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Synthesis of Sulfonylated 4-Amino-1H-Pyrazoles with Aryl and Methoxymethyl Substituents

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The experimental data on the sulfonylation of 4-amino-1H pyrazoles with p-toluenesulfonyl chloride are given in the paper. New compounds were obtained: 3,5-dimethyl-4-tosylamino-1H-pyrazole, 3-methoxymethyl-5-phenyl-4-tosylamino-1H-pyrazole, 3-methoxymethyl-5-naphthyl-4-tosylamino-1H-pyrazole, 3-methyl-5-naphthyl-4-tosylamino-1H-pyrazole. The structure of sulfonylated aminopyrazoles was proved by IR, UV, 1H NMR spectroscopy and mass spectrometry.

Keywords: pyrazole, aminopyrazole, sulfonylamide, sulfonylation, NMR, IR, UV spectroscopy, mass spectrometry.

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Синтез сульфонилированных 4-амино-1H-пиразолов с арильными и метоксиметильными заместителями

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*В статье приведены экспериментальные данные по сульфонилрованию 4-амино-1H-пиразолов *n*-толуолсульфохлоридом. Получены новые соединения: 3,5-диметил-4-тозиламино-1H-пиразол, 3-метоксиметил-5-фенил-4-тозиламино-1H-пиразол, 3-метоксиметил-5-нафтил-4-тозиламино-1H-пиразол, 3-метил-5-нафтил-4-тозиламино-1H-пиразол. Строение сульфонилированных аминопиразолов доказано с помощью ИК, УФ, ЯМР1H спектроскопии и масс-спектрометрии.*

Ключевые слова: пиразол, аминопиразол, сульфониламид, сульфонилирование, ЯМР1H-, ИК-, УФ-спектроскопия, масс-спектрометрия.

Introduction

An important priority for a person is to maintain healthy. Nowadays, there is a huge number of medicines in the world, but microbes progress with a great speed, constantly adapting to the activity of new drugs, and therefore the search and synthesis of new substances with antibacterial activity does not stop.

It is known that among the pyrazole derivatives there are a number of known highly effective drugs, such as antipyrine, analgin and others [1]. Therefore, new pyrazole derivatives by now continue to attract the attention of specialists engaged in the search for new effective biologically active substances, including chemical-pharmaceutical drugs, pesticides, bioprotectors for various materials, antioxidants, etc. Particularly interesting ones in this respect are amine-substituted pyrazoles. The disadvantages of known aminopyrazoles include their poor solubility and as a consequence the difficulty of removing the products of their metabolism from the body therefore they are toxic to the liver and kidneys, and also cause the manifestation of agranulocytosis [2].

Most often, amines are not used in a free form, but in the form of sulfonylated derivatives. So, sulfanilamide drugs are very widely used – a group of chemically synthesized compounds used for the treatment of infectious diseases, mainly of bacterial origin.

Sulfanilamides were the first drugs that allowed successful prevention and treatment of a variety of bacterial infections. Thanks to these drugs entered into medical practice since the 1930s, it was possible to significantly reduce the death rate from pneumonia, blood infection and many other bacterial infections. Their widespread use during the World War II saved many lives [3].

Therefore, the aim of our work was to obtain new sulfonyl derivatives of aminopyrazoles. Earlier at the department of organic chemistry and technology of organic substances, aminopyrazoles with aryl

and methoxymethyl substituents were obtained and characterized. Proceeding from this, we decided to synthesize previously unknown *p*-toluenesulfonyl (tosyl) derivatives of aminopyrazoles [4].

Materials and methods

The synthesis was carried out according to the scheme given below, carrying out the tosylation of various substituted aminopyrazoles [5], which may have biological activity. The synthesis scheme is shown in Fig. 1.

To carry out the synthesis, 0.1 g of substituted aminopyrazole and 4 ml of water were charged into a flask equipped with a magnetic stirrer. The mixture was stirred and heated to 60 °C. For 1 hour, 0.3 g of *p*-toluenesulfochloride and 0.1 g of sodium carbonate were added alternately in small portions, making sure that the reaction of the medium was neutral. The mixture was then stirred for 2 hours, and cooled down to room temperature. To purify from the original aminopyrazole, concentrated hydrochloric acid was added dropwise to the reaction mixture before the acidic Congo reaction, and the mixture was stirred for an additional 30 minutes at room temperature. The resulting precipitate was filtered off and washed with water from the acid to a neutral reaction, then dried under vacuum. Thin-layer chromatogram (TLC) in the eluent, toluene-ethyl acetate (1:1) showed the individuality of the products.

