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Transformations of 3-Alkyl-4-(methoxyphenyl)-1*H*-pyrazole-5-diazonium Salts

V. V. Didenko, V. A. Voronkova, and Kh. S. Shikhaliev

Voronezh State University, Voronezh, 394006 Russia
e-mail: chocd261@chem.vsu.ru

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Abstract—The coupling of 3-alkyl-4-(methoxyphenyl)-1*H*-pyrazole-5-diazonium salts with acetylacetone followed by cyclization of the formed heterylhydrazones resulted in pyrazolo[5,1-*c*][1,2,4]triazines. The 4-(3,4-dimethoxyphenyl)-3-methyl-1*H*-pyrazole-5-diazonium salt was not involved into a similar reaction but suffered an intramolecular azo coupling giving pyrazolo[3,4-*c*]-cinnoline.

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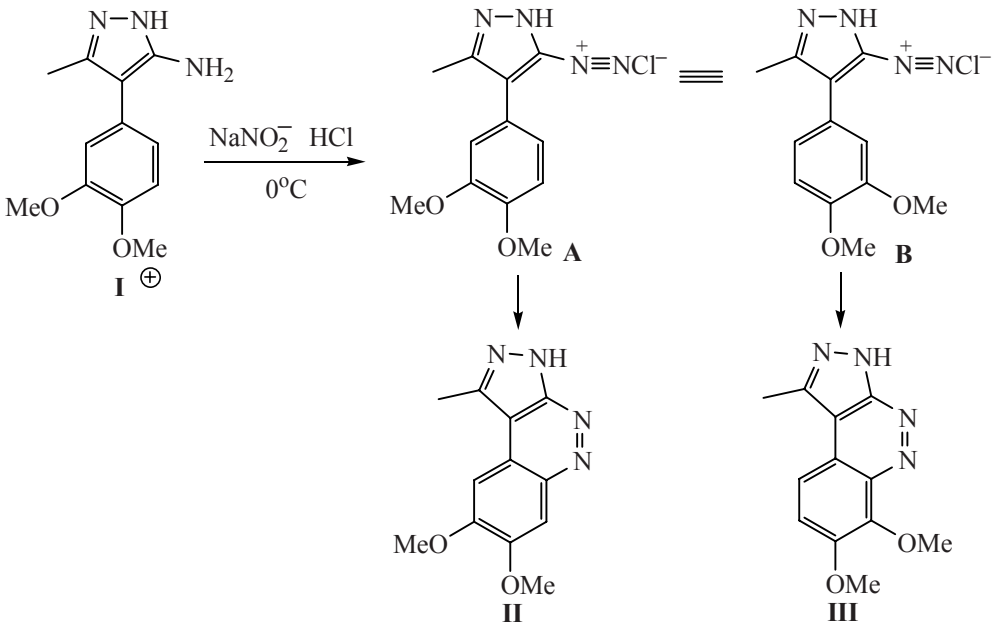
Diazopyrazoles are successfully used in buiding up a series of polycyclic nitrogen heterocycles. Among these compounds azo fused derivatives of 1,2,4-triazine, structural analogs of natural purine bases, are well known. The synthesis of pyrazolo[5,1-*c*][1,2,4]triazines consists in the azo coupling of pyrazolediazonium salts with compounds containing an active methylene group followed by the cyclization of the formed hydrazones [1–3].

The arenediazonium salts containing in the *ortho*-position to the formed diazo group a substituent active in an electrophilic attack (NH_2, NH, SH, Ar, multiple carbon-carbon bonds, etc.) are known to be considerably less stable and prone to intramolecular cyclization yielding the corresponding heterocycles [4–8]. This is also valid for some pyrazolediazonium salts [9–13].

As shown in [14] diazopyrazoles having in the position *4* a 3,4-dimethoxyphenyl group suffer this kind cyclization. We carried out an additional investigation in order to elucidate the direction of transformations of 3-alkyl-4-(methoxyphenyl)-1*H*-pyrazole-5-diazonium salts and the

Scheme 1.



structure of the reaction products. It was established that the diazotization of 3-methyl-4-(3,4-dimethoxyphenyl)-1*H*-5-aminopyrazole (**I**) under standard conditions led to the formation of brightly colored diazonium salt **A** that spontaneously underwent an intramolecular azo coupling giving 1-methyl-7,8-dimethoxy-3*H*-pyrazolo[3,4-*c*]-cinnoline (**II**) (Scheme 1).

