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LETTERS TO THE EDITOR

Three-Component Synthesis of 5-Aryl-3-amino-1*H*-pyrazole-4-carbonitriles and 3-Amino-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitriles

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Abstract—A multicomponent method of the synthesis of 5-aryl-3-amino-1*H*-pyrazole-4-carbonitrile and 3-amino-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitriles with thermal and microwave activation was developed.

Keywords: 5-aryl-3-amino-1*H*-pyrazole-4-carbonitrile, 3-amino-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitriles, microwave activation, multicomponent reaction

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Pyrazole derivatives are scaffolds for the creation of important pharmaceutical preparations and other biologically active compounds with anti-inflammatory, antimicrobial, antimycobacterial activity [1, 2].

Pyrazoles containing amino and cyano groups are of interest both for applied research and for the synthesis of other fused polyheterocyclic systems [3].

Synthesis of 5-aryl-3-amino-1*H*-pyrazole-4-carbonitrile has been previously carried out in two stages by reacting 3-oxo-3-phenylpropanenitrile with trichloroacetonitrile and subsequent condensation with hydrazine [4, 5]. Here we report on the synthesis of pyrazole and pyrazoline type aminocyanides through one-step three-component condensation.

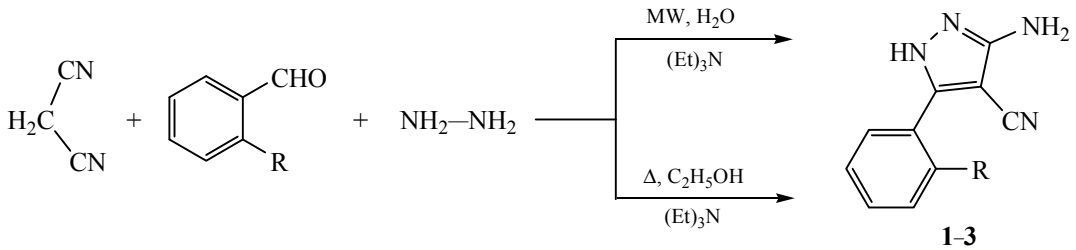
5-Aryl-3-amino-1*H*-pyrazole-4-carbonitriles **1–3** described previously [4] were obtained by three-component condensation of hydrazine hydrate, malonic acid dinitrile, and aromatic aldehydes (benzaldehyde, salicylaldehyde) in the presence of catalytic amounts of triethylamine under microwave or thermal activation (Scheme 1, Table 1).

The use of microwave irradiation does not change the direction of the three-component condensation, but it allows a significant decrease in the reaction time and an increase in the yield of the target compounds. In addition, the proposed method is environmentally friendly due to the use of water as a solvent.

Physicochemical characteristics of compound **1** completely coincided with those of the product obtained by the two-stage synthesis [4, 5].

The composition and the structure of compounds **2** and **3** were confirmed by the elemental analysis, ^{1}H

Scheme 1.



1–3

R = H (**1**), OH (**2**), NO_2 (**3**).

Table 1. Synthesis of 5-aryl-3-amino-1*H*-pyrazole-4-carbonitriles **1**–**3**

Comp. no.	R	Synthesis method	Time, min	Yield, %
1	H	Δ	180	31
		MW	2	88
2	OH	Δ	180	55
		MW	2	90
3	NO_2	Δ	240	25
		MW	4	82

Table 2. Synthesis of 3-amino-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitriles **4**–**6**

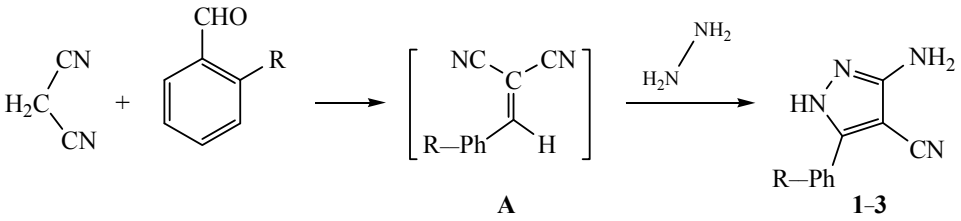
Comp. no.	R	Synthesis method	Time, min	Yield, %
4	H	Δ	360	30
		MW	4	88
5	Ph-NO_2-4	Δ	420	41
		MW	6	85
6	Ph	Δ	420	45
		MW	5	92

