ANRORC reactions of 3-methyl-1,4-dinitro-1*H*-pyrazole with arylhydrazines

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Abstract

Reactions of 3-methyl-1,4-dinitro-1*H*-pyrazole with phenylhydrazine and some *C*-substituted derivatives were studied. The reactions with arylhydrazines containing electron-withdrawing substituents afforded 1-aryl-5-methyl-4-nitro-1*H*-pyrazoles only. Unexpectedly, mixtures of two regioisomers, 1-aryl-3-methyl-4-nitro-1*H*-pyrazoles and 1-aryl-5-methyl-4-nitro-1*H*-pyrazoles, were obtained from the reaction with phenylhydrazine or 4-methyl- and 4-fluoro- derivatives. An *ANRORC* (Addition of the Nucleophile, Ring Opening, Ring Closure) mechanism was proposed for the reaction.

Keywords: *ANRORC*, arylnitropyrazole, arylhydrazines, 3-methyl-1,4-dinitro-1*H*-pyrazole

Introduction

The most common methods used for syntheses of 1-aryl-4-nitro-1*H*-pyrazoles are limited to nitration of 1-arylpyrazoles or nucleophilic substitution of halonitrobenzenes by nitropyrazole anions.[1] In our former work[2] we have shown that 1,4-dinitro-1*H*-pyrazole (**1**) could serve as a synthetic equivalent of *β*-formyl-*β*-nitroenamines[3] and unstable nitromalonaldehyde as well as its stable, but poorly soluble sodium salt in a preparation of 1-aryl-4-nitro-1*H*-pyrazoles.[4,5,6,7] This new method has proved to be very useful for the preparation of 4-nitropyrazoles particularly containing electron-donating substituents at 1-aryl substituent (Figure 1).

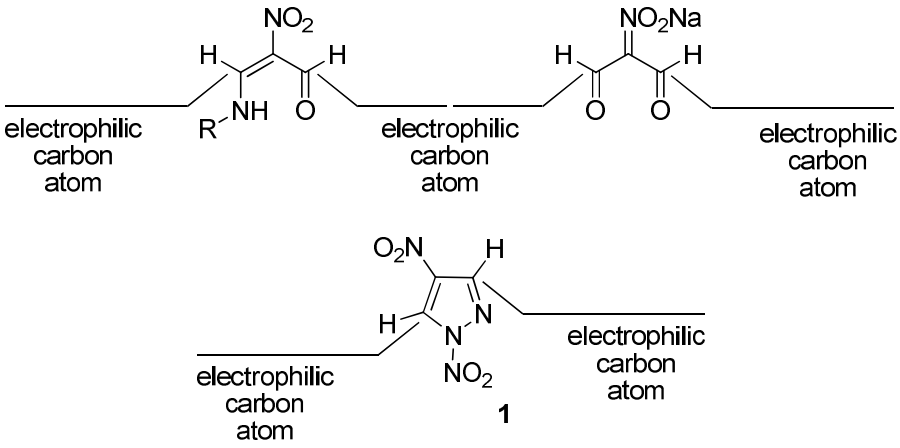
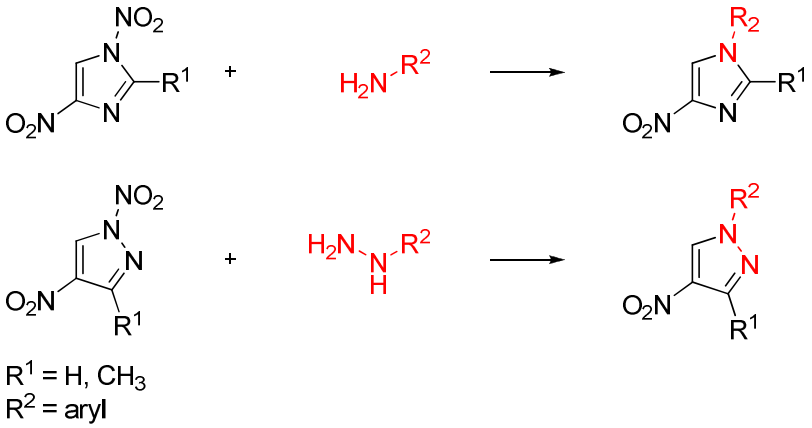


Figure 1. 1,4-Dinitro-1*H*-pyrazole (**1**) as an equivalent of tautomeric *β*-formyl-*β*-nitroenamine or nitromalonaldehyde salt.

1,4-Dinitro-1*H*-pyrazoles usually react with mononucleophiles according to the *cine* substitution pattern. The reactions proceed without ring transformation to give 5(4)-substituted 4(5)-nitro-1*H*-pyrazoles. Those reactions were studied and described earlier.[8,9] In turn, reactions of 1,4-dinitro-1*H*-pyrazole with equimolar amounts of arylhydrazines (1,2-dinucleophiles) - discovered by us - afforded 1-aryl-4-nitropyrazoles by a new *ANRORC* reaction.[2] It seems that the reactions of 1,4-dinitro-1*H*-pyrazole (**1**) with arylhydrazines and reactions of 1,4-dinitro-1*H*-imidazoles with primary amines, described also by us,[10] follow similar *ANRORC* pathways (Scheme 1).



Scheme 1. Postulated similarity of the two reactions: 1,4-dinitro-1*H*-imidazoles with anilines and 1,4-dinitro-1*H*-pyrazoles with arylhydrazines.

In this work, we studied reactions of 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) with arylhydrazines looking for a new approach to synthesis of 1-aryl-3(or 5)-methyl-4-nitro-1*H*-pyrazoles and trying to collect new data on *ANRORC* mechanism of the reactions.

