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Synthesis and Electrochemical Behavior of Some 1*H*-3-Methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazoles

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Summary. 1*H*-3-Methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazoles are key intermediates in obtaining various heterocyclic systems including pyrazolotriazoles. We present the voltammetric behavior of these compounds in nonaqueous media, with the following *para* substituents grafted on the benzene ring: $-N(CH_3)_2$, –OH, $-OCH_3$, –F, –Cl, $-CF_3$, $-NO_2$, as well as of the novel compounds with –Br, –I, and $-SCH_3$ in the *para* position, in order to elucidate the influence of the various substituents on the mechanism of anodic oxidation.

Keywords. Cyclic voltammetry; Donor-acceptor effects; Electrochemistry; Heterocycles; Linear free energy relationship.

Introduction

1*H*-3-Methyl-4-ethoxycarbonyl-5-(arylidenehydrazino)pyrazoles **1–11** are key intermediates in obtaining 1*H*-3-aryl-6-methyl-7-ethoxycarbonyl-pyrazolo[5,1-*c*][1,2,4]triazoles **12–22** (Scheme 1). The latter compounds are used as precursors of color photographic light sensitive materials [1], toners, and ink jet printer dyes [2].

In the presence of bromine and sodium acetate in glacial acetic acid, the hydrazones substituted with $-NO_2$, –Cl, and methyl yield the corresponding pyrazolotriazoles [1]. If the substrate contains substituents like –OH, $-OCH_3$, the non-desired brominated pyrazolotriazoles **14**, **15**, and **22** are formed (Scheme 1) [3]. In order to avoid this formation, we intended to obtain the desired compounds

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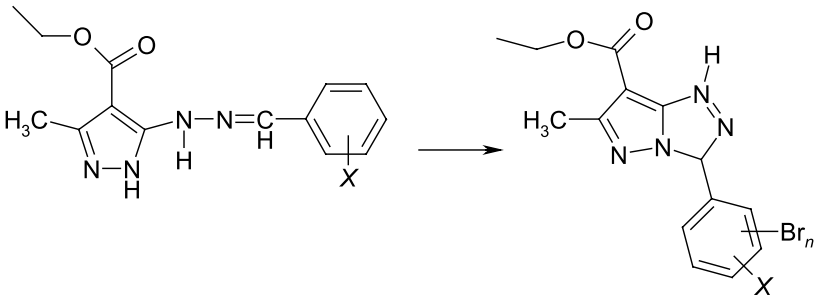


X = H (**1**); 4-N$(CH_3)_2$ (**2**); 4-OH (**3**); 4-OCH_3 (**4**); 4-NO_2 (**5**); 4-F (**6**); 4-Cl (**7**); 4-CF_3 (**8**); 4-Br (**9**); 4-I (**10**); 4-SCH_3(**11**)

X = H (**12**); 4-N$(CH_3)_2$ (**13**); 4-OH (**14**); 4-OCH_3 (**15**); 4-NO_2 (**16**); 4-F (**17**); 4-Cl (**18**); 4-CF_3 (**19**); 4-Br (**20**); 4-I (**21**); 4-SCH_3 (**22**)
n = 0 (**12, 13, 16–21**); 1 (**15, 22**); 2 (**14**)

Scheme 1

by electrosynthesis [4–8]. Because, to our knowledge, no electrochemical investigation of these compounds has been published so far, we present the results of an electrochemical investigation of the substituted 1*H*-3-methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazoles **1**–**11** in nonaqueous media in order to elucidate the mechanism of anodic oxidation. Intrinsic knowledge on the electrochemical processes that take place at the anode could help finding a more convenient way to obtain the desired pyrazolotriazoles by electrosynthesis.

Results and Discussions

The electrochemical behavior of the (benzylidenehydrazino)pyrazoles **1**–**11** in acetonitrile was investigated by cyclic voltammetry. The cyclic voltammograms of **1**–**11** showed two to three non-reversible oxidation peaks (Fig. 1) at potentials summarized in Table 1.

