The Synthesis of 4-Amino-3-(2-pyridyl)pyrazolo[5,1-*c*][1,2,4]triazine and Some of its Derivatives [1]

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A mixture of both geometrical isomers of hydrazones **3a-3e** was obtained by the coupling reactions of pyrazole-3-diazonium salts **2a-2d** and benzenediazonium chloride **2e** with 2-pyridylacetonitrile **1**. Hydrazones **3a-3d** were cyclized to the corresponding 4-amino-3-(2-pyridyl)pyrazolo[5,1-*c*][1,2,4]triazines **4a-4d**.

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It is known that during the cyclization reaction of 3-pyrazolylhydrazones of α-oxonitriles to 4-amino-3-substituted-pyrazolo[5,1-*c*][1,2,4]triazines [2-13] the N-H group of the pyrazole ring should be sterically close to the nitrile group. Consequently in case of 3-pyrazolylhydrazonomalonodinitriles where both nitrile groups are available for cyclization the ring closure takes place smoothly [4-7,9,11,12]. However, the cyclization of other 3-pyrazolylhydrazones of α-oxonitriles [2-8,10,12,13] due to the geometric isomerism should proceed only in case of one of the two possible geometric isomers. The fact that even in these cases the cyclization takes place in high yield indicates that during the cyclization isomerization between *E* and *Z* forms occurs. In the known coupling reaction of benzenediazonium salts with cyanoacetic acid derivatives both geometric isomers of the corresponding hydrazones were formed [14,15].

In the present communication we will report on the analogues reactions of (2-pyridyl)acetonitrile **1** [16] chosen as a model compound to study whether in this case the coupling reaction would lead to a mixture of both geometric isomers of the corresponding hydrazones and if there would be present also such azo-tautomeric forms where the pyridine nitrogen atom participates. These hydrazones also could be interesting from the point of view of biological activity because some hydrazones of similar structure are known as neoplastics [17,18].

In the coupling reaction of above mentioned nitrile **1** with pyrazole-3-diazonium salts **2a-2d** and benzenediazonium chloride **2e** in water solutions of sodium acetate we obtained corresponding hydrazones **3a-3e** in high yields.

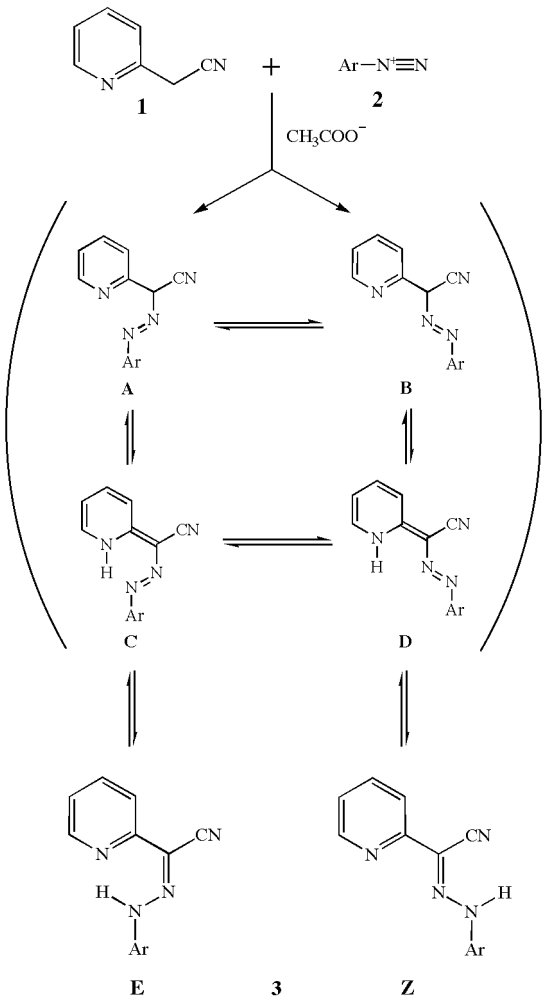
Derivatives **3** could exist as **3-E** or **3-Z** geometric isomers or their mixture. The formation and mutual interconversion of these isomers is possible through the free rotation around the C-N bond of tautomeric forms **A-D** which are probably also intermediates during their formation.