Results and Discussion

Nitration of 3(5)-methyl-1*H*-pyrazole (**3**) with ammonium nitrate and trifluoroacetic anhydride in trifluoroacetic acid according to the known method[11] afforded 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) in a satisfactory yield. Treatment of **2** with phenylhydrazine (**4′**) at room temperature gave only tars. When temperature of the reaction mixture was gradually raised from -18 up to ca +25 °C it was possible to obtain *C*-methyl-4-nitro-1-phenyl-1*H*-pyrazoles in moderate yields. Similar yields of *C*-methyl-4-nitro-1-phenyl-1*H*-pyrazoles were obtained regardless whether free phenylhydrazine (**4′**) or its hydrochloride (**4**) with sodium bicarbonate was used as the nucleophile. Unexpectedly, mixtures of two regioisomers of *C*-methyl-4-nitro-1-phenyl-1*H*-pyrazole were obtained after purification of the product from tars (Table). All the attempts to separate the regioisomers and isolate them in a pure form have failed. Formation of the two isomeric 1-aryl-3/5-methyl-4-nitro-1*H*-pyrazoles in the present studied reactions was surprising because until now all *ANRORC* reactions of 1,4-dinitro-1*H*-azoles have taken place with formation of only one desired product.[2,10] Chromatographically separable mixtures of two regioisomeric 1-aryl-3-methyl-4-nitro-1*H*-pyrazoles and 1-aryl-5-methyl-4-nitro-1*H*-pyrazoles were obtained in reactions of **2** with hydrochlorides of 4-fluorophenylhydrazine (**5**) or 4-methylphenylhydrazine (**6**). In contrast, hydrochlorides of 3-fluorophenylhydrazine (**7**), 3-chlorophenylhydrazine (**8**), 4-chlorophenylhydrazine (**9**), 3,5-dichlorophenylhydrazine (**10**) and 3,4-difluorophenylhydrazine (**11**) reacted with 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) to give corresponding 1-aryl-5-methyl-4-nitropyrazoles as the only isomers. The results of the experiments are shown in Table.

The reason for the lost regioselectivity in some of the reactions studied appears to be unclear. 3-Methyl-1,4-dinitro-1*H*-pyrazole (**2**) possesses two electrophilic ring carbon atoms, moreover arylhydrazines have two nucleophilic nitrogen atoms (Figure 2).

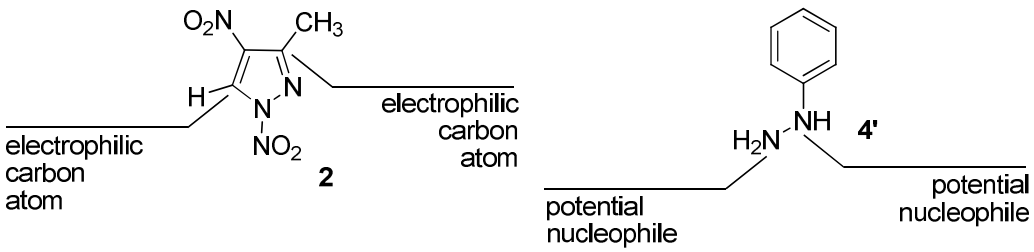


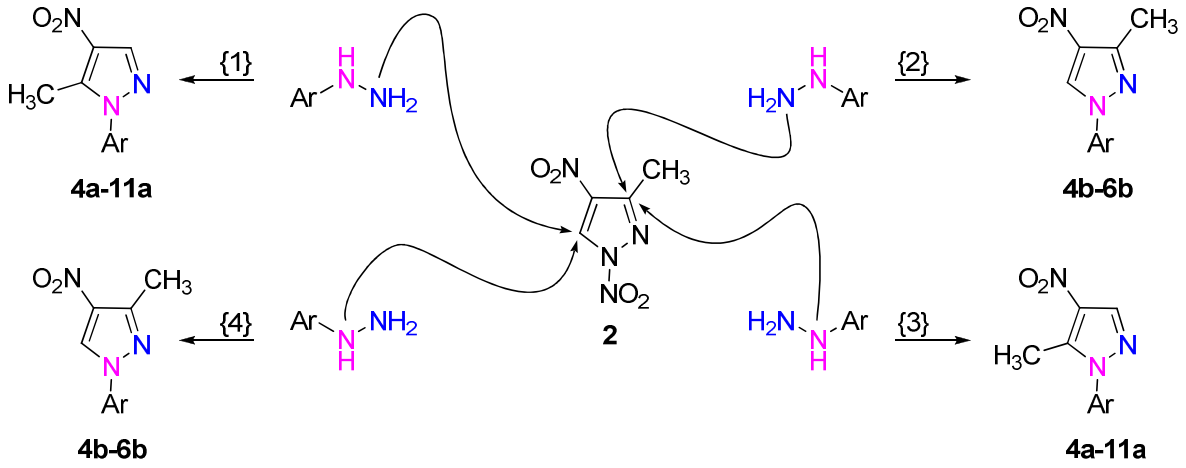
Figure 2. Electrophilic carbon atoms in 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) and nucleophilic nitrogen atoms in phenylhydrazine (**4′**).

It is possible to come up with at least four different reaction paths for the *ANRORC* reaction of **2** with arylhydrazines (Scheme 2). A nucleophilic attack of arylhydrazine terminal nitrogen atom on *C*-5 of pyrazole ring would result in the formation of 5-methyl isomer (path {1} Scheme 2). A formation of the same isomer would be also possible if the internal nitrogen atom of arylhydrazines attacked *C*-3 position of the starting pyrazole derivative (path {3} Scheme 2).

Table. Results of *ANRORC* reactions of 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) with arylhydrazines

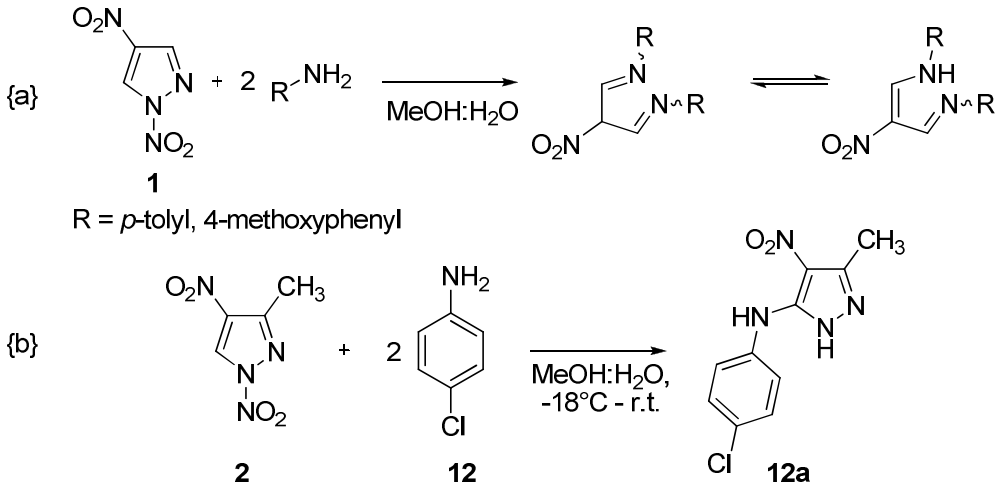
No.	Arylhydrazine substrate	Product(s) of reactions		Yield(s) **a**+**b** [%]
		a	**b**	
1.	**4′**	5-Methyl-4-nitro-1-phenyl-1*H*-pyrazole (**4a**)	3-Methyl-4-nitro-1-phenyl-1*H*-pyrazole (**4b**)	54+20*
2.	**4**	5-Methyl-4-nitro-1-phenyl-1*H*-pyrazole (**4a**)	3-Methyl-4-nitro-1-phenyl-1*H*-pyrazole (**4b**)	54+20*
3.	**5**	1-(4-Fluorophenyl)-5-methyl-4-nitro-1*H*-pyrazole (**5a**)	1-(4-Fluorophenyl)-3-methyl-4-nitro-1*H*-pyrazole (**5b**)	13+8
4.	**6**	5-Methyl-1-(*p*-tolyl)-4-nitro-1*H*-pyrazole (**6a**)	3-Methyl-1-(*p*-tolyl)-4-nitro-1*H*-pyrazole (**6b**)	23+17
5.	**7**	1-(3-Fluorophenyl)-5-methyl-4-nitro-1*H*-pyrazole (**7a**)	-	34+0
6.	**8**	1-(3-Chlorophenyl)-5-methyl-4-nitro-1*H*-pyrazole (**8a**)	-	69+0
7.	**9**	1-(4-Chlorophenyl)-5-methyl-4-nitro-1*H*-pyrazole (**9a**)	-	16+0
8.	**10**	1-(3,4-Dichlorophenyl)-5-methyl-4-nitro-1*H*-pyrazole (**10a**)	-	61+0
9.	**11**	1-(3,5-Dichlorophenyl)-5-methyl-4-nitro-1*H*-pyrazole (**11a**)	-	53+0