and ^{13}C NMR spectra. The ^{1}H NMR spectra contained the singlets of NH (11.08–11.85 ppm) and NH_2 (6.54–8.98 ppm) groups, the doublets of aromatic protons (6.93–7.88 ppm). In the spectrum of compound **2** there was a signal of a hydroxy group (4.98 ppm). The ^{13}C NMR spectra contained the signals of 9 sp^2- and 1*sp*-hybridized carbon atomsin agreement with the assumed structure.

The probable formation of pyrazolecarbonitriles **1–3** involves the initial condensation of malonic acid dinitrile with an aromatic aldehyde and the subsequent heterocyclization of the intermediate **A** with the binucleophilic reagent (Scheme 2).

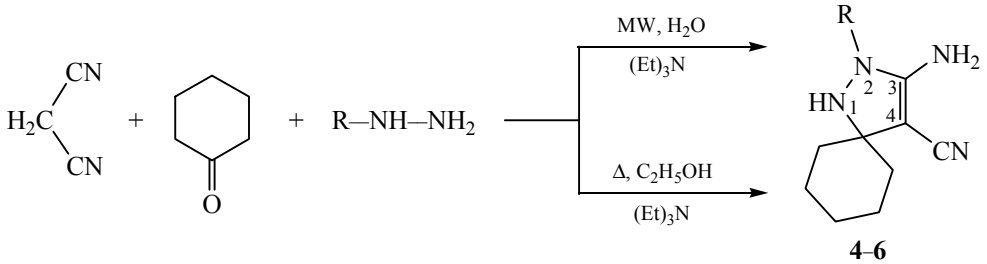
We have shown that this three-component condensation can also be used for the synthesis of spiropyrazolines. Thus, when changing the carbonyl component for cyclohexanone, the reaction proceeded smoothly to form previously unknown 3-amino-1,2-diazaspiro[4.5]-dec-3-ene-4-carbonitriles **4–6** (Scheme 3). The use of microwave irradiation in the synthesis of spiro compounds also led to a 2–3 times increase in the products yields and a 70–90 times decrease in the reaction time (Table 2). The composition and the structure of compounds **4–6** were confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra there were the singlets of NH (8.12–8.81 ppm) and NH_2 groups (6.24–6.60 ppm), the multiplets of the alicycle (1.08–1.70 ppm). The spectra of compounds **5** and **6** contained also the doublet signals of the aromatic protons (6.95–7.60 ppm). In the ^{13}C NMR spectra the characteristic signals of spiro-carbon atoms

Scheme 2.



A **1**–**3**

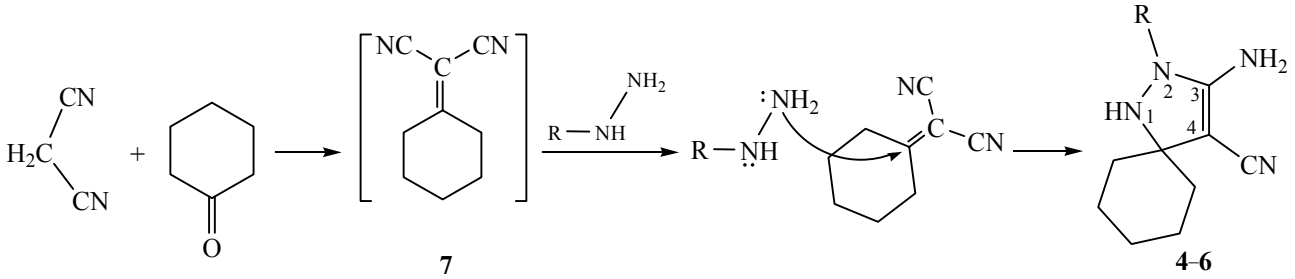
Scheme 3.