Results and discussion

The yield of 3,5-dimethyl-4-tosylamino-1H-pyrazole (I) was 68%, m.p. is 196-198 °C, TLC in the eluent of toluene-ethyl acetate (1:1) showed the individuality of the product. In the UV spectrum, there was a maximum absorption at the wavelength (ethanol): $\lambda_{\text{max}} = 224 \text{ nm}$, $\epsilon = 632$; $\lambda_{\text{max}} = 317 \text{ nm}$, $\epsilon = 96$. Mass Spectrum m/z : M^+ (265) 264 (100), 155(53), 91(68), 65(11), 42(15)

^1H NMR spectrum is shown in Fig. 2.

In the NMR spectrum in a weak field, signals are present ppm: 9.41 s (1H, NH), 7.26-7.73 (4H tosyl ring), 2.38-2.43 s (3H, CH_3 tosyl ring), 1.70-1.94 s (6H, 2CH_3 of the pyrazole ring). In the IR spectrum, a band of the stretching vibration of the SO_2 group is observed in the region of 1163 cm^{-1} . In the region of 3246 cm^{-1} , vibrations of the free NH group are observed.

The yield of 3-methoxymethyl-5-phenyl-4-tosylamino-1H-pyrazole (II) was 40%. m.p. 170-172 °C, TLC in the eluent of toluene-ethyl acetate (1:1) showed the individuality of the product. In the

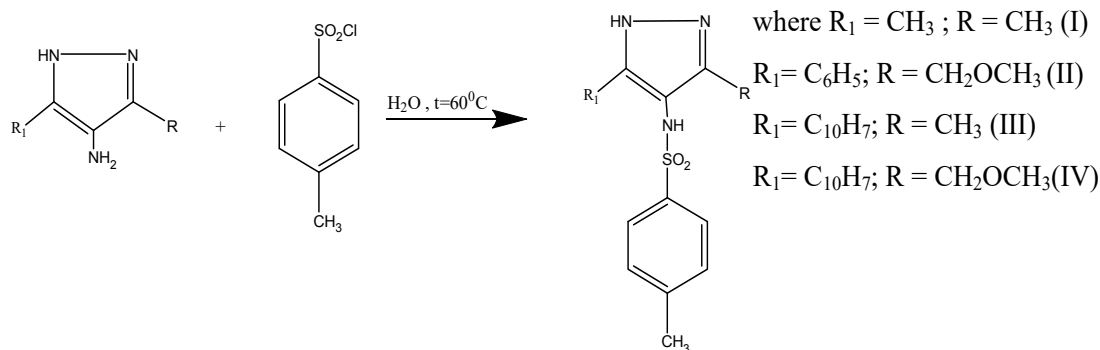


Fig. 1. Scheme for the preparation of sulfonylated derivatives

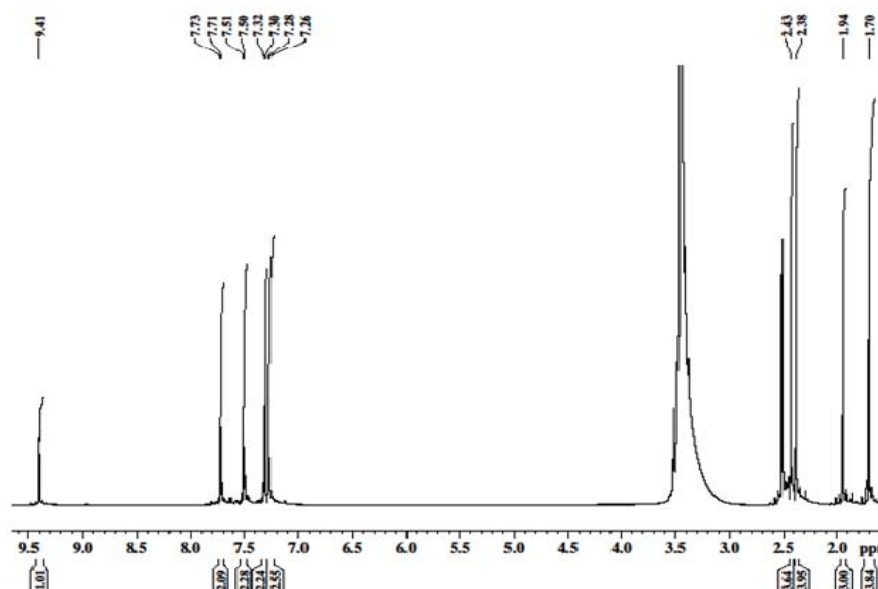


Fig. 2. NMR spectrum of 3,5-dimethyl-4-tosylamino-1H-pyrazole in DMSO-d₆.

