NEW FINDINGS IN THE RICHTER REACTION IN SERIES OF VICINAL ALKYNYLPYRAZOLYLDIAZONIUM SALTS

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Abstract: When treated with sodium nitrite in hydrochloric or hydrobromic acid, positional isomers of *vic*-alkynylaminopyrazoles were transformed to the pyrazolopyridazines *via* cyclization of the corresponding alkynylpyrazolyldiazonium salt. The reaction was found to depend on the position of alkynyl and diazonium group in pyrazole nuclei: the heterocyclization of 5-alkynylpyrazolyl-4-diazonium salts underwent at 100-105 °C and gave 7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines; the heterocyclization of 4-alkynylpyrazolyl-3-diazonium salts at 50-60 °C gave 6-hydroxy-2*H*-pyrazolo[3,4-*c*]pyridazines as major component and 6-halogeno-2*H*-pyrazolo[3,4-*c*]pyridazines as minor component; the cyclization of 3-alkynylpyrazolyl-4-diazonium salts accompanying with methyl group migration towards the neighbouring nitrogen atom afforded 7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines.

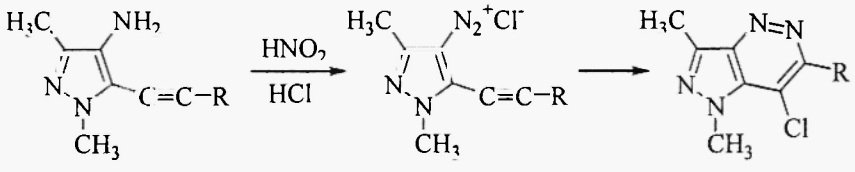
Introduction

Intramolecular cyclization of vicinal functionally substituted aromatic acetylenyc compounds has recently become increasingly important as a method for synthesis of heterocyclic condensed systems. This type of heterocyclization of acetylenic derivatives of pyrazolyldiazonium salts was virtually not known. It could be possible to prepare multinuclear heterocyclic compounds which are difficult to obtain by other methods with this reaction. The previous communications (1,2) have demonstrated that so-called Richter reaction (3) can be applied to the synthesis of 4-bromo- and 4-chlorocinnolines, as opposed to the known data. Attempting to extend the applicability of the reaction we have found that the behaviour of alkynylpyrazolyldiazonium chlorides differs from that of their benzene analogues. Thus, the cyclization of 1,3-dimethyl-5-phenylethynylpyrazolyl-4-diazonium salts have revealed no 4-hydroxydiazine (2). In similar conditions isomeric 1,5-dimethyl-

3-phenylethynylpyrazolyl-4-diazonium chloride did not enter Richter reaction (4). In addition, it is difficult to predict the direction of a cyclization of alkynylpyrazolyldiazonium salts with all possible versions of the arrangement of functional groups since the reaction is likely at both the β- and α-carbon atoms of the acetylenyl substituent. Moreover, it is known that the electrophilicity of the diazo group and the nucleophilicity of a triple bond depend markedly on their position in the pyrazole ring, and this can affect both the course and easiness of cyclization and even the possibility of the reaction (5).

Results and Discussion

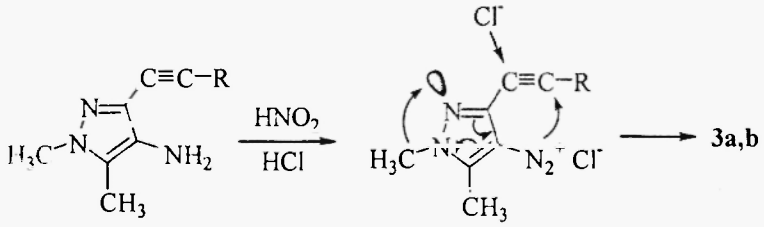
In the present work we report on the studying of heterocyclization of diazotized alkynylaminopyrazoles. 5-Alkynylpyrazolyl-4-diazonium chlorides 2a,b were cyclized in concentrated hydrochloric acid at 100-105 °C to 1,3-dimethyl-7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines 3a,b.