*Yields for regioisomers calculated from ^{1}H NMR spectrums integration.



Scheme 2. Four possible routes of the first nucleophilic attack of arylhydrazine on 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**).

On the other hand, the isomer with methyl substituent at *C*-3 would be formed when arylhydrazine terminal nitrogen atom attacked position *C*-3 of pyrazole ring or arylhydrazine internal nitrogen atom attacked the position *C*-5 (paths {2} and {4} in Scheme 2). Attacks of the nucleophiles at *C*-3 {paths {2} and {3} should rather be ruled out because 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) reaction with mononucleophiles afforded only *cine* products arising from attacks on the *C*-5 of pyrazole ring. We decided to check possibility of attack of mononucleophile at both electrophilic carbons in pyrazole ring in 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**). For this purpose we perform reaction of **2** with two molar excess of 4-chloroaniline. In our previous work we showed that 1,4-dinitro-1*H*-pyrazole (**1**) in aqueous methanol reacted with two molecules of 4-methylaniline or 4-methoxyaniline with a formation of mixtures of acyclic products (nitrodiazapentadienes reaction {a} in Scheme 3). In that case the nucleophilic attack took place at both *C*-3 and *C*-5 positions of the pyrazole substrate.[2] 3-Methyl-1,4-dinitro-1*H*-pyrazole (**2**) (under similar conditions to those used in the reactions with arylhydrazines) reacted with two molar excess of 4-chloroaniline (**12**) with the formation of *cine* product **12a** arising from attack only at the *C*-5 position of pyrazole ring ({b} Scheme 3).

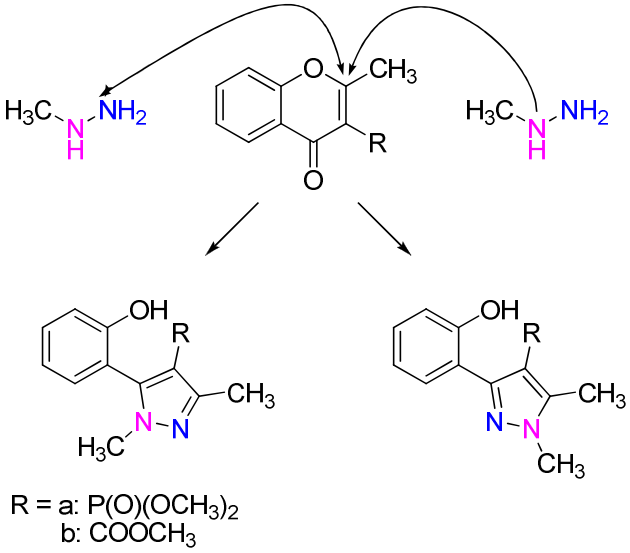


Scheme 3. Formation of the diferent products in the reactions of 1,4-dinitro-1*H*-pyrazole (**1**)[2] and 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) with aromatic amines.

Even traces of the corresponding regioisomer were not observed. In addition, electron donating and steric effects of the methyl group, significantly reduces susceptibility of *C*-3 atom to the nucleophilic attack. The presence of methyl group on the pyrazole ring especially hampers the reaction path {3} (Scheme 2), since two quite bulky groups are close to the reaction center. The steric effects and electrophilicity of the carbon atoms on the synthesis of pyrazole ring from 1,3-dicarbonyl compounds was discussed by Sloop *et al*. [12] 1,4-Dinitro-1*H*-pyrazoles are their synthetic equivalents. Nucleophiles usually attack less sterically hindered and more electrophilic carbon atom in nonsymmetrical 1,3-dicarbonyl compounds. In 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**), carbon atom in *C*-5 position is the most electropilic and the least sterically hindered. It means that paths {1} and {4} are much more prefered ways for the 1-aryl-methyl-4-nitro-1*H*-pyrazoles formation. Moreover, the formation of regioisomers probably depends on a type of substituents in arylhydrazines. Differences in the electron properties of the two arylhydrazines nucleophilic centers also depend on substituents in benzene ring.

Based on the measurement of relaxation times in ^{14}N NMR and ^{15}N NMR spectra of different arylhydrazines, it was found that phenylhydrazine and 4-nitrophenylhydrazine were protonated on the terminal nitrogen atom, but in case of 4-methoxyphenylhydrazine protonation of the internal nitrogen atom was also observed.[13] The methoxy group, methyl group, hydrogen atom and fluorine atom in the position 4 of benzene ring have electron donating or neutral properties (Hammett constans σ_p and σ_p^+ respectively: -0.268 and -0.170; 0.00, and +0.062; -0.778 and -0.311; 0.00 and -0.073).[14] We know that basicity and nucleophilicity of hydrazines not necessarily change paralelly. Nevertheless, one can suppose that the effect of the methyl group and fluorine atom in the 4- position of phenylhydrazine on both the basicity and nucleophilicity of two nitrogen atoms is similar and is also similar to the effect of 4-methoxy substituent. Therefore, it is evident that protonation of arylhydrazines can take place at both nitrogen atoms,

although protonation of the terminal nitrogen atom predominates. The NMR studies also showed that in contrast to the aryl derivatives, protonation of alkylhydrazines occurred almost solely on the internal nitrogen atom. On the other hand, data from studies on some reactions with the use of alkylhydrazines showed that each of the nitrogen atoms might react as a nucleophile. Reactions of chromen-4-one derivatives with methylhydrazine that affording pyrazoles with methyl group at position *C*-3 or *C*-5 (Scheme **4**) can serve as an example.[15] A course of the reaction depends on which of the nitrogen atoms of the hydrazine took part in the reaction earlier.