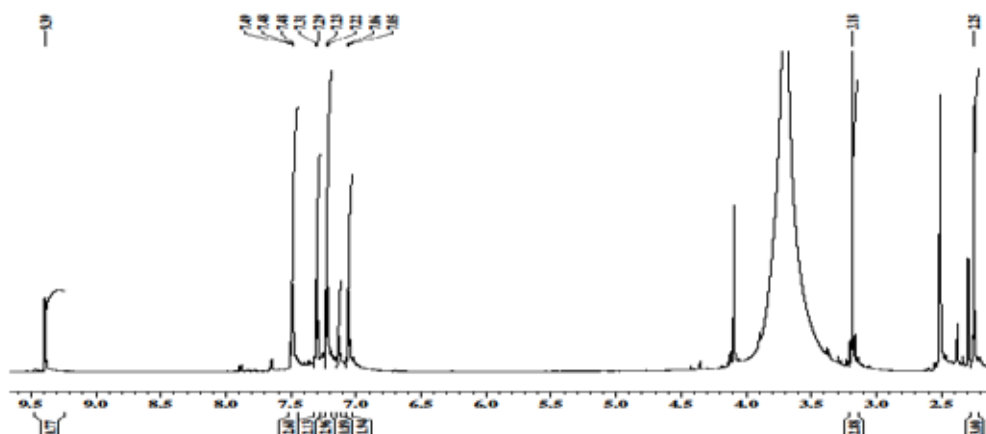


Fig. 3. NMR spectrum of 3-methoxymethyl-5-phenyl-4-tosylamino-1H-pyrazole in DMSO-d₆.

UV spectrum there was a maximum absorption at the wavelength (ethanol): $\lambda_{\text{max}} = 235 \text{ nm}$, $\epsilon = 694$; $\lambda_{\text{max}} = 352 \text{ nm}$, $\epsilon = 117$. Mass Spectrum m/z : M^+ (357) 357 (100), 202(47), 172(43), 104(15), 91(30), 65(12)

¹H NMR spectrum is shown in Fig. 3.

In the NMR spectrum in a weak field, signals are present ppm: 9.39 s (1H, NH), 7.05-7.49 m (11H, tosyl and the naphthalene rings) 3.18 (2H, CH₂), 2.25 s (3H, CH₃). In the IR spectrum, a band of the stretching vibration of the SO₂ group is observed in the region of 1157 cm⁻¹. In the region of 2359 cm⁻¹, vibrations of the free NH group are observed.

The yield of 3-methyl-5-naphthyl-4-tosylamino-1H-pyrazole (III) was 80%, m.p. = 160-163 °C. A thin layer chromatogram in the eluent of toluene-ethyl acetate (1:1) showed the individuality of the

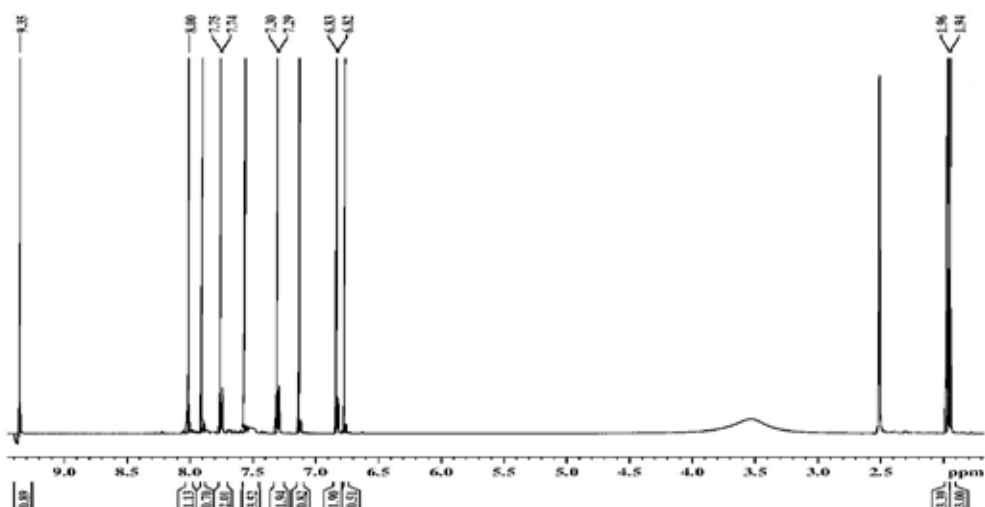


Fig. 4. NMR spectrum of 3-methyl-5-naphthyl-4-tosylamino-1H-pyrazole in DMSO- d_6

product. In the UV spectrum, there was a maximum absorption at the wavelength: $\lambda_{\max} = 232$ nm (ethanol) with a molar extinction coefficient $\epsilon = 351$. Mass Spectrum m/z : M^+ (377) 377 (100), 222(88), 205(24), 195(26), 154(35), 127(31), 91(35), 65(11), 42(15)

The ^1H NMR spectrum is shown in Fig. 4.