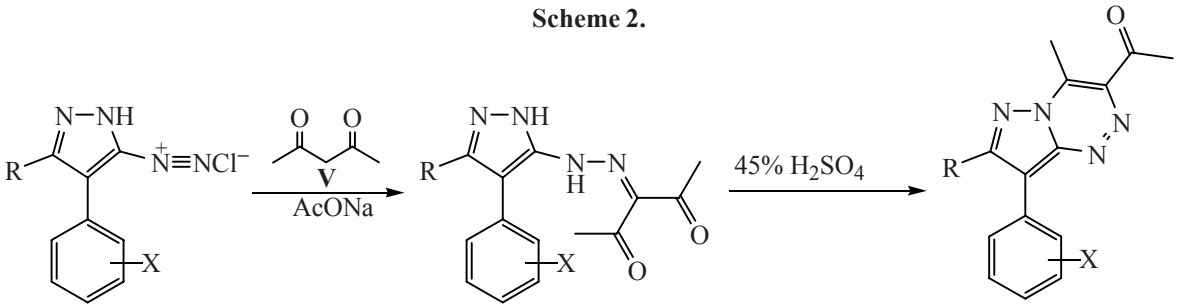
The analysis of ^{1}H NMR spectrum proved that the reaction under study resulted exclusively in compound **II**. The second presumable regioisomer **III** did not form. This conclusion was based on the fact that in the aromatic region the two proton signals were observed as two singlets at δ 7.58 and 7.98 ppm but not as doublets as should have happened in compound **III**. Presumably since in **A** conformation the 3-methoxy and diazo groups are the farthest from each other the reaction is directed in the discovered sense.

At the same time 4-(3,4-dimethoxyphenyl)-3-ethylpyrazole-5-diazonium salt (**IVa**) and also analogous salts containing a single methoxy group in the *ortho*- or *para*-position **IVb–IVd** are more stable and easily undergo coupling with acetylacetone (**V**) forming pyrazolylhydrazones **VIa–VId** in high yields. The hydrazones obtained are substances of bright color melting with decomposition. We failed to perform their spectral identification since they underwent spontaneous cyclization occurring partly already at 30–40°C (TLC data).

The cyclization of hydrazones **VIa–VId** in sulfuric acid at cold yielded pyrazolotriazine **VIIa–VIId** (Scheme 2).

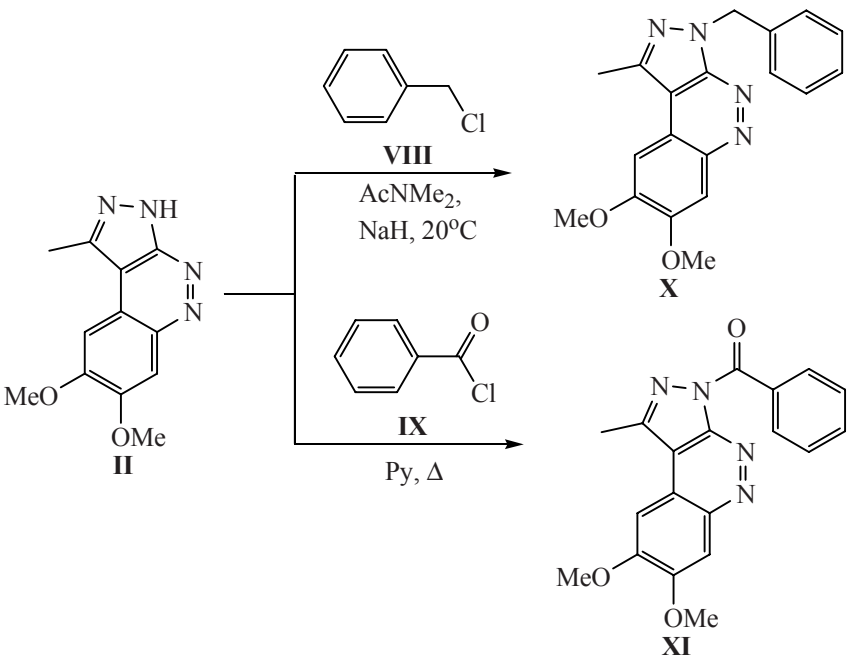
We believe that the different behavior of salts **IVa** and **A** is due to the steric effect of the ethyl group. Its large volume causes the substituted benzene ring to deviate from the plane of the molecucle and thus prevents the electrophilic attack of the diazo group in compound

Scheme 2.



R = Et, X = 3,4-(MeO)$_2$ (**a**), 4-MeO (**d**); R = Me, X = 2-MeO (**b**), 4-MeO (**c**).