4–**6**

R = H (**4**), Ph-NO_2-4 (**5**), Ph (**6**).

Scheme 4.



are observed at 53.25–55.76 ppm. The presence of the aryl substituent in the position **2** was proved by HMBC correlation between the signals of the protons of the secondary and primary amino groups and the carbon atom C^3 (6.99–7.58 ppm/144.19 ppm).

By the example of compound **6** we performed the two-stage authentic synthesis by reacting 2-cyclohexylidene malononitrile **7** and phenylhydrazine (refluxing equimolar amounts of the reagents in ethanol). As a result, the expected 3-amino-2-phenyl-2-diazaspiro[4.5]dec-3-ene-4-carbonitrile **6** was isolated in 40% yield (Scheme 4) whose characteristics coincided with the product, obtained by the three-component reaction.

In conclusion, the three-component condensation of malonic acid dinitrile, hydrazines, and oxo compounds under microwave irradiation can be used for convenient one-pot synthesis of aminocyanides of pyrazole and spiropyrazoline series.

5-Aryl-3-amino-1*H*-pyrazole-4-carbonitriles (1–3). *a*. A mixture of 3 mmol of aromatic aldehyde, 3 mmol of malonic acid dinitrile, and 0.08 mol % of triethylamine in ethanol was refluxed for 20 min, then 3 mmol of hydrazine hydrate was added. The reaction mixture was heated for 180–240 min. After the reaction completed the crystals were filtered off, washed with hexane, and dried in air.

b. A mixture of 3 mmol of an aromatic aldehyde, 3 mmol of malonic acid dinitrile, 3 mmol of hydrazine hydrate, and 0.08 mol % of triethylamine in water was subjected to microwave irradiation for 2–4 min. The crystals were filtered off, washed with water, and dried in a vacuum.

5-Phenyl-3-amino-1*H*-pyrazole-4-carbonitrile (1). Yield 0.19 g (31%, method *a*), 0.55 g (88%, method *b*), mp 200–202°C (mp 200–202°C [4, 5]). Found, %: C 63.11; H 4.44; N 30.39. $C_{10}H_8N_4$. Calculated, %: C 63.22; H 4.35; N 30.43.

5-(2-Hydroxyphenyl)-3-amino-1*H*-pyrazole-4-carbonitrile (2). Yield 0.47 g (55%, method *a*), 0.77 g (90%, method *b*), mp 218–221°C. ^{1}H NMR spectrum, δ, ppm: 11.08 s (1H, NH), 8.98 s (2H, NH_2), 7.30 d (4H, C_6H_4, J = 8.0 Hz), 4.97 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 162.8 (C≡N), 158.56 (C^7), 155.9 (C^3), 143.9 (C^5), 128.9, 128.7, 127.6, 119.20, 116.21, 116.05 (C_6H_5), 85.30 (C^4). Found, %: C 60.03; H 4.23; N 28.09. $C_{10}H_8N_4O$. Calculated, %: C 59.99; H 4.03; N 27.99.

5-(2-Nitrophenyl)-3-amino-1*H*-pyrazole-4-carbonitrile (3). Yield 0.20 g (25%, method *a*), 0.66 g (82%, method *b*), mp 201–203°C. ^{1}H NMR spectrum, δ, ppm: 11.85 s (1H, NH), 7.65 d (4H, C_6H_4, J = 8.0 Hz), 6.54 s (2H, NH_2). Found, %: C 52.05; H 3.13; N 30.93. $C_{10}H_7N_5O_2$. Calculated, %: C 52.40; H 3.08; N 30.56.