At first we have studied the geometric isomerism of phenylhydrazone **3e** where neither the tautomerism at the aryl group nor the cyclization to pyrazolotriazines **4** can occur.

For that purpose we prepared not only phenylhydrazone ^{14}N, but also both isomeric hydrazones with the isotope ^{15}N using aniline ^{15}N **3e-I** and $Na^{15}NO_2$ **3e-II**.

The identification of geometric isomers of hydrazone **3e** was carried out by the use of coupling constants $^2J(^{15}N^{13}C)$ (see Table 1). The coupling constant of *E*-isomer having value 12.1 Hz corresponds with the results in the communication [14]. From the signal intensities of the

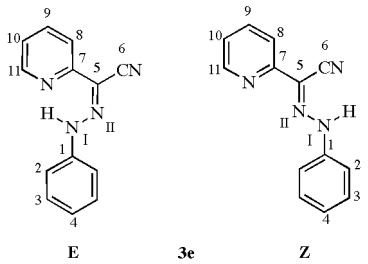
Scheme 1



a) Ar= 3-pyrazolyl
b) Ar= 5-methyl-3-pyrazolyl
c) Ar= 5-phenyl-3-pyrazolyl
d) Ar= 4-ethoxycarbonyl-3-pyrazolyl
e) Ar= phenyl

cmr spectroscopy we have concluded that hydrazone **3e** formed by the coupling reaction of the benzenediazonium salt **2e** with the nitrile **1** is a mixture of *E* and *Z*-isomers, where the *E*-isomer is predominant. Therefore, from the pmr spectrum of a freshly prepared sample it was possible to estimate that the ratio (*E*/*Z*) was 3:2. For further details, see Scheme 2 and Table 1.

Scheme 2



E **3e** **Z**

Table 1

The cmr Chemical Shifts and Coupling Constants of **3e**

Carbon number	Isomer					
	E (J in Hz)			Z (J in Hz)		
	ppm	$^{n}J(^{15}N_{I}{}^{13}C)$	$^{n}J(^{15}N_{II}{}^{13}C)$	ppm	$^{n}J(^{15}N_{I}{}^{13}C)$	$^{n}J(^{15}N_{II}{}^{13}C)$
1	142.3	18.7	6.6	141.6	19.2	6.0
2	115.0	2.2	2.2	114.7	2.2	2.7
3	129.5	2.2	-	129.7	2.2	-
4	124.0	-	-	123.8	-	-
5	111.3	-	7.7	111.1	3.3	6.6
6	117.6	3.8	12.1	115.9	-	6.0
7	152.3	-	1.1	151.5	2.7	9.9
8	122.0	-	1.1	118.8	-	2.2
9	137.7	-	-	136.7	-	-
10	122.8	-	-	123.2	-	-
11	147.2	-	-	149.4	-	-

The question of the geometric isomerism of the prepared 3-pyrazolylhydrazones **3a-3d** was solved in the similar way. On the basis of pmr spectra we inferred that the hydrazone **3a** contained approximately 66% of *E*- isomer and 34% of *Z*-isomer. Similarly hydrazones **3b** and **3c** have the ratio *E*/*Z*= 2:1, and the hydrazone **3d** has the ratio *E*/*Z*= 4:3.

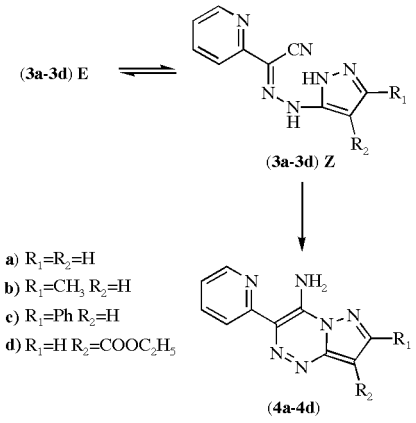
Hydrazones **3a-3e** are yellow crystalline compounds of somewhat unsharp mp due to a mixture of both geometric isomers and except for **3e** also due to their cyclization. Hydrazones **3a-3d** were cyclized to compounds **4a-4d** during heating up above their melting points. Solidifying of the melt reveals the completed reaction. In their ir spectra all hydrazones **3a-3e** have an absorption band corresponding to the nitrile group between 2212-2219 cm^{-1}. The absorption maximum of the NH group is between 3169-3354 cm^{-1}. It was found that the unlabelled hydrazone **3e** shows, in the region of N-H stretching vibrations, an absorption maximum at 3301 cm^{-1} while labelled hydrazone **3e-I** with the isotope ^{15}N has the absorption maximum shifted to 3294 cm^{-1}. This shift is in accordance with the formula $\nu = 1/2\pi(K/\mu)^{1/2}$. Then it was found that the coupling constant $^{1}J(^{15}N^{1}H)$= 94.9 Hz. Showing that the hydrazone **3e** contains approximately 99% of the hydrazono tautomer according to the results published in the communication [19]. This fact eliminates tautomers **A-D**.