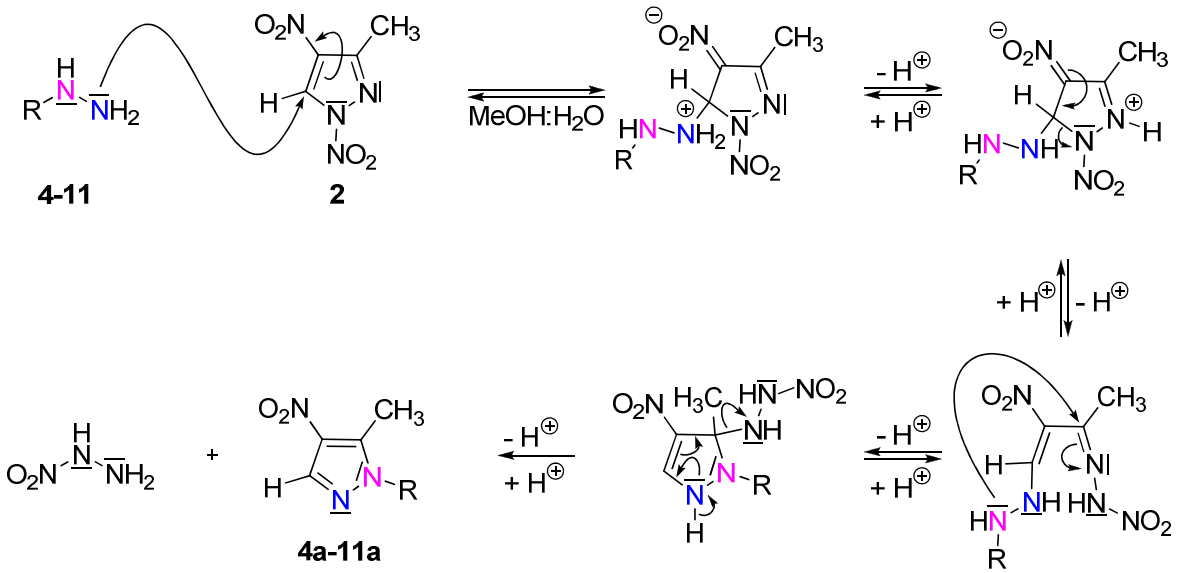


Scheme 4. The reactions of chromen-4-one derivatives with methylhydrazine.

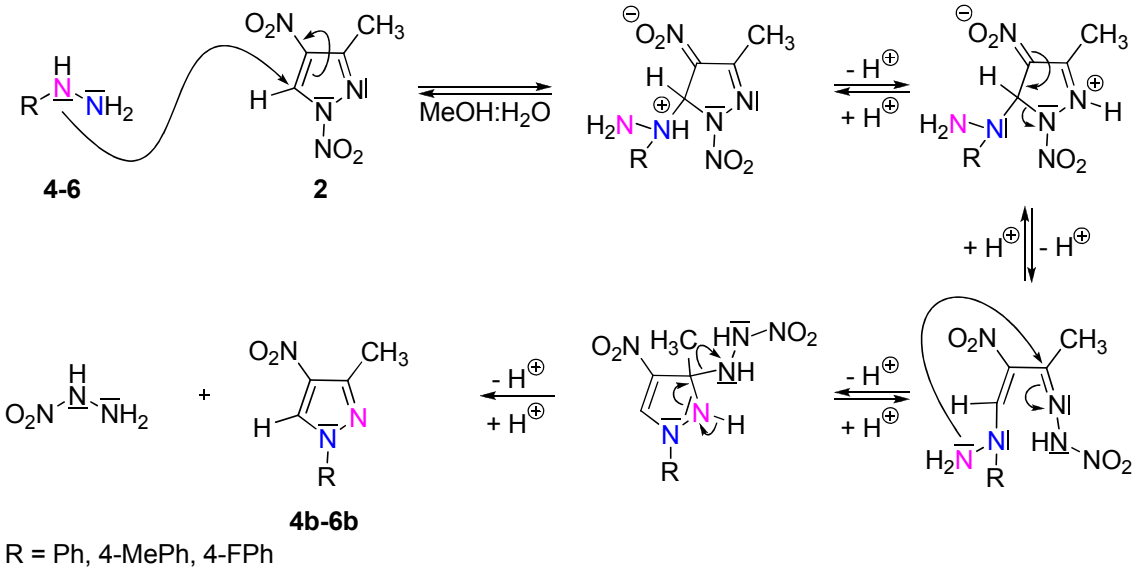
Taking into account the facts mentioned above, the following mechanism of reaction of 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) with arylhydrazines, similar to the *ANRORC* mechanisms of 1,4-dinitro-1*H*-imidazoles with anilines, may be proposed. As shown before, the possiblility of formation of two regioisomers in *ANRORC* reactions of **2** with arylhydrazines depends on the substituents in the hydrazine reagent. The arylhydrazine as a nucleophile predominantly attacks *C*-5 atom of 1,4-dinitro-1*H*-pyrazoles (**1** and **2**). As a result of the attack by terminal nitrogen atom of arylhydrazine onto pyrazole ring, an adduct is formed. Then by a solvent-assisted transfer of protons, the adduct is converted to the open-chain form. In the next step, an intramolecular nucleophilic attack of the internal nitrogen atom of the starting arylhydrazine on carbon *C*-3 atom takes place. Finally, restoration of aromaticity of the pyrazole ring accomplishes the *ANRORC* reaction (Scheme 5).

A formation of 1-aryl-3-methyl-4-nitro-1*H*-pyrazole may proceed in accordance to the next proposed path (Scheme 6). In this case, a nucleophilic attack of phenylhydrazine internal nitrogen atom (see arguments mentioned above) probably takes also place only on carbon atom in position *C*-5. Then, in opposition to the former path for 3-methyl- isomer formation, an

intramolecular nucleophilic attack of terminal nitrogen atom leads to rearomatization of the *ANRORC* product.