3-Amino-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitriles (4–6). *a*. A mixture of 3 mmol of cyclohexanone, 3 mmol of dinitrile, and 0.08 mol % of triethylamine in ethanol was refluxed for 20 min, then 3 mmol of hydrazine was added. The reaction mixture was heated for 360–420 min. The crystals were filtered off, washed with hexane, and dried in air.

b. A mixture of 3 mmol of cyclohexanone, 3 mmol of dinitrile, 3 mmol of hydrazine, and 0.08 mol % of triethylamine in water was subjected to microwave irradiation for 4–6 min. The crystals were filtered off, washed with water, and dried in a vacuum.

c. For the preparation of compound **6** a mixture of 1 mmol of 2-cyclohexylidene malononitrile and 1 mmol of phenylhydrazine in ethyl alcohol was refluxed for 360 min. The crystals were filtered off, washed with hexane, and dried in air.

3-Amino-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitrile (4). Yield 0.19 g (30%, method *a*), 0.56 g (88%, method *b*), mp 245–248°C. ^{1}H NMR spectrum, δ, ppm: 8.81 s (1H, NH), 8.12 s (1H, NH), 6.24 s (2H, NH_2), 1.37–1.08 m [10H, $(CH_2)_5$]. Found, %: C 60.25;

H 7.45; N 31.04. $C_9H_{14}N_4$. Calculated, %: C 60.65; H 7.92; N 31.43.

3-Amino-2-(4-nitrophenyl)-2-diazaspiro[4.5]dec-3-ene-4-carbonitrile (5). Yield 0.39 g (41%, method *a*), 0.81 g (85%, method *b*), mp 253–255°C. ^{1}H NMR spectrum, δ, ppm: 8.05 s (1H, NH), 7.27 d (4H, C_6H_4, J = 8.0 Hz), 6.60 s (2H, NH_2), 1.69–1.17 m [10H, $(CH_2)_5$]. ^{13}C NMR spectrum, δ_C, ppm: 162.96 (C≡N), 157.45 (C^3), 146.23 (C^{11}), 142.35 (C^{14}), 125.83, 125.71, 116.30, 115.42 (C_6H_5), 98.65 (C^4), 55.76 (C^5), 39.19, 39.15, 24.41, 23.54, 23.52. Found, %: C 60.05; H 5.73; N 23.43. $C_{15}H_{17}N_5O_2$. Calculated, %: C 60.19; H 5.72; N 23.40.

3-Amino-2-phenyl-2-diazaspiro[4.5]dec-3-ene-4-carbonitrile (6). Yield 0.36 g (45%, method *a*), 0.75 g (92%, method *b*), 0.14 g (40%, method *c*), mp > 250°C. ^{1}H NMR spectrum, δ, ppm: 8.00 s (1H, NH), 7.28 d (4H, C_6H_5, J = 8.0 Hz), 6.54 s (2H, NH_2), 1.70–1.13 m [10H, $(CH_2)_5$]. ^{13}C NMR spectrum, δ_C, ppm: 152.19 (C≡N), 144.19 (C^{11}), 129.72, 123.65, 120.12, 119.24, 116.44, 113.33 (C_6H_5), 90.26 (C^4), 69.23 (C^3), 53.25 (C^5), 39.52, 39.31, 37.22, 25.13, 20.86. Found, %: C 70.55; H 7.33; N 22.01. $C_{15}H_{18}N_4$. Calculated, %: C 70.84; H 7.13; N 22.03.

2-Cyclohexylidene malononitrile (7). A mixture of 1 mmol of cyclohexanone, 1 mmol of malonic acid dinitrile, and 0.08 mol % of triethylamine in ethyl alcohol was refluxed for 30 min. The crystals were filtered off, washed with cold ethanol, and dried in air. Yield 0.40 g (60%), mp 172–174°C (mp 173.5–174.5°C [6]). Found, %: C 72.99; H 6.93; N 19.79. $C_9H_{10}N_2$. Calculated: C 73.79; H 6.85; N 19.27.

^{1}H and ^{13}C, HSQC, and HMBC NMR spectra were recorded on a Varian 400 spectrometer (400 and 100 MHz, DMSO-d_6). Elemental analysis was performed on a Vario MICRO cube CHNS analyzer. For the reactions, an Anton Paar Monowave 300 microwave reactor (constant temperature mode technique) was used. Temperature control was carried out using a fiber optic temperature sensor (630 W).

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