We believe that the substituents grafted on the phenyl ring play an important role in the formation and stability of the radical cations that may be generated during the anodic oxidation of the substrate (Scheme 2). The data of Table 1 reveal that the anodic peak potential (E_{pA}) is shifted to more positive values due to the presence of the electron-withdrawing groups on the *para* position of the phenyl ring and the reverse is observed for electron-donating groups. This is because oxidation will be thermodynamically more facile when electron density flows to the benzene ring leading to the stabilization of the positive charge of the cation radical [9].

Under the given conditions and according to the preliminary results obtained in the controlled potential electrolysis of 1*H*-3-methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazole (**1**) [8] resulting in the formation of the pyrazolotriazole **12**, we believe that the σ-state prevails thus having a positive reaction center localized at the hydrazonic carbon atom (Scheme 2).

The non-reversibility of the first oxidation peak of the (benzylidenehydrazino)pyrazoles **1**–**11** may arise from the loss of protons from the iminium-

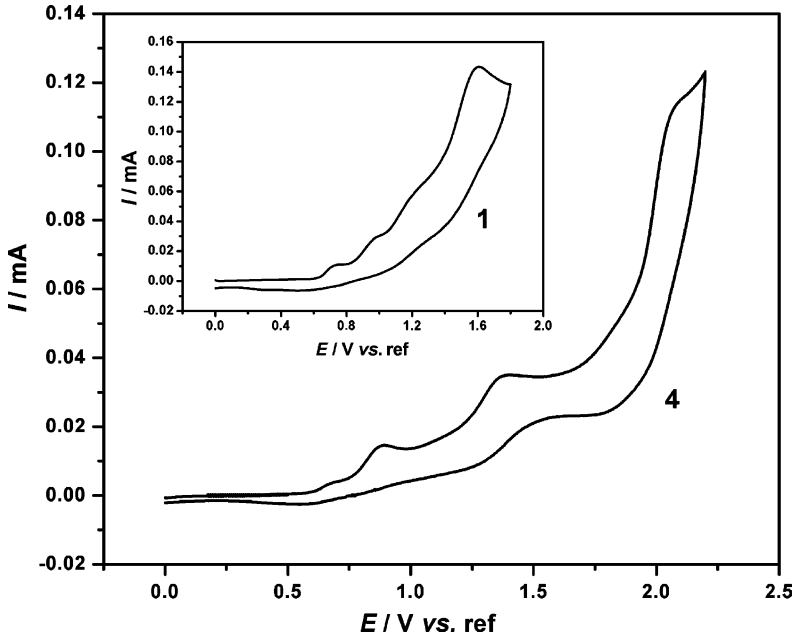


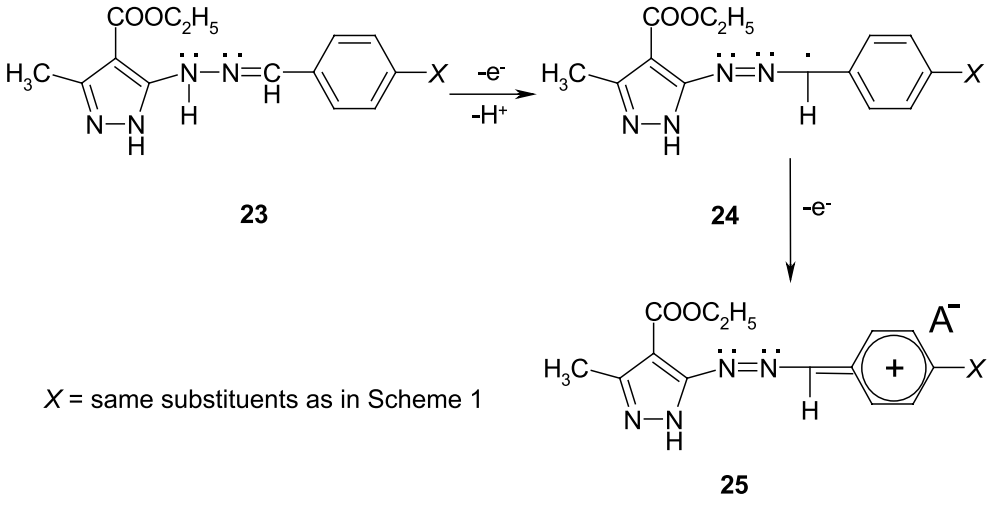
Fig. 1. Cyclic voltammogram of **4** in anhydrous acetonitrile; conditions: substrate concentration $c = 2 \cdot 10^{-3}\,\mathrm{mol \cdot dm^{-3}}$, supporting electrolyte $c = 0.1\,\mathrm{mol \cdot dm^{-3}}$ tetra-*n*-butylammonium tetrafluororborate, solvent anhydrous acetonitrile, working electrode Pt, auxiliary electrode Pt wire, reference electrode Ag/AgCl, scan rate $50 \cdot 10^{-3}\,\mathrm{V \cdot s^{-1}}$; inset: cyclic voltammogram of **1** under the same experimental conditions