1a,b **2a,b** **3a,b**

1-3	R
a	C_6H_5
b	4-CH_3O-C_6H_4

3-Alkynylpyrazolyl-4-diazonium chlorides 5a,b were heterocyclized much slower than the isomeric derivatives 2a,b (concentrated HCl, 100-105 °C, 6 h). The reaction products were identical to compounds 3a,b produced by cyclization of diazotized amines 1a,b. Thus, the cyclization of pyrazolyl-4-diazonium chlorides 5a,b caused methyl group migration towards the neighbouring nitrogen atom.

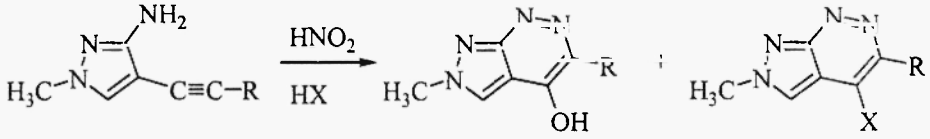


4a,b **5a,b**

3-5	R
a	C_6H_5
b	4-CH_3O-C_6H_4

To create a complete pattern of transformations of aminoacetylenes of the pyrazole series in the Richter reaction, we have studied the cyclization of 4-alkynylpyrazolyl-3-diazonium salts containing no methyl groups in position 5 of the cycle that excludes a possible reaction of intermolecular

condensation involving methyl and diazonium groups (4). 4-Alkynyl-3-aminopyrazoles 6a,b were diazotized under standard conditions. The heating of the forming alkynylpyrazolyldiazonium salts (50-60 °C) caused cyclization, resulting mainly to 5-substituted 6-hydroxy-1-methyl-2*H*-pyrazolo[3,4-*c*]pyridazines 7a,b and 6-chloropyrazolopyridazines 8a,b or 6-bromoderivative 9a as minor components.

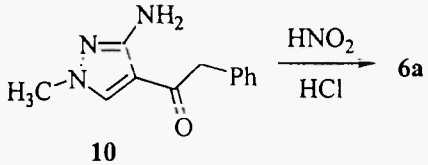


6a,b **7a,b** **8a,b; 9a**

6-9	R
a	C_6H_5
b	4-CH_3O-C_6H_4

	X
8	Cl
9	Br

To determine the size of heterocycle in a pyrazolopyridazine 7a molecule we performed the opposing synthesis of this compound by diazotization of 4-acetyl-3-amino-1-methylpyrazole 10. We obtained the product identical to compound 7a, produced by cyclization of diazotized amine 6a.



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However, taking into account a possible migration of the methyl group to the neighbouring nitrogen atom, 7a,b could display the structure of 1*H*-pyrazolo[3,4-*c*]pyridazines. The structure of products 7a,b as substituted 2*H*-pyrazolo[3,4-*c*]pyridazines was confirmed additionally. It was shown that under the action of phosphorus oxychloride (80 °C, 10 min) pyridazines 7a,b transformed almost quantitatively into chloroderivatives 8a,b. Being heated in the concentrated HCl (95-100 °C, 2 h), chloropyridazines 8a,b were completely hydrolyzed into 7a,b whereas 4-chloro-1,3-dimethyl-5-phenyl-1*H*-pyrazolo[3,4-*c*]pyridazine (2) did not enter this reaction.

It is concluded then that the cyclization of diazotized aminopyrazoles 6a,b conserves the structure of a pyrazole ring and leads to the formation of 2*H*-pyrazolo[3,4-*c*]pyridazines 7, 8. On the other hand, the cyclization of diazonium salts - aminopyrazole 4a,b derivatives is followed by methyl group migration to the neighbouring nitrogen atom.