Then our attention was paid to the possibility of the mutual *E*/*Z* isomerization of **3a-3e** and in the case of hydrazones **3a-3d** to cyclization conditions to the compounds **4a-4d**.

We found that the hydrazone **3e** is a mixture of *E* and *Z* isomers in the ratio *E*/*Z*= 3/2 after the coupling reaction and this ratio is changed to 1/1 after the refluxing in acetic acid. In addition we found that the hydrazone **3e** contained 96% of *E*-isomer and 4% of *Z*-isomer after two weeks standing of the sample solution in deuterochloroform at room temperature, which was inferred from the signal intensities of the pmr spectrum. It is interesting that the ratio of geometric isomers of hydrazone **3e** after the standing of the sample solution is exactly opposite to hydrazones prepared by the coupling reaction of diazonium salts with derivatives of cyanoacetic acid [14]. The isomerization is evidently enabled by the tautomerism to azo-forms **A-D** due to the possibility of the free rotation around C-N bounds.

The cyclization of hydrazones **3a-3d** to the corresponding 4-amino-3-(2-pyridyl)pyrazolo[5,1-*c*][1,2,4]triazines is carried out both by thermal heating up above their melting points and by boiling in the appropriate solvent.

Scheme 3



a) R_1=R_2=H
b) R_1=CH_3 R_2=H
c) R_1=Ph R_2=H
d) R_1=H R_2=$COOC_2H_5$

(3a-3d) E **(3a-3d) Z** **(4a-4d)**

Unlike the hydrazones prepared by the coupling of pyrazole-3-diazonium salts with malonodinitrile [5,11] or with derivatives of cyanoacetic acid [3], where boiling in ethanol is sufficient for the cyclization, for hydrazones **3a-3d** under these cyclization conditions the reaction does not

Table 2

Physical and Analytical Data of Compounds **3**

Compound	mp [°C]	yield (%)	Formula M.W.	Elemental Analysis (Calcd./Found) % C	% H	% N
3a	173-174	99	$C_{10}H_8N_6$	56.60	3.80	39.60
			212.2	56.37	3.65	39.95
3b	169-171	77	$C_{11}H_{10}N_6$	58.40	4.46	37.15
			226.2	58.29	4.18	36.77
3c	176-179	93	$C_{16}H_{12}N_6$	66.66	4.20	29.15
			288.3	66.38	4.09	28.97
3d	150-153	97	$C_{13}H_{12}N_6O_2$	54.93	4.25	29.56
			284.3	54.67	4.46	29.33
3e	118-119	91	$C_{13}H_{10}N_4$	70.26	4.54	25.21
			222.3	70.41	4.39	25.29
3e-I	118-119	94	$C_{13}H_{10}N_4$	69.94	4.52	25.55
			223.3	70.15	4.67	25.42
3e-II	118-119	90	$C_{13}H_{10}N_4$	69.94	4.52	25.55
			223.3	69.83	4.41	25.31

proceed. Not even using of higher boiling solvents such as pyridine or anisole is successful. Only by refluxing in *N*-methylpyrrolidone at 202 °C does the cyclization proceed to completion during 30 minutes.

When acid catalysis is used the cyclization proceeds smoothly, for example, by refluxing in ethanol with a catalytic amount of *p*-toluenesulfonic acid or by refluxing in acetic acid.

Due to *E*/*Z* isomerization the cyclization of a mixture of isomers of all hydrazones **3a-3d** to pyrazolotriazines **4a-4d** proceeds in high yields.