Scheme 5. The proposed *ANRORC* mechanism of 1-aryl-5-methyl-4-nitro-1*H*-pyrazoles formation from 1,4-dinitro-3-methyl-1*H*-pyrazole (**2**) starting from the attack of arylhydrazine terminal nitrogen atom on pyrazole ring carbon atom at the position *C*-5.



Scheme 6. The proposed *ANRORC* mechanism of 1-aryl-3-methyl-4-nitro-1*H*-pyrazoles formation from 1,4-dinitro-3-methyl-1*H*-pyrazole (**2**) starting from the attack of arylhydrazine internal nitrogen atom on pyrazole ring carbon atom at the position *C*-5.

Reactions of 1,4-dinitro-1*H*-pyrazole itself with phenylhydrazine, 4-methylphenylhydrazine and 4-fluorophenylhydrazine probably followed these same two routes as the reactions discussed in this work. Unfortunately, due to the presence of hydrogen atoms at both electrophilic centers of azole substrate **1**, two reaction paths lead to the same regioisomers. Therefore, an answer to the question which nitrogen atom from arylhydrazine attacks 1,4-dinitro-1*H*-pyrazole ring in the first stage of the *ANRORC* reaction might be achieved e.g., by the use of starting pyrazole with deuterium monosubstituted ring. No answer can be drawn from the structure of product from unlabelled reagents.

Conclusions

Reactions of 1,4-dinitro-3-methyl-1*H*-pyrazole (**2**) with arylhydrazines lead either to 1-aryl-3-methyl-4-nitro-1*H*-pyrazoles or to mixtures of 1-aryl-3-methyl-4-nitro-1*H*-pyrazoles and 1-aryl-5-methyl-4-nitro-1*H*-pyrazoles. Only the reactions with phenylhydrazines *C*-substituted with electron-withdrawing substituents can serve as a useful new method for synthesis of 1-aryl-5-methyl-4-nitro-1*H*-pyrazoles. The reactions with phenylhydrazine and its derivatives with electron–donating substituents are rather of no interest from synthetic point of view but their results shed new light on the *ANRORC* mechanism of 1,4-dinitropyrazoles reaction with arylhydrazines.

Experimental Section

General. Melting points (not corrected) were determined in open capillary tubes or Boetius HMK apparatus. NMR spectra were taken in hexadeuterodimethyl sulfoxide with TMS as an internal reference by Varian XL-300 (at 300 MHz for ^{1}H and at 75.5 MHz for ^{13}C) or Varian System 600 MHz (600 MHz for ^{1}H and at 150.8 MHz for ^{13}C). EA was determined on CHNS PERKIN ELMER 2400 Serie II apparatus. Commercially available phenylhydrazines (or its hydrochlorides) were used without purification. 1,4-dinitro-3-methyl-1*H*-pyrazole was obtained according to known procedure.[11]

CAUTION: To the best of our knowledge use of 3-methyl-1,4-dinitro-1*H*-pyrazole in small scale is safe but some dinitroazoles are classified as explosives[16] and for this reason and high content of nitrogen atoms in molecule,[17] special care and attention should be taken during synthesis, storage and operation with 3-methyl-1,4-dinitro-1*H*-pyrazole.

3-Methyl-1,4-dinitro-1*H*-pyrazole (2). Trifluoroacetic acid anhydride (6.5 mL) was added dropwise to the vigorously stirred and cooled to -18 °C suspension of ammonium nitrate (3.6 g) in solution of 3-methylpyrazole (0.82 g) in trifluoroacetic acid (25 mL). Low temperature was

kept 4 hours, then it was allowed to warm to room temperature. The reaction mixture was poured onto ice and extracted with dichloromethane (5×20 mL). Extract was washed with cold solution of sodium bicarbonate (0.25 mol/l, 15 mL), cold saturated brine and cold water to the neutral reaction. After drying with magnesium sulfate, solvent was evaporated and residue oil was purified by column chromatography (ethyl acetate:hexane $1:3_{v:v}$). Yield 44%, mp 40-43 °C (from ethyl acetate:hexane $1:3_{v:v}$; lit.[11] 47-48 °C from hexane), white powder. ^{1}H-NMR δ (ppm): 2.53 (s, 3H, $-CH_{3\ pyr}$), 9.91 (s, 1H, $H\text{-}5_{pyr}$). ^{13}C-NMR δ (ppm): 13.24 (s, $-CH_{3\ pyr}$), 127.22 (s, $C\text{-}5_{pyr}$), 134.28 (s, $C\text{-}4_{pyr}$), 144.77 (s, $C\text{-}3_{pyr}$).

5-Methyl-4-nitro-1-phenyl-1*H*-pyrazole (4a) and 3-methyl-4-nitro-1-phenyl-1*H*-pyrazole (4b) from 1,4-dinitro-3-methyl-1*H*-pyrazole and phenylhydrazine (4′). A solution of phenylhydrazine (1 mmol) in methanol (5 mL), was gradually added to a stirred solution of 3-methyl-1,4-dinitro-1*H*-pyrazole (1 mmol) in methanol (15 mL). The stirring was continued in darkness at -18-0 °C for the first 3-4 hours, then at ambient temperature for 44 hours. Solvent was evaporated and the precipitate was purified from the rest of the substrates and colored impurities by column chromatography methanol:chloroform $1:19_{v:v}$, to afford a mixture of 5-methyl-4-nitro-1-phenyl-1*H*-pyrazole (**4a**) and 3-methyl-4-nitro-1-phenyl-1*H*-pyrazole (**4b**). All the attempts to separate mixtures of isomeric **4a** and **4b** obtained in reaction by chromatography and fractional crystallization has failed. Total yield of both isomers 74%, mp 76-105.5 °C (from methanol:chloroform $1:19_{v:v}$; lit.[18] **4a** 113-114 °C from benzene:light petroleum; **4b** 109-110.5 °C from benzene:light petroleum), creamy-colored powder, ^{1}H-NMR δ (ppm) for compound **4a**: 2.60 (s, 3H, $-CH_3$), 7.57-7-65 (m, 5H, Ar-H), 8.47 (s, 1H, $H\text{-}3_{pyr}$). For compound **4b**: 2.55 (s, 3H, $-CH_3$), 7.40-7.45 (m, 1H, H-4'), 7.52-7.55 (m, 2H, Ar-H), 7.91-7.95 (m, 2H, Ar-H), 9.58 (s, 1H, $H\text{-}5_{pyr}$). EA (C%, H%, N%): found 59.20, 4.43, 20.55, calc. for $C_{10}H_9N_3O_2$ 59.11, 4.46, 20.68.