Experimental

General Remarks: Alkynylaminopyrazoles were synthesised according to our procedure (7). ^{1}H NMR spectra were recorded using a «Jeol FX-90Q» and «Bruker 400» spectrometer at room temperature locked to deuterium resonance of the solvent ($CDCl_3$). The chemical shifts were calculated relative to the solvent signal using as internal standard δ_H 7.24 ppm. IR spectra were obtained on a UR-20 spectrophotometer. Melting points were determined with a Kofler apparatus.

7-Chloro-1,3-dimethyl-6-phenyl-1H-pyrazolo[4,3-c]pyridazine 3a. *a)* Solution of sodium nitrite (0.35 g, 5.1 mmole) in water (5 ml) was added dropwise at -10 °C to a stirred suspension of 1a (0.90 g, 4.3 mmole) in a 36% aqueous solution of hydrochloric acid (50 ml). Then the mixture was stirred at room temp. for 1 h, heated to boiling point and allowed to reflux for 2 h. The reaction mixture was poured into water (50 ml), treated with sodium bicarbonate, and extracted with trichloromethane (3×70 ml). The combined extracts were passed through silica gel (3 cm in length). The filtrate was concentrated at reduced pressure to give 0.90 g (81.6%) of the title compound as brown crystals. Recrystallization of the crude product from benzene-hexane (1:1, v/v) gave an analytical sample of 3a as yellow crystal, m.p. 175-176 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.97 (s, 3 H, 3-CH_3), 4.28 (s, 3 H, *N*-CH_3), 7.51 (m_c, 3 H, 3', 4', 5'-H), 7.90 (m_c, 2 H, 2', 6'-H). – $C_{13}H_{11}N_4Cl$: calcd. C 60.35, H 4.29, Cl 13.70; found C 60.23, H 4.28, Cl 13.43.

b) Solution of sodium nitrite (0.07 g, 1.0 mmole) in water (1 ml) was added dropwise at -15 °C to a stirred suspension of 4a (0.20 g, 0.95 mmole) in a 36% aqueous solution of hydrochloric acid (40 ml). Then the mixture was stirred at room temp. for 1 h, heated to boiling point and allowed to reflux for 6 h. The usual workup yielded 0.12 g (65.3%) of 3a.

7-Chloro-1,3-dimethyl-6-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazine 3b. From 0.90 g (3.7 mmole) of 1b (0.82 g (76.1%)) and from 0.90 g (3.7 mmole) of 4b (0.69 g (64.0%)) those were reacted in the predescribed manners; yellow crystals, m.p. 186-187 °C (benzene - hexane). – ^{1}H NMR ($CDCl_3$): δ = 2.91 (s, 3 H, 3-CH_3), 3.87 (s, 3 H, OCH_3), 4.11 (s, 3 H, *N*-CH_3), 7.21 (d, 2 H, 3', 5'-H), 7.98 (d, 2 H, 2', 6'-H). – $C_{14}H_{13}N_4OCl$: calcd. C 58.23, H 4.54, Cl 12.28; found C 58.59, H 4.69, Cl 11.88.

6-Chloro-1-methyl-5-phenyl-2H-pyrazolo[3,4-c]pyridazine 8a: *a)* A solution of sodium nitrite (0.35 g, 5.1 mmole) in water (3 ml) was added dropwise at -15 °C to a stirred suspension of 6a (0.57 g, 4.3 mmole) in a 36% aqueous solution of hydrochloric acid (20 ml). Then the mixture was stirred at 50-60 °C for 2 h. The solution was neutralized with a concentrated aqueous solution of sodium bicarbonate. The resultant suspension was extracted with benzene (2×50 ml). The combined benzene extracts were filtered as well as water layer to give a white solid. The crude product was washed with water (5 ml), dried and twice recrystallized from dioxane to afford an analytical sample of 7a (0.51 g, 73.5%). The benzene solution was dried over $MgSO_4$, concentrated under reduced