Table 1. Electrochemical data from cyclic voltammetry for the *para*-substituted (benzylidenehydrazino)pyrazoles **1**–**11**[a]

Substituent	E_{pA1}/V	E_{pA2}/V	ΔE_{X1}[b]/V	$\Delta \log K_{X1}$	σ_p^+[c]
–H	1.000	1.600	0.000	0.000	0.00
$-N(CH_3)_2$	0.660	1.190	0.340	5.758	−1.70
–OH	0.850	1.360	0.150	2.540	−0.92
$-OCH_3$	0.890	1.400	0.110	1.863	−0.78
$-NO_2$	1.127	–	−0.127	−2.151	0.79
–F	1.003	1.563	−0.002	−0.042	−0.07
–Cl	1.025	1.638	−0.025	−0.423	0.11
$-CF_3$	1.120	1.800	−0.120	−2.032	0.61
–Br	1.017	1.640	−0.017	−0.288	0.15
–I	1.038	1.638	−0.038	−0.635	0.14
$-SCH_3$	0.898	1.330	0.103	1.736	−0.60

[a] Conditions: compound concentration $c = 2 \cdot 10^{-3}\,\mathrm{mol \cdot dm^{-3}}$, *ref.* Ag/AgCl, scan rate $50 \cdot 10^{-3}\,\mathrm{V \cdot s^{-1}}$; [b] $\Delta E_{X1} = E_{pA1\mathrm{H}} - E_{pA1X}$; [c] data taken from Ref. [17]

like nitrogen atom after oxidation occurs (Scheme 2), and thus the system is likely non-chemically reversible. We can assume that the first oxidation exhibits classical *EC* mechanism behavior [10], and if the rate of chemical reaction is much faster than the rate of electrochemical reaction, the electrochemical step becomes



Scheme 2

pseudo-first-order, albeit non-reversible. This is most likely the case for our systems, as changes in scan rate for the cyclic voltammograms have no effect on the lack of observed reduction peaks and little effect on the position of E_{pA}.

It has been shown [11] that if E_{pA} is measured for each substituent by cyclic voltammetry using the same scan rate, working electrode, electrolyte concentration, and compound concentration, the differences in the oxidation potentials E_{pA} should reasonably reflect free energy differences and allow for a correlation using the *Hammett* linear free energy relationship [12].

The potential difference between the oxidation peaks of the unsubstituted (benzylidenehydrazino)pyrazole **1** and the (benzylidenehydrazino)pyrazole with the substituent *X* attached to the benzene ring (Eq. (1)) can be used to obtain the following correlations [11]:

$$\Delta E_X = E_{pA\mathrm{H}} - E_{pAX} \tag{1}$$

$$\Delta E_X = (2.3 \cdot RT/nF) \cdot \Delta \log K_X \tag{2}$$

$$\Delta \log K_X = \sigma^+ \cdot \rho^+ \tag{3}$$

Plotting $\Delta \log K_X$ for the first oxidation potentials against the resonance-enhanced substituent constants σ_p^+ (Fig. 2) gives a linear correlation of the obtained data points (*e.g.* correlation coefficient $R = 0.99$). A positive value of ρ indicates that the reaction is enhanced by electron-withdrawing groups, whereas a negative value denotes enhancement by electron-donating groups. The magnitude of ρ indicates whether the reaction is more or less sensitive to substituent electronic effects than benzoic acid dissociation [13].