4-Amino-3-(2-pyridyl)pyrazolo[5,1-*c*][1,2,4]triazines **4a-4d** are yellow crystalline compounds. Their melting points are higher than the corresponding starting hydrazones **3**. In their ir spectra an absorption band corresponding to the nitrile group is not present as it is in the case of hydrazones **3**, which disappear due to their cyclization. However, their pmr spectra are relatively simple in com-

Table 3

Physical and Analytical Data of Compounds **4**

Compound	mp [°C]	yield (%) method A	B	C	Formula M.W.	Elemental Analysis (Calcd./Found) % C	% H	% N
4a	218-221	85	78	75	$C_{10}H_8N_6$	56.60	3.80	39.60
					212.2	56.66	3.73	39.95
4b	227-228	70	70	73	$C_{11}H_{10}N_6$	58.40	4.46	37.15
					226.2	58.56	4.09	36.86
4c	293-296	72	74	71	$C_{16}H_{12}N_6$	66.66	4.20	29.15
					288.3	66.51	3.95	28.95
4d	208-210	75	87	80	$C_{13}H_{12}N_6O_2$	54.93	4.25	29.56
					284.3	54.96	3.94	29.62

Table 4

Pmr Spectral Data of Compounds **3** and **4**

Compound	Solvent	pmr spectrum
3a	DMSO-d_6	6.23 and 6.28 (s, 1H), 7.34 and 7.53 (t, 1H), 7.69-8.17 (m, 3H), 8.57 and 8.77 (d, 1H), 11.59, 12.46, 12.61 and 15.04 (s, 2H, NH, D_2O-exchangeable)
3b	DMSO-d_6	2,22 and 2,23 (s, 3H, methyl), 6.00 and 6.05 (s, 1H), 7.33 and 7.53 (m, 1H), 7.64-8.17 (m, 2H), 8.56 and 8.76 (d, 1H), 11.46, 12.12, 12.28 and 14.96 (s, 2H, NH, D_2O-exchangeable).
3c	DMSO-d_6	6.78 and 6.82 (s, 1H), 7.34-7.70 (m, 4H), 7.76-7.98 (m, 3H), 8.13-8.34 (m, 1H), 8.65 and 8.88 (d, 1H), 11.72, 12.96, 13.14 and 15.13 (s, 2H, NH, D_2O-exchangeable)
3d	DMSO-d_6	1,30 and 1,33 (t, 3H, methyl), 4.28 and 4.34 (q, 2H, CH_2O), 7.41 and 7.60 (t, 1H), 7.70-8.44 (m, 3H), 8.62 and 8.78 (d, 1H), 10.51, 13.21, 13.60, 15.31 and 15.51 (broad s, 2H, NH, D_2O-exchangeable)
3e	$CDCl_3$	7.05-7.18 (m, 1H), 7.22-7.48 (m, 5H), 7.71-7.83 (m, 1H), 7.86-8.02 (m, 1H), 8.62-8.72 (d, 1H), 9.1 and 14.95 (s, 1H, NH, D_2O-exchangeable)
3e-I	$CDCl_3$	Identical with **3e**, but the signals 9.02 and 14.95 (d, 1H, NH, D_2O exchangeable)
3e-II	$CDCl_3$	Identical with **3e**
4a	DMSO-d_6	6.97 (d, 1H), 7.38 (m, 1H), 7.97 (m, 1H), 8.35 (d, 1H), 8.56-8.71 (m, 2H), 9.12 and 10.35 (broad s, 2H, NH_2, D_2O-exchangeable)
4b	DMSO-d_6	2.55 (s, 3H), 6.74 (s, 1H), 7.38 (m, 1H), 7.97 (m, 1H), 8.56-8.68 (m, 2H), 8.97 and 10.27 (broad s, 2H, NH_2, D_2O-exchangeable)
4c	DMSO-d_6	7.16-7.63 (m, 5H), 7.83-7.97 (m, 1H), 8.00-8.21 (m, 2H), 8.47-8.74 (m, 2H), 8.85 and 10.23 (broad s, 2H, NH_2, D_2O-exchangeable)
4d	DMSO-d_6	1.36 (t, 3H), 4.35 (q, 2H), 7.44-7.52 (m, 1H), 7.98-8.39 (m, 2H), 8.63-8.75 (m, 2H), 9.53 and 10.57 (broad s, 2H, NH_2, D_2O-exchangeable)