pressure, and chromatographed on silica gel (trichlorometane) to afford 0.015 g (1.9%) of 7a, m.p. 247-248 °C (trichloromethane). – ^{1}H NMR ($CDCl_3$): δ = 4.42 (s, 3 H, *N*-CH_3), 7.53 (m_c, 3 H, 3', 4', 5'-H), 7.80 (m_c, 2 H, 2', 6'-H), 8.20 (s, 1 H, 7-H). – MS (70 eV) *m/z* (I): 247.0 (3.25) [M+3$^+$], 245.9 (24.03) [M+2$^+$], 244.9 (9.82) [M+1$^+$], 243.9 (67.55) [M$^+$], 208.9 (68.04) [M$^+$-Cl]. – $C_{12}H_9N_4Cl$: calcd. C 57.91, H 3.71, Cl 14.49; found C 58.00, H 3.55, Cl 14.14.

b) Phosphorus oxychloride (1 ml) was added to a stirred solution of pyrazolopyridazine 7a (0.25 g, 1.5 mmole) in dioxane (10 ml) at 0 °C. The reaction mixture was heated to boiling point and allowed to reflux for 5 min. The mixture was cooled to room temp., quenched with water (50 ml) and neutralized with sodium bicarbonate. The yellow solids were filtered off, washed with water (5ml), and purified by column chromatography on silica gel (trichlorometane) to afford 8a as yellowish crystals, 0.22 g (79.0%).

6-Bromo-1-methyl-5-phenyl-2H-pyrazolo[3,4-c]pyridazine 9a: Solution of sodium nitrite (0.36 g, 5.2 mmole) in water (2 ml) was added dropwise at -15 °C to a stirred suspension of 6a (0.42 g, 3.2 mmole) in a 47% aqueous solution of hydrobromic acid (20 ml). Then the mixture was stirred at 25-28 °C for 3 h. After the workup described for 8a, the crude product was chromatographed on a silica gel column (trichlorometane), followed by recrystallization from benzene and hexane (1:1 v/v) to give 9a as yellowish crystals (0.06 g, 8.4%), m.p. 256-257 °C (trichloromethane). – ^{1}H NMR ($CDCl_3$): δ = 4.12 (s, 3 H, *N*-CH_3), 7.56 (m_c, 5 H, C_6H_5), 8.15 (s, 1 H, 7-H). – MS (70 eV) *m/z* (I): 290.9 (2.01) [M+3$^+$], 289.9 (14.03) [M+2$^+$], 288.9 (2.30) [M+1$^+$], 287.9 (14.00) [M$^+$], 208.9 (68.04) [M$^+$-Br].

6-Hydroxy-1-methyl-5-phenyl-2H-pyrazolo[3,4-c]pyridazine 7a. *a)* Solution of sodium nitrite (0.35 g, 5.1 mmole) in water (2 ml) was added dropwise at -10 °C to a stirred suspension of 6a (0.90 g, 4.6 mmole) in a 36% aqueous solution of hydrochloric acid (40 ml). The reaction mixture was heated to boiling point and allowed to reflux for 3 h. The mixture was cooled to room temp., diluted with water (100 ml) and neutralized with sodium bicarbonate. The yellowish precipitate was filtered off, washed with water (5ml), and purified by twice-repeated recrystallization from dioxane to give an analytical sample of the diazine 7a as colourless crystals (0.94 g, 91.0%), m.p. 273-274 °C (dioxane). – ^{1}H NMR ($CDCl_3$): δ = 4.10 (s, 3 H, *N*-CH_3), 7.52 (m_c, 5 H, C_6H_5), 8.13 (s, 1 H, 7-H). – IR (1% in KBr): ν = 1635 cm^{-1} (C=O), 3480 (NH), 3560 (OH). – $C_{12}H_{10}N_4O$: calcd. C 63.71, H 4.46; C 62.46; H 4.45.

b) A suspension of 8a (0.50 g, 2.0 mmole) in a 36% aqueous solution of hydrochloric acid (20 ml) was stirred at 100-105 °C for 1 h. Then above described treatments afforded the title product (0.41 g, 88.7%).

