. S. Zaks, *Khim.-Farm. Zh.*, 1994, **28**, 33 [*Pharm. Chem. J.*, 1994, **28** (Engl. Transl.)].
3. E. I. Klimova, V. N. Postnov, N. N. Meleshonkova, A. S. Zaks, and E. M. Chukichev, *Khim.-Farm. Zh.*, 1992, **26**, 34 [*Pharm. Chem. J.*, 1992, **26** (Engl. Transl.)].
4. E. I. Klimova, V. N. Postnov, N. N. Meleshonkova, A. S. Zaks, and V. V. Yushkov, *Khim.-Farm. Zh.*, 1992, **26**, 69 [*Pharm. Chem. J.*, 1992, **26** (Engl. Transl.)].
5. A. N. Nesmeyanov, V. N. Postnov, E. I. Klimova, and V. A. Sazonova, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1979, 239 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28** (Engl. Transl.)].
6. E. I. Klimova, L. Ruiz Ramirez, M. Martinez Garcia, R. G. Espinosa, and N. N. Meleshonkova, *Izv. Akad. Nauk. Ser. Khim.*, 1996, 2743 [*Russ. Chem. Bull.*, 1996, **45**, 2702 (Engl. Transl.)].
7. E. I. Klimova, M. Martinez Garcia, T. Klimova-Berestneva, C. Alvarez Toledano, R. A. Toscano, and L. Ruiz Ramirez, *J. Organomet. Chem.*, 1999, **585**, 106.
8. E. I. Klimova, M. Martinez Garcia, T. Klimova-Berestneva, L. Ruiz Ramirez, S. Al'vares Toledano, and R. A. Toscano, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 765 [*Russ. Chem. Bull.*, 1999, **48**, 761 (Engl. Transl.)].
9. A. N. Nesmeyanov, V. A. Sazonova, V. N. Postnov, and A. M. Baran, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 902 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28** (Engl. Transl.)].
10. B. T. Gillis and P. E. Beck, *J. Org. Chem.*, 1962, **27**, 1947.
11. B. Franzus, *J. Org. Chem.*, 1963, **28**, 2954.
12. W. A. Thaler and B. Franzus, *J. Org. Chem.*, 1964, **29**, 2226.

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