Table 5

Ir Spectral Data (in cm^{-1}) of Compounds **3** and **4** (KBr-technique)

Compound	**3a**	**3b**	**3c**	**3d**	**3e**	**3e-I**	**3e-II**	**4a**	**4b**	**4c**	**4d**
ν(CN)	2217	2218	2215	2212	2219	2219	2219	-	-	-	-
ν(NH)	3354	3333	3330	3169	3235	3225	3236	-	-	-	-
$\nu(NH_2)$	-	-	-	-	-	-	-	3257	3249	3299	3281

Table 6

UV Spectral Data of Compounds **4** (measured in methanol)

Compound	λ_{max} [nm], (ε)
4a	216 (22100), 244 (13300), 328 (18100), 368 (12800)
4b	220 (21100), 244 (14900), 328 (17300), 368 (12000)
4c	208 (20700), 268 (28300), 344 (20300)
4d	212 (21000), 236 (9900), 284 (6500), 320 (11800), 372 (16500)

parison with hydrazones **3a-3d** because there is no geometric isomerism.

EXPERIMENTAL

Melting points were determined on a Boetius stage and are not corrected. Infrared spectra were scanned on an ATI Unicam Genesis FTIR instrument using KBr technique (diffuse reflectance) and $CHCl_3$ solutions (transmittance), and the wave numbers are expressed in cm^{-1}. Elemental analyses were performed using an EA 1108 Elemental Analyser (Fision Instrument). Nmr spectra were measured on a Bruker Avance 300 MHz DRX spectrometer in DMSO-d_6 and deuterochloroform solutions. Values of the chemical shifts (δ) and the coupling constants (J) are given in (ppm), respectively in (Hz). UV spectra were measured on an Unicam UV-VIS Helios Alpha spectrometer in 10^{-5} *M* methanol solutions.

General Procedure of the Synthesis of Substituted Arylhydrazono-(2-pyridyl)acetonitriles (**3**).

To a pre-cooled solution of 2.0 mmol of the corresponding 3-aminopyrazole [20-23] or aniline in a mixture of 10 ml water and 2 ml 37% hydrochloric acid was added drop wise a solution of 138 mg (2 mmol) of $NaNO_2$ in 3 ml ice-cold water with the continuous stirring at 0-5 °C. The rose solution was left for 30 minutes in an ice bath and then added drop wise to a solution of 0.24 ml (2.2 mmol) (2-pyridyl)acetonitrile [16] and 4 g sodium acetate in 40 ml ice-cold water with continuous stirring and cooling. The reaction mixture was then stirred for 30 minutes in an ice bath and placed in a refrigerator. The next day the precipitated crystalline compound of the corresponding hydrazone was collected by filtration, washed with water and dried in air and finally recrystallized from ethanol. In the same way, the hydrazones **3e-I** and **3e-II** were prepared by using aniline ^{15}N, respectively $Na^{15}NO_2$. For further details, see Tables 2,4 and 5.

General Procedure of the Synthesis of Substituted 4-Amino-3-(2-pyridyl)pyrazolo[5,1-*c*][1,2,4]triazines (**4a-4d**).

The Cyclization in Acetic Acid.

A mixture of 1 mmol of the corresponding hydrazone **3a-3d** and 20 ml of acetic acid was refluxed for 30 minutes after which the solvent was removed by distillation. The remaining residue was recrystallized from ethanol. For further details, see Tables 3,4,5 and 6.

Cyclization in Ethanol with Catalytic Amount of *p*-Toulensulfonic Acid.

A mixture of 1 mmol of the corresponding hydrazone **3a-3d** and 20 ml ethanol with 17.2 mg (0.1 mmol) of *p*-toluenesulfonic acid was refluxed for 30 minutes, concentrated to a small volume and cooled. The crystalline solid was collected by filtration the next day, washed with a small amount of ethanol and dried in air.

The Cyclization in *N*-Methylpyrrolidone.

A mixture of 1 mmol of the corresponding hydrazone **3a-3d** and 20 ml of *N*-methylpyrrolidone was refluxed for 30 minutes, after which the mixture was concentrated to approximately to 5 ml, poured into 30 ml of water and placed into refrigerator. The next day the crystalline solid was collected by filtration, washed with water, dried in air and recrystallized from ethanol.

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