General procedure for synthesis of 1-aryl-3/5-methyl-4-nitro-1*H*-pyrazoles from 3-methyl-1,4-dinitro-1*H*-pyrazole and arylhydrazines hydrochlorides: To the vigorously stirred slurry of arylhydrazine hydrochloride (3 mmol) in methanol (6 mL) solution of sodium bicarbonate (3 mmol) in water (6 mL) was added. After 10 minutes, resulting suspension was cooled to 0 °C and added in small portions to the cooled to -18 °C solution of 1,4-dinitro-3-methyl-1*H*-pyrazole (3 mmol) in methanol (6 mL). The stirring was continued in darkness at -18 to -10 °C for the first 3-4 hours, then at ambient temperature for a given number of hours. Then, in some cases, refluxing of the mixture was necessary until decay of a corresponding spot on TLC. The precipitates were collected, separated and purified as indicated. Details of the reaction conditions like proportion of the solvents, reaction time, yield, melting point of product and solvents used for crystallization, results of NMR and EA analyses for each compound are disclosed below.

5-Methyl-4-nitro-1-phenyl-1*H*-pyrazole (4a) and 3-methyl-4-nitro-1-phenyl-1*H*-pyrazole (4b). from 1,4-dinitro-3-methyl-1*H*-pyrazole and phenylhydrazine hydrochloride. Reaction time 48 h. All attempts to separate mixtures of isomeric **4a** and **4b** obtained in reaction of 3-methyl-1,4-dinitro-1*H*-pyrazole (**2**) with phenylhydrazine hydrochloride (**4**) by chromatography and fractionated crystallization has failed. Total yield of both isomers 74%, mp 76-103 °C (lit.[18]

as described above) creamy-colored powder. ^{1}H-NMR δ (ppm): for compound **4a**: 2.60 (s, 3H, -CH_3), 7.57-7-65 (m, 5H, Ar-H), 8.47 (s, 1H, H-3_{pyr}). For compound **4b**: 2.55 (s, 3H, -CH_3), 7.40-7.45 (m, 1H, H-4'), 7.52-7.55 (m, 2H, Ar-H), 7.91-7.95 (m, 2H, Ar-H), 9.58 (s, 1H, H-5_{pyr}). EA (C%, H%, N%):found 59.29, 4.40, 20.55, calc. for $C_{10}H_9N_3O_2$ 59.11, 4.46, 20.68., found 59.29, 4.40, 20.55, calc. for $C_{10}H_9N_3O_2$ 59.11, 4.46, 20.68. Purification from the rest of the substrates and colored impurities: column chromatography, methanol:chloroform $1:19_{v:v}$.

5-Methyl-4-nitro-1-(*p*-tolyl)-1*H*-pyrazole (**6a**). Yield 23%, creamy-colored powder, mp 99-102 °C (from diethyl ether). ^{1}H-NMR δ (ppm): 2.47 (s, 3H, -CH_3), 2.58 (s, 3H, -$CH_{3\ pyr}$), 7.39-7.47 (m, 4H, Ar-H), 8.45 (s, 1H, H-3_{pyr}). ^{13}C-NMR δ ppm: 11.99 (s, 1C, -$CH_{3\ pyr}$), 20.70 (s, 1C, -CH_3), 125.45 (s, 2C, C-2', C-6'), 129.90 (s, 2C, C-3', C-5'), 133.30 (s, 1C, C-4_{pyr}), 135.29 (s, 1C, C-1'), 136.76 (s, 1C, C-3_{pyr}), 139.26 (s, 1C, C-4'), 140.33 (s, 1C, C-5_{pyr}). EA (C%, H%, N%): found 60.94, 5.22, 18.99, calc. for $C_{11}H_{11}N_3O_2$ 60.82, 5.10, 19.34. Separation and purification: preparative TLC, ethyl acetate:hexane $1:3_{v:v}$, extraction from gel – diethyl ether.

3-Methyl-4-nitro-1-(*p*-tolyl)-1*H*-pyrazole (**6b**). Yield 17%, mp 111-113 °C, (from diethyl ether) light yellow powder.^{1}H-NMR δ (ppm): 2.36 (s, 3H, -CH_3), 2.53 (s, 3H, -$CH_{3\ pyr}$), 7.34 (d, 2H, *J* 8.7 Hz, Ar-H), 7.81 (d, 2H, *J* 8.7 Hz, Ar-H), 9.51 (s, 1H, H-5_{pyr}). **^{13}C**-NMR δ ppm: 13.32 (s, 1C, -$CH_{3\ pyr}$), 20.48 (s, 1C, -CH_3), 119.02 (s, 2C, C-2', C-6'), 128.85 (s, 1C, C-5_{pyr}), 130.01 (s, 2C, C-3', C-5'), 134.35 (s, 1C, C-4_{pyr}), 135.94 (s, 1C, C-4'), 137.56 (s, 1C, C-1'), 146.01 (s, 1C, C-3_{pyr})., EA (C%, H%, N%): found 60.89, 5.24, 19.09, calc. for $C_{11}H_{11}N_3O_2$ 60.82, 5.10, 19.34. Separation and purification: preparative TLC, ethyl acetate:hexane $1:3_{v:v}$, extraction from gel – diethyl ether.

5-Methyl-4-nitro-1-(3-fluorophenyl)-1*H*-pyrazole (**7a**). Yield 34%, mp 74-75.5 °C, (from methanol), yellow powder. ^{1}H-NMR δ (ppm): 2.64 (s, 3H, -CH_3), 7.41-7.48 (m, 2H, H-4', H-6'), 7.55 (dt, 1H, *J* 9.6 Hz, *J* 2.3 Hz, H-2'), 7.66 (dt, 1H, *J* 8.1 Hz, *J* 6.3 Hz, H-5'), 8.49 (s, 1H, H-3_{pyr}). ^{13}C-NMR δ ppm: 11.95 (s, 1C, -CH_3), 113.18 (d, 1C, *J* 25.1 Hz, C-2'), 116.47 (d, 1C, *J* 20.6 Hz, C-4'), 121.83 (d, 1C, *J* 3.5 Hz, C-6'), 131.27 (d, 1C, *J* 9.6 Hz, C-5'), 133.56 (s, 1C, C-4_{pyr}), 137.08 (s, 1C, C-3_{pyr}), 138.94 (d, 1C, *J* 10.0 Hz, C-1'), 140.70 (s, 1C, C-5_{pyr}), 161.90 (d, 1C, *J* 244.9 Hz, C-3'). EA (C%, H%, N%): found 54.34, 3.58, 18.88, calc. for $C_{10}H_8FN_3O_2$ 54.30, 3.65, 19.00.