The *Hammett* plot $\Delta \log K_X$ against σ_p^+ gave a ρ^+ value of about -3.10 suggesting a direct influence of the substituents attached to the phenyl ring on the mechanism of anodic oxidation of the studied compounds. The linear correlation between the resonance enhanced substituent constants and $\Delta \log K_X$ shows a direct influence of the *para* – substituents on the mechanism of anodic oxidation, reflected in the

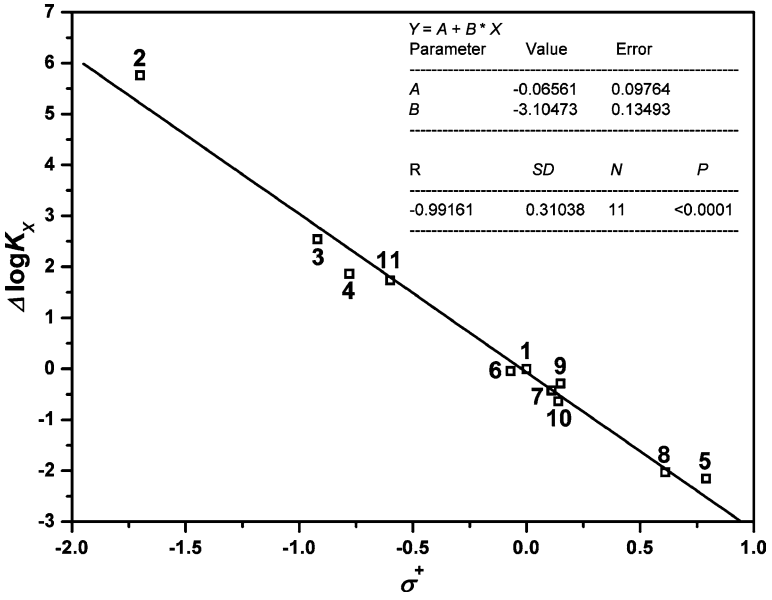


Fig. 2. *Hammett* plots of $\Delta\log K_X$ *vs.* σ_p^+ for the first oxidation peaks of the substituted (benzylidenehydrazino)pyrazoles **1**–**11** in anhydrous acetonitrile; exp. data ▫, linear regression (solid line)

relatively large value of the reaction constant ρ. This can be explained by a significant delocalization of charge onto the phenyl ring in the molecular orbitals of the corresponding radical cations **25** (Scheme 2). The predictive capabilities of the correlation between $\Delta\log K_X$ and σ_p^+ have not been tested yet but there is a good chance that the predictions will hold since R closely approaches 1.

Following the electrochemical investigation of **1**–**11**, we conducted a controlled potential electrolysis of **1** at the potential of the first oxidation peak [8]. The formation of the pyrazolotriazole **12** as a result of the anodic oxidation comes to confirm the proposed *EC* mechanism.

Experimental

The study of the electrochemical properties of the (benzylidenehydrazino)pyrazoles was conducted by recording the cyclic voltammograms over the potential range of interest. While the anodic polarization limit was set to about 2 V *vs.* ref., the solvent-supporting electrolyte system consisted of dry acetonitrile and tetra-*n*-butylammonium tetrafluoroborate. Solutions for all voltammetric analyses were deoxygenated by bubbling with dry N_2 and this atmosphere was maintained throughout the experiments. The working electrode consisted of a Pt disc ($d = 3$ mm), the auxiliary electrode was a Pt wire. The cyclic voltammetry experiments were performed using a Princeton Applied Research model M273A potentiostat in a single compartment cell with 7 cm^3 of electrolyte solution containing $c = 2 \cdot 10^{-3}$ mol $\cdot$ dm^{-3} of substrate at rt. No correction was applied to compensate for the solution resistance. The voltammograms were recorded and processed using the EG&G M273 software. All potentials were measured with respect to the Ag/AgCl electrode at rt, which corresponds to a potential difference from that of Fc/Fc^+ (Fc = ferrocene) standard redox couple [14, 15] of +0.45 V in *DMSO*/tetra-*n*-butylammonium tetrafluororborate.

Melting points were recorded with a Boetius PHMK (Veb – Analytik Dresden) apparatus; thin layer chromatography was performed using $60F_{254}$ silica gel plates (Merck) and a mixture of

benzene:ethyl acetate = 1:1 as eluant. Elemental analyses (C, H, N) were conducted using the Perkin Elemer 2400 Elementar Analyser; their results were found to be in good agreement (±0.2%) with the calculated values.