In the NMR spectrum in a weak field, there is a singlet of the proton NH group of the pyrazole ring $\delta = 9.35$ ppm, seven protons of the naphthalene ring and four protons of the tosyl ring with the chemical shift $\delta = 6.82$ -8.00 (m) ppm, the signal of three protons CH_3 of the tosyl ring group $\delta = 1.96$ ppm and three protons of the CH_3 group of the pyrazole ring, $\delta = 1.94$ ppm. In the IR spectrum, a band of the stretching vibration of the SO_2 group is observed in the region of 1162 cm^{-1} . In the region of 3264 cm^{-1} , vibrations of the free NH group are observed.

The yield of 3-methoxymethyl-5-naphthyl-4-tosylamino-1H-pyrazole (IV) was 77%, m.p. = 141 - 144°C . TLC in toluene-ethyl acetate (1:1) eluent showed the individuality of the product. In the UV spectrum, there was a maximum absorption at the wavelength: $\lambda_{\max} = 235$ nm (ethanol) $\epsilon = 694$ and $\lambda_{\max} = 352$ nm and (ethanol) $\epsilon = 108$. Mass Spectrum m/z : M^+ (407) 407 (100), 252(73), 220(90), 192(17), 154(26), 127(24), 91(33), 65(11), 45(15)

^1H NMR spectrum is shown in Fig. 5.

In the NMR spectrum in a weak field, there is a proton singlet of the NH group of the pyrazole ring $\delta = 9.52$ ppm, eleven protons of the naphthalene and tosyl rings with the chemical shift $\delta = 6.74$ -7.95 (m) ppm, two CH_2 protons with the chemical shift $\delta = 4.28$ ppm, the signal of three protons of the CH_3 group of the tosyl ring $\delta = 3.26$ ppm and three protons of the CH_3 group of the pyrazole ring $\delta = 1.88$ ppm. In the IR spectrum, a band of the stretching vibration of the SO_2 group is observed in the region of 1198 cm^{-1} . In the region of 2995 cm^{-1} , vibrations of the free NH group are observed.

Conclusion

- 1) General methodological principles for the synthesis of new p-toluenesulfonyl (tosyl) derivatives of aminopyrazoles have been developed.

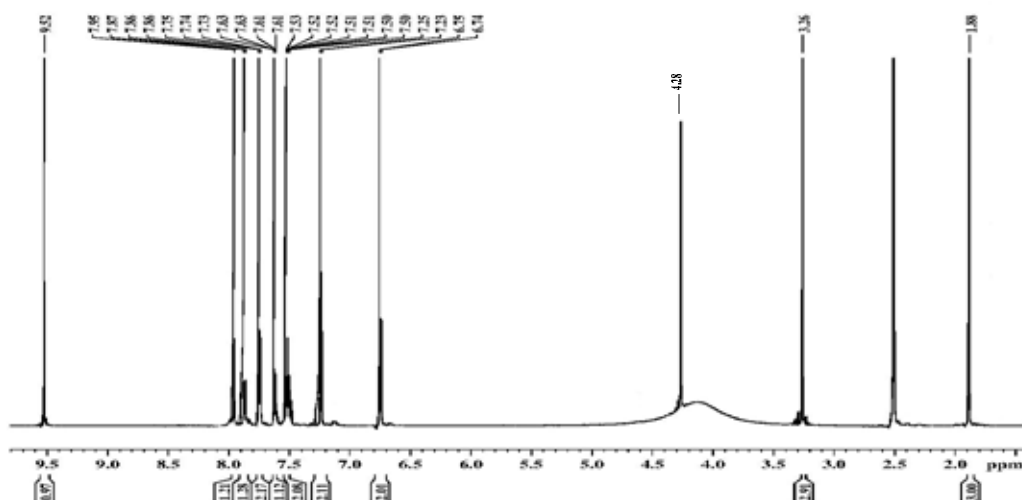


Fig. 5. NMR spectrum of 3-methoxymethyl-5-naphthyl-4-tosylamino-1H-pyrazole in DMSO-d₆

- 2) As a result of the work, four new previously unknown multifunctional aminopyrazoles were synthesized.
- 3) The structure of all newly synthesized compounds has been proved with the help of modern methods of spectral analysis: ¹H NMR, IR, UV spectroscopy and mass spectrometry.

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