5-Methyl-4-nitro-1-(4-fluorophenyl)-1*H*-pyrazole (**5a**). Yield 13%, mp 118-119 °C (from diethyl ether), creamy-colored powder.^{1}H-NMR δ (ppm): 2.58 (s, 3H, -CH_3), 7.40-7.48 (m, 2H, Ar-H), 7.61-7.68 (m, 2H, Ar-H), 8.45 (s, 1H, H-3_{pyr}). ^{13}C-NMR δ ppm: 11.89 (s, 1C, -CH_3), 116.40 (d, 2C, *J* 23.7 Hz, C-3', C-5'), 128,05 (d, 2C, *J* 9.1 Hz, C-2', C-6'), 133.35 (s, 1C, C-4_{pyr}), 134.05 (d, 1C, *J* 3.0 Hz, C-1'), 136.05 (s, 1C, C-3_{pyr}), 140.60 (s, 1C, C-5_{pyr}), 162.09 (d, 1C, *J* 247.3 Hz, C-4'). EA (C%, H%, N%): found 54.48, 3.62, 18.88, calc. for $C_{10}H_8FN_3O_2$ 54.30, 3.65, 19.00. Separation and purification: preparative TLC, ethyl acetate:hexane $1:3_{v:v}$, extraction from gel – diethyl ether.

3-Methyl-4-nitro-1-(4-fluorophenyl)-1*H*-pyrazole (**5b**). Yield 8%, mp 137-140 °C (from diethyl ether), small, creamy-colored plates.^{1}H-NMR δ (ppm): 2.53 (s, 3H, -CH_3), 7.36-7.42 (m, 2H, H-Ar), 7.93-7.99 (m, 2H, Ar-H), 9.54 (s, 1H, H-5_{pyr}). ^{13}C-NMR δ ppm: 13.26 (s, 1C, -CH_3),

116.43 (d, 2C, *J* 23.2 Hz, C-3', C-5'), 121.42 (d, 2C, *J* 9.1 Hz, C-2', C-6'), 129.27 (s, 1C, C-5_{pyr}), 134.53 (s, 1C, C-4_{pyr}), 134.70 (d, 2C, *J* 2.5 Hz, C-1'), 146.19 (s, 1C, C-3_{pyr}), 161.23 (d, 2C, *J* 245.2 Hz, C-4'). EA (C%, H%, N%): found 54.50, 3.70, 18.30, calc. for $C_{10}H_8FN_3O_2$ 54.30, 3.65, 19.00. Separation and purification: preparative TLC, ethyl acetate:hexane $1:3_{v:v}$, extraction from gel – diethyl ether.

5-Methyl-4-nitro-1-(3-chlorophenyl)-1*H*-pyrazole (**8a**). Yield 69%, mp 66-68 °C (from ethyl acetate:hexane $1:3_{v:v}$) white powder. ^{1}H-NMR δ (ppm): 2.62 (s, 3H, -CH_3), 7.57-7.62 (m, 1H, Ar-H), 7.64-7.68 (m, 2H, Ar-H), 7.73-7.75 (m, 1H, Ar-H), 8.49 (s, 1H, H-3_{pyr}). ^{13}C-NMR δ ppm: 11.98 (s, 1C, -CH_3), 124.45 (s, 1C, C-6'), 125.62 (s, 1C), 129.52 (s, 1C), 131.13 (s, 1C), 133.55 (s, 1C, C-4_{pyr}), 133.70, 137.17 (s, 1C, C-3_{pyr}), 138.83 (s, 1C, C-1'), 140.81 (s, 1C, C-5_{pyr}). EA (C%, H%, N%): found 50.71, 3.30, 17.41, calc. for $C_{10}H_8ClN_3O_2$ 50.54, 3.39, 17.68. Separation and purification: column chromatography, ethyl acetate:hexane $1:3_{v:v}$.

5-Methyl-4-nitro-1-(4-chlorophenyl)-1*H*-pyrazole (**9a**) Yield 16%, mp 97-98 °C (from methanol), creamy-colored powder. ^{1}H-NMR δ (ppm): 2.61 (s, 3H, -CH_3), 7.61-7.69 (m, 4H, Ar-H), 8.48 (s, 1H, H-3_{pyr}). ^{13}C-NMR δ ppm: 11.92 (s, 1C, -CH_3), 127.34 (s, 1C, C-2', C-6'), 129.49 (s, 1C, C-3', C-5'), 133.52 (s, 1C, C-4_{pyr}), 134.07 (s, 1C, C-4'), 136.48 (s, 1C, C-1'), 137.04 (s, 1C, C-3_{pyr}), 140.57 (s, 1C, C-5_{pyr}). EA (C%, H%, N%): found 50.74, 3.30, 17.41, calc. for $C_{10}H_8ClN_3O_2$ 50.54, 3.27, 17.30. Separation and purification: column chromatography, methanol:chloroform $1:19_{v:v}$ then recrystallization from methanol with charcoal.

5-Methyl-4-nitro-1-(3,5-difluorophenyl)-1*H*-pyrazole (**11a**). Yield 61%, mp 117-119 °C (from methanol), creamy-colored needles.^{1}H-NMR δ (ppm): 2.66 (s, 3H, -CH_3), 7.46-7.59 (m, 3H, Ar-H), 8.51 (s, 1H, H-3_{pyr}). ^{13}C-NMR δ ppm: 11.95 (s, 1C, -CH_3), 105.26 (t, 1C, *J* 25.7 Hz, C-4'), 109.67-110.52 (m, 2C, C-2', C-6'), 133.79 (s, 1C, C-4_{pyr}), 137.37 (s, 1C, C-3_{pyr}), 139.60 (t, 1C, *J*=12.9 Hz, C-1'), 141.09 (s, 1C, C-5_{pyr}), 162,25 (dd, 2C, *J* 246.3 Hz, *J* 14.4 Hz, C-3', C-5'). **EA** (C%, H%, N%): found 50.20, 2.98, 17.41, calc. for $C_{10}H_7F_2N_3O_2$ 50.22, 2.95, 17.57. Separation and purification: column chromatography, methanol:chloroform $1:99_{v:v}$, then recrystallization from methanol.