Scheme 3.



IVa. In 3-methylpyrazole-5-diazonium salt **A** a free rotation occurs around the σ-bond connecting the pyrazole and benzene rings. The molecule acquires the conformation where all the substituents get into the same plane and as a result the intramolecular azo coupling takes place. The single methoxy group in diazonium salts **IVb–IVd** insufficiently activated the benzene ring and therefore it was possible to obtain from these compounds the target products **VIIb–VIId**.

In order to carry out a secondary functionalization of the pyrazolocinnoline we obtained it was subjected to alkylation with benzyl chloride (**VIII**) and acylation with benzoyl chloride (**IX**). We thus prepared in high yields *N*-benzyl- and *N*-benzoylpyrazolo[3,4-*c*]cinnolines (**X, XI**) respectively (Scheme 3).

Hence the discovered direction of the transformations of pyrazole-5-diazonium salts depending on their structure makes it possible to forecast the synthetic routes of pyrazolo[5,1-*c*][1,2,4]triazines or pyrazolo[3,4-*c*]-cinnoline. These fused heterocycles are interesting as probable biologically active substances.

EXPERIMENTAL

The homogeneity of the reagents and obtained products was checked and the qualitative analysis of the reaction mixtures was carried out by TLC on Silufol UV-254 plates, eluents chloroform, ethyl acetate, and their mixtures. ^{1}H NMR spectra were registered on a spectrometer Bruker AC-300 (300 MHz) in DMSO-d_6, internal reference TMS. Mass spectra were measured on an LKB-9000 instrument, ionizing electrons energy 70 eV. Elemental analysis was performed on an analyzer Carlo Erba NA 1500.

1-Methyl-7,8-dimethoxy-3*H*-pyrazolo[3,4-*c*]-cinnoline (II). A solution of 2.3 g (1.0 mmol) of aminopyrazole **I** [15] in 20 ml of water and 3 ml of concn. HCl was treated with 0.7 g (1.0 mmol) of sodium nitrite maintaining the temeperature of the reaction mixture at 0°C. The mixture was stirred additionally for 1 h at room temperature. The separated precipitate was filtered off, washed with water and with cold 2-propanol. Yield 1.9 g (78%), mp >300°C (AcOH–DMF, 2:1). ^{1}H NMR spectrum, δ, ppm: 2.86 s (3H, CH_3), 4.02 s (3H, OCH_3), 4.09 s (3H, OCH_3), 7.58 s (1H$_{arom}$), 7.98 s (1H$_{arom}$), 14.10 s (1H, NH). Found, %: C 59.12; H 4.89; N 23.00. M^+ 244. $C_{12}H_{12}N_4O_2$. Calculated, %: C 59.01; H 4.95; N 22.94. *M* 244.25.

8-Aryl-7-R-4-methylpyrazolo[5,1-*c*][1,2,4]-triazin-3-ylethanones VIIa–VIId. A solution of diazo salt **IVa–IVd** prepared similarly from 1.0 mmol of an appropriate aminopyrazole, 1.0 mmol of sodium nitrite, and 3 ml of hydrochloric acid was brought by portions at stirring into a cooled solution of 1.0 g (1.0 mmol) of acetylacetone (**V**) in 15 ml of ethanol and 12 g of saturated water solution of sodium acetate. The reaction mixture was stirred for 1 h, the separated precipitate was filtered off and washed with water. Yields of the hydrazones were 89–95%. Then 20–30 ml of 45% H_2SO_4 was added, the reaction mixture was stirred at room temperature for 15–30 min and poured into 300 ml of water. The separated precipitate was filtered off, washed with water till neutral reaction, and recrystallized from a mixture 2-propanol–acetic acid, 2:1.

1-{8-(3,4-Dimethoxyphenyl)-4-methyl-7-ethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl}ethanone (VIIa). Yield 2.3 g (69%), mp 152–154°C. ^{1}H NMR spectrum, δ, ppm: 1.37 t (3H, CH_3CH_2, *J* 7.5 Hz), 2.85 s (3H, CH_3), 3.12 q (5H, CH_3CH_2 + CH_3, *J* 7.8 Hz), 3.84 s (6H, 2OCH_3), 7.10 d (1H$_{arom}$, *J* 8.5 Hz), 7.29 d (1H$_{arom}$, *J* 8.5 Hz), 7.39 s (1H$_{arom}$). Found, %: C 63.59; H 5.89; N 16.40. M^+ 340. $C_{18}H_{20}N_4O_3$. Calculated, %: C 63.52; H 5.92; N 16.46. *M* 340.38.

