Direct C—C-coupling of ferrocenyl- and cymantrenyllithium with 5-(het)aryl-1,2,5-oxadiazolo[3,4-b]pyrazines*

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A direct C—C-coupling of ferrocenyl- and cymantrenyllithium with 5-(het)aryl-1,2,5oxadiazolo[3,4-*b*]pyrazines was accomplished. Main characteristics of the $S_N^{\rm H}$ -reaction products were obtained, as well as crystallographic data on the spatial structure of oxadiazolopyrazinylferrocenes and -cymantrenes synthesized.

Key words: ferrocenyllithium, cymantrenyllithium, 5-(het)aryl-1,2,5-oxadiazolo[3,4-*b*]-pyrazines, σ^{H} -adducts, nucleophilic substitution of hydrogen.

Metallocene heterocyclic derivatives are usually obtained by two synthetic approaches.¹ Hetarylmetallocenes can be constructed either by building-up a heterocyclic subunit based on the groups pre-introduced into the substrate (metallocene) structure, or as a result of the direct coupling of functional blocks (metallocene and heterocycle) with each other. The use of the former method is limited since it is labor-consuming and in some case because of impossibility to obtain metallocene synthons. Therefore, a direct C-C-coupling of metallocenes with heterocyclic derivatives is recently under intensive development. Different versions of cross-coupling reactions are most frequently used as such synthetic approaches.¹ In addition, a synthetic strategy of the oxidative nucleophilic substitution of hydrogen $(S_N^H(AO))$ can be also successfully used for the preparation of ferrocene^{1,2} and cymantrene³ heterocyclic derivatives.

Ferrocene⁴⁻⁷ and cymantrene^{8,9} heterocyclic derivatives possess a wide range of various applied properties. Therefore, preparation of such compounds and studies of their properties is a relevant synthetic problem.

In the present work, we studied a possibility of the use of 5-(het)aryl-1,2,5-oxadiazolo[3,4-*b*]pyrazines as substrates in the reaction of nucleophilic substitution of hydrogen with ferrocenyl- and cymantrenyllithium. Furazanopyrazines and their derivatives manifest high activity in the $S_{\rm N}^{\rm H}$ -reactions with different nucleophilic agents.¹⁰ According to the common knowledge, oxidative nucleophilic substitution of hydrogen of the type $S_N^H(AO)$ occurs in two steps (Scheme 1).¹¹ In the first step, a nucleophilic fragment adds to the substrates 1 bearing electron-withdrawing substituents to form σ^H -adducts 2. In the second step, aromatization of these intermediates to the corresponding S_N^H -products 3 occurs upon the action of oxidants.



EWG is the electron-withdrawing group, Nu is the nucleophile

Results and Discussion

Earlier, we have accomplished a series of work devoted to the studies of reactions of ferrocenyllithium with azines and optimization of the reaction conditions (ratio of reagents, temperature, solvent, *etc.*). It was found² that the transformation occurs according to the mechanism described above *via* formation of σ^{H} -adducts.

When ferrocenyllithium (4) (obtained by the reaction of bromoferrocene with BuLi in THF at $0 \,^{\circ}$ C) reacted with oxadiazolopyrazines **5a**–c as electrophilic agents,

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the corresponding S_N^{H} -products **6a**—**c** were successfully obtained (Scheme 2). 5-(Het)aryl-1,2,5-oxadiazolo-[3,4-*b*]pyrazines **5a**—**c** react with ferrocenyllithium (**4**) in the ratio 1 : 1 in anhydrous THF at 0 °C to initially form the salt **A1**, which then upon the action of the air moisture is spontaneously hydrolyzed to the adduct **B1**. The latter upon the action of DDQ is oxidized to the substitution products **6a**—**c**. Oxidation of the σ^{H} -adducts **B1** can occur by exposure to air, as well. Note that the reaction results in higher yields (by 15% on average) when DDQ was used as an oxidant.

5-(Het)aryl-1,2,5-oxadiazolo[3,4-*b*]pyrazines **5a**,**b** also react with cymantrenyllithium (7), obtained by metallation of cymantrene with BuLi in THF at -78 °C. The lithium derivative 7 readily reacts with azines **5a**,**b** with the formation of azinylcymantrenes **8a**,**b** (Scheme 3). After electrophilic agents were added to cymantrenyllithium at -78 °C, the reaction mixture was kept for 1.5 h at this temperature, then the temperature was gradually raised to ambient. Earlier,³ it has been shown that these transformations also proceeded in two steps according to the mechanism given in Scheme 1. Oxidation of the σ^{H} -adduct **B2** takes place only in the presence of DDQ. If the reaction mixture was exposed to air for a long time, adducts **B2** are converted to a mixture of compounds of unestablished structure.