The purity of the compounds was >99%, as determined by HPLC. HPLC analyses were conducted with a Merck Chromolith Performance 2 column, using acetonitrile/H_2O as eluant. IR spectra were recorded with a Jasco FT/IR-410 Infrared Spectrophotometer using KBr disks and Bruker Avance 300 spectrometers were used for ^1H and ^{13}C NMR spectroscopy. All chemical shift values are given *vs*. the *TMS* internal reference.

Anhydrous *DMSO* (analytical grade, Fluka) and methanol (for synthesis Fluka) were used as purchased.

*General Preparation Method for the Substituted 1H-3-Methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazoles **1–11*** [16]

A mixture of 25 mmol 1*H*-3-methyl-4-ethoxycarbonyl-5-hydrazino-pyrazole chlorohydrate, 25 mmol substituted benzaldehyde, and 75 cm^3 absolute ethyl alcohol is refluxed for 2–4 h under chromatographic control. The turbid solution formed is filtered over active C and the filtrate is diluted with 75 cm^3 cold H_2O (0–5°C). The resulting suspension is filtered off and the crude product is recrystallized from an adequate solvent.

1H-3-Methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazole (**1**)

White powder, mp 165–167°C (C_2H_5OH) (Ref. [1] 167°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-N,N-dimethylaminobenzylidenehydrazino)pyrazole (**2**)

White powder, mp 198–200°C (Ref. [16] 198–200°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-hydroxybenzylidenehydrazino)pyrazole (**3**)

White powder, mp 212–216°C (CH_3OH) (Ref. [16] 212–216°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-methoxybenzylidenehydrazino)pyrazole (**4**)

White-yellowish powder, mp 170–173°C (CH_3OH) (Ref. [16] 170–173°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-nitrobenzylidenehydrazino)pyrazole (**5**)

White powder (96%), mp 284–286°C (C_2H_5OH) (Ref. [1] 285–286°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-fluorobenzylidenehydrazino)pyrazole (**6**)

White-yellowish needles (80%), mp 185–187°C (CH_3OH) (Ref. [1] 185–186°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-chlorobenzylidenehydrazino)pyrazole (**7**)

White plates (74%), mp 224–226°C (C_2H_5OH) (Ref. [1] 230–231°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-trifluoromethylbenzylidenehydrazino)pyrazole (**8**)

White powder, mp 203–206°C (Ref. [16] 203–206°C).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-bromobenzylidenehydrazino)-pyrazole (**9**, $C_{14}H_{15}BrN_4O_2$)

White powder (71%), mp 177–178°C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 10.16$ (bs, –NHpyr), 8.24 (s, 1H, –N=CH–), 7.71 (d, 2H, $J = 8.5$ Hz, H-3′, H-5′), 7.58 (d, 2H, $J = 8.5$ Hz, H-2′, H-6′), 4.21 (q, 2H, $J = 7.0$ Hz, O–C<u>H</u>$_2$–CH_3), 2.29 (s, 3H, –CH_3), 1.28 (t, 3H, $J = 7.0$ Hz, O–CH_2–C<u>H</u>$_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 163.43$ (C=O), 149.40 (C-3), 147.41 (C-5), 141.22 (–N=CH–), 134.16 (C-1′), 131.47 (C-3′, C-5′), 128.43 (C-2′, C-6′), 122.01 (C-4′), 92.29 (C-4), 59.02 (O–<u>C</u>H_2–CH_3), 14.36 (–CH_3), 13.59 (O–CH_2–<u>C</u>H3) ppm; IR (KBr): $\bar{\nu} = 3316$, 3134, 3095, 3034, 2977, 2929, 1674,