1-{4,7-Dimethyl-8-(2-methoxyphenyl)pyrazolo-[5,1-*c*][1,2,4]triazin-3-yl}ethanone (VIIb). Yield 1.8 g (61%), mp 141–143°C. ^{1}H NMR spectrum, δ, ppm: 1.35 s (3H, CH_3), 2.71 s (3H, CH_3), 2.70 s (3H, CH_3), 3.85 s (3H, OCH_3), 7.17 m (2H$_{arom}$), 7.46 m (2H$_{arom}$). Found, %: C 64.94; H 5.39; N 18.87. M^+ 296. $C_{16}H_{16}N_4O_2$. Calculated, %: C 64.85; H 5.44; N 18.91. *M* 296.33.

1-{4,7-Dimethyl-8-(4-methoxyphenyl)pyrazolo-[5,1-*c*][1,2,4]triazin-3-yl}ethanone (VIIc). Yield 2.0 g (68%), mp 120–122°C. ^{1}H NMR spectrum, δ, ppm: 1.37 s (3H, CH_3), 2.58 s (3H, CH_3), 3.89 s (3H, OCH_3), 7.00 d (2H$_{arom}$, *J* 8.4 Hz), 7.27 d (2H$_{arom}$, *J* 8.4 Hz). Found, %: C 64.90; H 5.41; N 18.82. M^+ 296. $C_{16}H_{16}N_4O_2$. Calculated, %: C 64.85; H 5.44; N 18.91. *M* 296.33.

1-{4-Methyl-8-(4-methoxyphenyl)-7-ethylpyrazolo-[5,1-*c*][1,2,4]triazin-3-yl}ethanone (VIId). Yield 2.3 g (70%), mp 123–125°C. ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, CH_3CH_2, *J* 7.5 Hz), 2.85 s (3H, CH_3), 2.97 s (3H, CH_3), 3.10 q (2H, CH_3CH_2, *J* 7.8 Hz), 3.85 s (3H, OCH_3), 7.02 d (2H$_{arom}$, *J* 8.4 Hz), 7.67 d (2H$_{arom}$, *J* 8.4 Hz). Found, %: C 65.70; H 5.90; N 18.10. M^+ 310. $C_{17}H_{18}N_4O_2$. Calculated, %: C 65.79; H 5.85; N 18.05. *M* 310.35.

3-Benzyl-1-methyl-7,8-dimethoxy-3*H*-pyrazolo-[3,4-*c*]cinnoline (X). To a solution of 2.4 g (1.0 mmol)

of compound **II** in 20 ml of hot anhydrous dimethylacetamide was added 0.3 g (1.3 mmol) of sodium hydride, and the reaction mixture was stirred at room temperature till it got colored. Then 1.5 g (1.2 mmol) of benzyl chloride (**VIII**) was added, the mixture was stirred for 3–3.5 h, and poured into water. The separated precipitate was crystallized from DMF. Yield 2.9 g (85%), mp 195–197°C. ^{1}H NMR spectrum, δ, ppm: 2.84 s (3H, CH_3), 4.05 s (3H, OCH_3), 4.10 s (3H, OCH_3), 5.90 s (2H, CH_2), 7.24–7.45 m (6H_{arom}), 7.93 s (1H_{arom}). Found, %: C 68.19; H 5.48; N 16.72. M^+ 334. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.25; H 5.43; N 16.76. *M* 334.37.

3-Benzoyl-1-methyl-7,8-dimethoxy-3*H*-pyrazolo-[3,4-*c*]cinnoline (XI). A mixture of 2.4 g (1.0 mmol) of compound **II**, 1.7 g (1.2 mmol) of benzoyl chloride (**IX**), and 15 ml of pyridine was boiled for 20 h, poured into hot water, the separated precipitate was filtered off and repeatedly washed with hot water. Yield 2.8 g (80%), mp 257°C (decomp.) (from DMF). ^{1}H NMR spectrum, δ, ppm: 2.86 s (3H, CH_3), 4.05 s (3H, OCH_3), 4.11 s (3H, OCH_3), 7.57–7.74 m (4H_{arom}), 8.02 t (3H_{arom}, *J* 7.4 Hz). Found, %: C 65.29; H 4.73; N 16.20. M^+ 348. $C_{19}H_{16}N_4O_3$. Calculated, %: C 65.51; H 4.63; N 16.08. *M* 348.36.

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