Compounds 6a-c were obtained in 60-75% yields, compounds 8a,b, in 50-60% yields. Products 6a-c and

8a,b were isolated by column chromatography on Al_2O_3 and SiO_2 , respectively. The products synthesized are deeply colored crystalline compounds, ranging from dark green to dark blue in the case of hetarylferrocenes **6a**-**c** and being dark red in color in the case of hetarylcymantrenes **8a,b**.

The ¹H NMR spectra of products **6a**–**c** exhibit signals for the protons of the monosubstituted ferrocene system as a single five-proton singlet for the unsubstituted cyclopentadienyl ferrocene fragment (δ 4.1–4.2) and two triplets with the intensities for two protons for the monosubstituted cyclopentadienyl fragment (δ 4.4–4.7), as well as signals for the corresponding aryl substituents. The IR spectrum of compound **6b** exhibits an absorption band related to the stretching vibrations of the NO₂ group in the region 1530 cm⁻¹. Mass spectra contain peaks of molecular ions.

The ¹H NMR spectra of compounds **8a,b** exhibit signals characteristic of the protons of monosubstituted cymantrene cyclopentadienyl ring as two multiplets with intensity of two proton (δ 4.8–5.2), as well as signals for the protons of aryl substituents. Mass spectra contain peaks of molecular ions. In the IR spectra of these compounds, absorption bands characteristic of the corresponding vibrations of the CO group of cymantrene are observed (1900–2020 cm⁻¹).

Molecular and crystal structure of derivatives **6** and **8** were studied by X-ray crystallography (Figs 1 and 2).



Scheme 2

 $R = Ph(a), 3-NO_2C_6H_4(b), 3-thienyl(c)$

Scheme 3



 $R = Ph (a), 3-NO_2C_6H_4 (b)$



Fig. 1. Molecular structure of compound **6a** in thermal ellipsoids of 50% probability.



Fig. 2. Molecular structure of compound **8a** in thermal ellipsoids of 50% probability.

In conclusion, the studies accomplished resulted in the direct C–C-coupling of ferrocenyl- and cymantrenyllithium with 5-(het)aryl-1,2,5-oxadiazolo[3,4-*b*]pyrazines. Main characteristics were obtained for the products of the S_N^H -reaction, as well as crystallographic data on the spatial structure of the synthesized oxadiazolopyrazinylferrocenes and -cymantrenes.

Experimental

¹H NMR spectra (400 MHz) were recorded on a Bruker-400 AVANCE II spectrometer, chemical shifts are given in the δ scale

relatively to Me_4Si . IR spectra were recorded on a Bruker Alpha IR Fourier-spectrometer with an FTIR accessory. Mass spectra were recorded on a Bruker Daltonics MicrOTOF-Q II mass spectrometer equipped with a source of electro-spray ionization, six-way stopcock, and a kd Scientific direct injection facility. Elemental analysis was performed on a Perkin—Elmer 2400-II instrument. Melting points were measured on a Boetius apparatus. TLC was performed on Alugram Sil G/UV254 or Poligram Alox N/UV-254 plates, using visualization with the UV light.

Solvents were purified and dried according to the standard procedures. Silica gel and alumina (for column chromatography), ferrocene, cymantrene, and THF were purchased from Aldrich. Other reagents and solvents are of home-country made.

Bromoferrocene,¹² 5-phenyl-1,2,5-oxadiazolo[3,4-*b*]pyrazine (**5a**),¹³ 5-(3-nitrophenyl)-1,2,5-oxadiazolo[3,4-*b*]pyrazine (**5b**),¹³ and 5-(thien-3-yl)-1,2,5-oxadiazolo[3,4-*b*]pyrazine (**5c**)¹⁰ were obtained according to the known procedures.

Synthesis of compounds 6a-c (general procedure). A 1.6 *M* solution of BuLi in hexane (0.63 mL, 1 mmol) was added to a solution of bromoferrocene (1 mmol) in THF (5 mL) at 0 °C under argon, and the mixture was stirred for 10-15 min, followed by addition of a solution of furazanopyrazine 5a-c (1 mmol) in THF (5 mL). The reaction mixture was stirred for 30 min at 0 °C, then for another 1 h at room temperature. Then, a solution of DDQ (1 mmol) in THF (5 mL) was added. A suspension that formed was immediately filtered through a layer of Al₂O₃. The solution was concentrated at reduced pressure. The thus obtained residue was subjected to preparative column chromatography on Al₂O₃. The fraction that collected was concentrated.