5-Methyl-4-nitro-1-(3,4-dichlorophenyl)-1*H*-pyrazole (**10a**). Yield 53%, mp 134-135 °C (from methanol), small, creamy-colored needles.^{1}H-NMR δ (ppm): 2.64 (s, 3H, -CH_3), 7.64 (dd, 1H, *J* 8.7 Hz, *J* 2.4 Hz, H-6'), 7.88 (d, 1H, *J* 8.7 Hz, H-5'), 7.96 (d, 1H, *J* 2.4 Hz, H-2'), 8.49 (s, 1H, H-3_{pir}), ^{13}C-NMR δ ppm: 11.94 (s, 1C, -CH_3), 125.92 (s, 1C, C-H), 127.59 (s, 1C, C-H), 131.42 (s, 1C, C-H), 131.96 (s, 1C, C-Cl), 132.41 (s, 1C, C-Cl), 133.63 (s, 1C, C-4_{pir}), 137.31 (s, 1C, C-3_{pir}), 141.01 (s, 1C, C-5_{pir}). EA (C%, H%, N%): found 44.26, 2.52, 15.14, calc. for $C_{10}H_7Cl_2N_3O_2$ 44.14, 2.59, 15.44. Separation and purification: column chromatography, methanol:chloroform $1:99_{v:v}$, then recrystallization from methanol.

3(5)-Methyl-5(3)-(4-chlorophenyl)amino-4-nitro-1*H*-pyrazole (**12a**). Cooled to 0 °C solution of 4-chloroaniline (3 mmol) in methanol (5 mL) was slowly dropwise added to the cooled (-18 °C) and vigorously stirred solution of 3-methyl-1,4-dinitro-1*H*-pyrazole (1.5 mmol) in methanol (12 mL). After half an hour, water (5 mL) was added to above mixture and stirring and cooling were continued for the next 4 hours and then allowed to warm the mixture to room temperature

and stirring was continued for the next 48 hours. After evaporating of the solvents and re crystallization from ethanol 3(5)-methyl-5(3)-(4-chlorophenyl)amino-4-nitro-1*H*-pyrazole was obtained. Yield 45%, mp 225-227 °C (with sublimation) (from ethanol), yellow, glossy plates.^{1}H-NMR δ (ppm): 2.53 (s, 3H, -CH_3), 7.31 (d, 2H, *J* 9.0 Hz, Ar-H) 7.75 (d, 2H, *J* 9.0 Hz, Ar-H) 8.65 (s, 1H, -NH-), 13.18 (s, 1H, -NH_{pyr}). ^{13}C-NMR δ ppm: 11.93 (s, 1C, -CH_3), 119.18 (s, 2C), 119.45 (s, 1C), 124.48 (s, 1C), 128.42 (s, 1C), 139.40 (s, 1C), 140.68 (s, 1C), 146.89 (s, 1C). EA (C%, H%, N%): found 47.79, 3.56, 21.49 calc. for $C_{10}H_9ClN_4O_2$ 47.54, 3.59, 22.17.

References

1. Walczak, K.; Gondela, A., Suwiński, J. *Eur. J. Med. Chem.* **2004**, *39*, 849-853. http://dx.doi.org/10.1016/j.ejmech.2004.06.014
2. Jędrysiak, R.; Sawicki, M.; Wagner, P.; Suwiński, J. *ARKIVOC* **2007**, (vi), 103-111.
3. Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem.* **2004**, *69*, 8382-8386. http://dx.doi.org/10.1021/jo0488513
4. Fanta, P.E. *Organic Syntheses.Coll. Vol.* **1963**, *4*, 844-845. http://dx.doi.org/10.15227/orgsyn.032.0095
5. Grimmett, M.R.; Hartshorn, S.R.; Schofield, K. *J. Chem. Soc., Perkin Trans. II*. **1972**, 1654-1660. http://dx.doi.org/10.1039/P29720001654
6. Finar, I.L.; Hurlock, R.J. *J. Chem. Soc.* **1957**, 3024-3027. http://dx.doi.org/10.1039/JR9570003024
7. Hill, H.B.; Torrey, S. *Chem. Ber*. **1895**, *28*, 2597-2599. http://dx.doi.org/10.1002/cber.18950280353
8. Buchanan, J.G.; Stobie, A.; Wightman, R.H. *Canadian J. Chem.* **1980**, *58*, 2624-2627. http://dx.doi.org/10.1139/v80-419
9. Habraken, C.L.; Poels, E.K. *J. Org. Chem.* **1977**, *42*, 2893-2895. http://dx.doi.org/10.1021/jo00437a024
10. Salwińska, E.; Suwiński, J. *Polish J. Chem.* **1990**, *64*, 813-817.
11. Buchanan, J.G.; Harrison, M.; Wightman, R.H.; Harnden, M.R. *J. Chem. Soc., Perkin Trans. I*. **1989**, 925-930. http://dx.doi.org/10.1039/P19890000925
12. Sloop, J.C.; Bumgardner, C.L.; David Loehle, W. *J. Fluor. Chem.* **2002**, *118*, 135-147. http://dx.doi.org/10.1016/S0022-1139(02)00221-X
13. Bagno, A.; Menna, E.; Mezzina, E.; Scorrano, G.; Spineli, D. *J. Phys. Chem. A.* **1998**, *102*, 2888-2892. http://dx.doi.org/10.1021/jp972461l

14. Hammett, L.P. *Fizyczna Chemia Organiczna. Szybkość, Równowagi i Mechanizmy reakcji*, PWN: Warszawa, 1976; p 332*;* translated from: Hammett, L.P. *Physical Organic Chemistry. Reaction Rates, Equilibria, and Mechanism*, 2nd Ed.; McGraw-Hill: New York, 1970.
15. Małecka, M.; Massa, W.; Harms, K.; Budzisz, E. *J. Mol. Struc.*, **2005**, *737*, 259-265. http://dx.doi.org/10.1016/j.molstruc.2004.09.028
16. Larina, L.; Lopyrev, V. *Nitroazoles: Synthesis, Structure and Applications*; Springer: New York, 2009; pp 60-65. http://dx.doi.org/10.1007/978-0-387-98070-6
17. Bräse, S.; Gil C.; Knepper K.; Zimmermann V. *Angew.Chem. Int. Ed.* **2005**, *44*, 5188-5240. http://dx.doi.org/10.1002/anie.200400657
18. Finar I.L.; Hurlock, R.J. *J. Chem. Soc.* **1958**, 3259-3263. http://dx.doi.org/10.1039/JR9580003259