1610, 1548, 1484, 1347, 1277, 1131, 814, 780, 507 cm^{-1}; MS (54 eV): $m/z = 352$ [$(M+2)^+$, 50%], 350 (M^+, 49%), 306 [$(M+2)^+$ $-C_2H_5OH$, 72%], 304 (M^+ $-C_2H_5OH$, 63%).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-iodobenzylidenehydrazino)pyrazole (**10**, $C_{14}H_{15}IN_4O_2$)
White-yellowish needles (86%), mp 208–210°C (C_2H_5OH); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 12.40$ (bs, –NHpyr), 10.15 (bs, 1H, –NH–N=), 8.19 (s, 1H, –N=CH–), 7.75 (d, 2H, $J = 8.1$ Hz, H-2′, H-6′), 7.54 (d, 2H, $J = 8.0$ Hz, H-3′, H-5′), 4.20 (q, 2H, $J = 7.1$ Hz, O–C$\underline{H}_2$–CH_3), 2.27 (s, 3H, –CH_3), 1.28 (t, 3H, $J = 7.1$ Hz, O–CH_2–C$\underline{H}_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 163.58$ (–$\underline{C}OOC_2H_5$), 148.80 (C-3), 147.17 (C-5), 141.11 (–N=CH–), 137.28 (C-3′, C-5′), 134.54 (C-1′), 128.40 (C-2′, C-6′), 95.08 (C-4′), 92.03 (C-4), 58.89 (O–$\underline{C}H_2$–CH_3), 14.36 (–CH_3), 13.96 (O–CH_2–$\underline{C}H3$) ppm; IR (KBr): $\bar{\nu} = 3290$, 3198, 2988, 2973, 2927, 2905, 1660, 1602, 1584, 1546, 1481,1282, 820, 785, 541 cm^{-1}; MS (54 eV): $m/z = 398$ (M^+, 84%), 352 (M^+ $-C_2H_5OH$, 100%).

1H-3-Methyl-4-ethoxycarbonyl-5-(4-methylmercapto-benzylidenehydrazino)pyrazole
(**11**, $C_{15}H_{18}N_4O_2S$)
White-yellowish needles (75%), mp 166–167°C (C_2H_5OH); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.40$ (bs, –NHpyr), 8.85 (bs, 1H, –NH–N=), 7.75 (s, 1H, –N=CH–), 7.49 (d, 2H, H-2′, H-6′), 7.11 (d, 2H, H-3′, H-5′), 4.19 (q, 2H, $J = 7.1$ Hz, O–C$\underline{H}_2$–CH_3), 2.38 (s, 3H, –CH_3), 1.27 (t, 3H, $J = 7.1$ Hz, O–CH_2–C$\underline{H}_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 163.53$ (C=O), 149.52 (C-3), 147.44 (C-5), 142.06 (–N=CH–), 139.38 (C-4′), 131.42 (C-1′), 127.02 (C-2′, C-6′), 125.59 (C-3′, C-5′), 91.93 (C-4), 58.91 (O–$\underline{C}H_2$–CH_3), 15.06 (SCH_3), 14.36 (–CH_3), 13.71 (O–CH_2–$\underline{C}H3$) ppm; IR (KBr): $\bar{\nu} = 3317$, 3206, 3163, 3025, 2982, 2903, 1667, 1609, 1546, 1495, 1278, 1134, 837, 528 cm^{-1}; MS (54 eV): $m/z = 319$ [$(M+1)^+$, 84%], 318 (M^+, 100%), 272 (M^+ $-C_2H_5OH$, 77%).

Electrolysis of 1H-3-Methyl-4-ethoxycarbonyl-5-(benzylidenehydrazino)pyrazole (***1***) [8]
A solution of 0.02 $mol \cdot dm^{-3}$ of **1** in *DMSO* was electrolyzed in a divided cell (diaphragm: glass frit, porosity *G*4) using tetra-*n*-butylammonium tetrafluororborate as supporting electrolyte. The working electrode consisted of a Pt disc ($d = 5$ mm), the auxiliary electrode was a Pt wire. The reaction was conducted at the potential of the first anodic peak of **1** as determined by cyclic voltammetry. The progress of the electrolysis was followed by recording the decrease of the current with time. The electrolysis was stopped when the current reached about 20% of its starting value. The crude product obtained after extraction with diethyl ether and evaporation of the solvent was recrystallized from an adequate solvent. The resulting product was analyzed by thin layer chromatography, as well as by IR, ^1H and ^{13}C NMR spectroscopy and the results were found to be in good agreement with those gathered for the reference compound **12** obtained as described in Ref. [1].

1H-3-Phenyl-6-methyl-7-(ethoxycarbonyl)pyrazolo[5,1-c][1,2,4]triazole (**12**)
White-yellowish powder (65%), mp 172–176°C (Ref. [1] 176°C).

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