1-(5-Phenyl-1,2,5-oxadiazolo[3,4-*b***]pyrazin-6-yl)ferrocene (6a).** Dark blue crystals. The yield was 0.29 g (75%), m.p. 226 °C, $R_{\rm f}$ 0.4 (hexane—ethyl acetate, 8 : 2). ¹H NMR (DMSO-d₆—CCl₄), δ : 4.13 (m, 5 H, CpH); 4.42, 4.60 (both m, 2 H each, C₅H₄); 7.58 (m, 5 H, Ph). IR, v/cm⁻¹: 1450, 1356, 1014. MS (EI, 70 eV), m/z: 383 [M + H]⁺. Found (%): C, 62.57; H, 3.31; N, 14.46. $C_{20}H_{14}$ FeN₄O. Calculated (%): C, 62.83; H, 3.66; N, 14.66.

1-[5-(3-Nitrophenyl)-1,2,5-oxadiazolo[3,4-*b***]pyrazin-6-yl]ferrocene (6b).** Dark blue crystals. The yield was 0.30 g (70%), m.p. 296 °C, $R_{\rm f}$ 0.4 (hexane—ethyl acetate, 7 : 3). ¹H NMR (DMSO-d₆—CCl₄), δ : 4.19 (m, 5 H, CpH); 4.40, 4.62 (both m, 2 H each, C₅H₄); 7.87 (m, 1 H, H_{Ar}); 8.04 (d, 1 H, H_{Ar}, ³J = 8.0 Hz); 8.48, 8.54 (both m, 1 H each, H_{Ar}). IR, v/cm⁻¹: 1530, 1454, 1327, 1251. MS (EI, 70 eV), *m/z*: 428 [M + H]⁺. Found (%): C, 56.27; H, 3.11; N, 16.62. C₂₀H₁₃FeN₅O₃. Calculated (%): C, 56.21; H, 3.04; N, 16.39.

1-[5-(Thien-3-yl)-1,2,5-oxadiazolo[3,4-b]pyrazin-6-yl]ferrocene (6c). Dark green crystals. The yield was 0.23 g (60%), m.p. 220 °C, R_f 0.45 (hexane—ethyl acetate, 9 : 1). ¹H NMR (DMSO-d₆—CCl₄), δ : 4.14 (m, 5 H, CpH); 4.59, 4.64 (both m, 2 H each, C₅H₄); 7.30 (d, 1 H, C₄H₃S, ³J = 4.8 Hz); 7.62 (m, 1 H, C₄H₃S); 7.88 (d, 1 H, C₄H₃S, ³J = 2.5 Hz). IR, v/cm⁻¹: 3095, 1633, 1495, 1446, 1381, 1236. MS (EI, 70 eV), *m/z*: 389 [M + H]⁺. Found (%): C, 55.53; H, 3.21; N, 14.51. C₁₈H₁₂FeN₄OS. Calculated (%): C, 55.67; H, 3.09; N, 14.43.

Synthesis of compounds 8a,b (general procedure). A 1.6 M solution of BuLi in hexane (0.63 mL, 1 mmol) was added to a solution of cymantrene (1.2 mmol) in THF (5 mL) at -78 °C under argon. After the mixture was stirred for 30 min, a solution of furazanopyrazine 5a,b (1 mmol) in THF (5 mL) was added, followed by stirring first for 1.5 h at -78 °C and then for another

1 h at room temperature. The reaction mixture was worked-up with a solution of DDQ in THF (7 mL), immediately filtered through a layer of Al_2O_3 , and concentrated at reduced pressure. The thus obtained residue was subjected to preparative column chromatography on SiO₂. The fraction that collected was concentrated.

1-(5-Phenyl-1,2,5-oxadiazolo[3,4-*b***]pyrazin-6-yl)cymantrene (8a).** Dark red crystals. The yield was 0.22 g (55%), m.p. 188 °C, $R_{\rm f}$ 0.5 (CH₂Cl₂). ¹H NMR (CDCl₃), δ : 4.80, 5.14

Table 1. Principal crystallographic data and parameters of theX-ray diffraction experiments for compounds 6a and 8a