c) The hydroxydiazine 7a was prepared from corresponding bromodiazine 9a (0.10 g, 0.35 mmole) by a method that was the same as in the case of *b*, 0.07 g (89.5%).

d) Solution of sodium nitrite (0.05 g, 0.72 mmole) in water (1 ml) was added dropwise at -10 °C to a stirred suspension of 10 (0.10 g, 0.47 mmole) in a 36% aqueous solution of hydrochloric acid (10 ml). Then the mixture was stirred at 100-105 °C for 4 h, diluted with water (40 ml), neutralized with sodium bicarbonate, and extracted with trichlorometane (5×50 ml). The usual workup gave 0.04 g (37.9%) of 7a.

6-Hydroxy-1-methyl-5-(4-methoxyphenyl)-2H-pyrazolo[3,4-c]pyridazine 7b: Solution of sodium nitrite (0.35 g, 5.1 mmole) in water (2 ml) was added dropwise at -15 °C to a stirred suspension of 6b (0.80 g, 3.5 mmole) in a 36% aqueous solution of hydrochloric acid (40 ml). The reaction mixture was heated to boiling point and allowed to reflux for 1 h. The mixture was cooled to room temp., diluted with water (100 ml) and neutralized with sodium bicarbonate. The yellowish precipitate was filtered off, washed with water (5ml), and purified by thrice-repeated recrystallization from dioxane to give an analytical sample of the diazine 7b as colourless crystals (0.76 g, 84.2%), m.p. 284-285 °C (dioxane). – ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 4.15 (s, 3 H, *N*-CH_3), 7.03 (d, 2 H, 2', 6'-H), 7.40 (d, 2 H, 3', 5'-H), 7.90 (s, 1 H, 7-H). – IR (1% in KBr): ν = 1630 cm^{-1} (C=O), 3490 (NH), 3620 (OH). – $C_{13}H_{12}N_4O_2$: calcd. C 60.13, H 4.81; found C 60.93, H 4.72.

6-Chloro-1-methyl-5-(4-methoxyphenyl)-2H-pyrazolo[3,4-c]pyridazine 8b: A mixture of 7b (0.17 g, 0.66 mmole) and phosphorus oxychloride (0.5 ml) in dioxane (10 ml) was heated to boiling point and allowed to reflux for 10 min. The workup gave 8b as colourless crystals (0.13 g, 71.3%), m.p. 258-259 °C (CCl_4). – ^{1}H NMR ($CDCl_3$): δ = 3.90 (s, 3 H, OCH_3), 4.42 (s, 3 H, *N*-CH_3), 7.04 (d, 2 H, 2', 6'-H), 7.75 (d, 2 H, 3', 5'-H), 8.15 (s, 1 H, 7-H). – $C_{13}H_{11}N_4OCl$: calcd. C 59.50, H 4.99, Cl 11.71; found C 59.89, H 4.89, Cl 11.92.

References

(1) S. F. Vasilevsky, E. V. Tretyakov, H. D. Verkruijsse, Synth. Commun. 24, 1733 (1994).

(2) S. F. Vasilevsky, E. V. Tretyakov, Liebigs Ann. Chem. 775 (1995).

(3) A. E. A. Porter in Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds (Ed.: D. Barton and W. D. Ollis). Volume 4. Heterocyclic Compounds (Ed.: P. G. Sammes), Pergamon Press, Oxford - New York - Toronto - Sydney - Paris - Frankfurt, 1979.

(4) E. V. Tretyakov, S. F. Vasilevsky, Mendeleev Commun. 5, 190 (1996).

(5) S. F. Vasilevsky, T. V. Anisimova, M. S. Shvartsberg, Izv. Akad. Nauk SSSR, Ser. Khim. 3, 688 (1983) (Russ). C.A. 98:198102z.

(6) J. M. Lee, A. Matsumoto, M. Yoshida, O. Simamura, Bull. Chem. Soc Japan. 47, 1039 (1974)

(7) E. V. Tretyakov, S. F. Vasilevsky, manuscript in preparation.

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