Parameter	6a	8a
Formula	C ₂₀ H ₁₄ FeN ₄ O	C ₁₈ H ₉ MnN ₄ O ₄
M	382.20	400.23
λ/Å	0.71073	0.71073
Crystal system	Monoclinic	Triclinic
Space group	$P2_{1}/c$	$P\overline{1}$
a/Å	11.2860(13)	9.2253(4)
b/Å	8.1939(9)	10.0114(4)
c/Å	17.791(2)	10.2396(4)
α/deg	90.00	84.038(3)
β/deg	95.830(9)	88.523(3)
γ/deg	90.00	63.796(4)
$V/Å^3$	1636.7(3)	843.71(6)
Ζ	4	2
$d_{\rm calc}/{\rm g~cm^{-3}}$	1.551	1.575
μ/mm^{-1}	0.938	0.816
<i>F</i> (000)	784	404
Crystal size/mm	$0.25 \times 0.16 \times 0.02$	0.22×0.14×0.03
Region of scanning, 20/deg	2.74-33.51	2.87-30.50
Completeness on $2\theta_{max}$ (%)	88.7	97.9
Ranges of indices	$-17 \le h \le 16$,	$-13 \le h \le 13$,
of reflections	-12 < k < 10,	-14 < k < 14,
	-27 < l < 12	-14 < l < 11
Total number of reflections	15684	12305
Number of independent reflections	5751	5062
R _{int}	0.0271	0.0190
Number of reflections with $L \ge 2\sigma(L)$	2744	3494
Number of refined	235	244
Correction on absorption	Analytical	
Transmission (max/min)	0 941/0 737	0 925/0 787
$GOOF(on F^2)$	1 006	1 005
<i>R</i> -Factors (on reflections with $L \ge 2\sigma(L)$)	1.000	1.005
R_1	0.0316	0.0340
WR_2	0.0665	0.0941
<i>R</i> -Factors (on all	0.0000	0.0911
reflections)		
R_1	0.0867	0.0503
wR ₂	0.0697	0.0981
$\Delta \rho_{\text{max}} / \Delta \rho_{\text{min}} / e \text{ Å}^{-3}$	0.414/-0.377	0.375/-0.319

(both m, 2 H each, C_5H_4); 7.58 (m, 5 H, Ph). IR, v/cm^{-1} : 3090, 2025, 1935, 1432, 1259, 980. MS (EI, 70 eV), m/z: 401 [M + H]⁺. Found (%): C, 53.97; H, 2.31; N, 14.06. $C_{18}H_9MnN_4O_4$. Calculated (%): C, 54.00; H, 2.25; N, 14.00.

1-[5-(3-Nitrophenyl)-1,2,5-oxadiazolo[3,4-*b***]pyrazin-6yl]cymantrene (8b).** Dark red crystals. The yield was 0.27 g (60%), m.p. 184 °C, R_f 0.5 (CH₂Cl₂). ¹H NMR (CDCl₃), δ : 4.87, 5.16 (both m, 2 H each, C₅H₄); 7.83 (t, 1 H, H_{Ar}, ³*J* = 7.3 Hz); 7.99 (d, 1 H, H_{Ar}, ³*J* = 7.0 Hz); 8.48 (d, 1 H, H_{Ar}, ³*J* = 6.0 Hz); 8.55 (s, 1 H, H_{Ar}). IR, v/cm⁻¹: 2017, 1921, 1527, 1350. MS (EI, 70 eV), *m/z*: 446 [M + H]⁺. Found (%): C, 48.27; H, 1.31; N, 15.66. C₁₈H₈MnN₅O₆. Calculated (%): C, 48.54; H, 1.80; N, 15.73.

X-ray diffraction studies. For X-ray crystallography, the dark blue plates of crystals 6a were obtained by slow concentration of their solution in CH_2Cl_2 , whereas the red prisms of crystals 8a by slow concentration of their solution in Et₂O. The experimental set of reflections was obtained on a Xcalibur 3 (λ (Mo) diffractometer, graphite monochromator, T = 295(2) K, ω -scanning, the step of scanning 1°). The structures were solved by the direct method using the SHELXS97 program¹⁴ and refined using the SHELXL97 program by the least squares method in the anisotropic (isotropic for the H atoms) full-matrix approximation on F^2 . The hydrogen atoms were placed in the geometrically calculated positions and refined in the isotropic approximation with the dependent thermal parameters.¹⁵ The bond angles and bond distances are close to the standard values. The oxadiazolopyrazine fragment is planar, with deviation of the atoms from the mean-square plane being <0.025 Å. The plane of the phenyl ring in compound **6a** is turned with respect to the plane of the oxadiazolopyrazine fragment by 84.5°, in compound 8a, by 60°. The results of the X-ray diffraction studies of compounds 6a and 8a are given in Table 1.

The results of the X-ray diffraction studies were deposited with the Cambrige Structural Database (CCDC 856598 (**6a**) and CCDC 856599 (**8a**)). These materials are available for no charge at www.ccdc.cam.ac.uk/data_request/cif.

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