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PROPERTIES OF 4-NITROSOPYRAZOLES WITH PERFLUOROALKYL SUBSTITUENT

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Abstract. *The paper investigates the structure and physicochemical properties of nitrosopyrazoles with perfluoroalkyl substituents. The authors pay special attention to the effect of fluorine atoms on the physicochemical properties of compounds and their acidity. IR spectroscopy confirms the existence of the dimer of 4-nitrosopyrazoles. In establishing the structure of the mass spectrum fragmentation ions, we assumed an aziridine rearrangement accompanying the decomposition of the compounds. The authors determined pKa for the synthesised hydroxyimino-β-diketones and nitrosopyrazoles by spectrophotometric method. Moreover, the authors determined the optical density of the solutions on a spectrophotometer and the acidity constant by graphical and analytical methods.*

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Introduction

Pyrazole is one of the most common heterocyclic compounds and used as an antifungal agent in agro-industry and as a modifier of various materials [1-3]. The presence of a nitroso group makes it possible to obtain various organic substances, change their functional groups, while changing their biological activity [4-7]. Therefore, the synthesis and study of the

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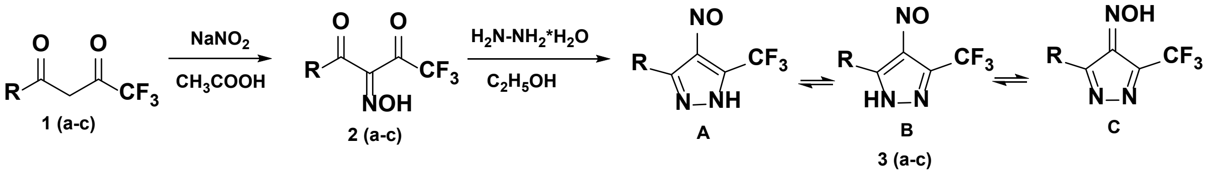
properties of nitrosopyrazoles with different functional groups [8] is an interesting issue of synthetic organic chemistry. Thus, the introduction of fluorine atoms into the side chain of substituted nitrosopyrazole is often used to precisely modify the physicochemical properties of such compounds: changing the *pKa* values of functional groups, increasing the stability, efficiency and the possibility of selective use of the substance [9, 10]. It is due to the high strength of the C-F bond and its polarity.

Previously, we synthesised 3(5)-(thiophen-2-yl)-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole, 3(5)-phenyl-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole, 3(5)-(naphthalene-2-yl)-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole; their structure was not proved. The purpose of this study is to prove the structure and study the properties of previously obtained nitrosopyrazoles with perfluoroalkyl substituent. One of the properties characterising the measure of chemical activity of a compound is the ability to donate a proton through a quantitative expression of the acidity index (*pKa*). In this study, we determined the acidity constant by graphical and analytical methods. To prove the structure of the synthesised compounds, ^{1}H NMR, ^{13}C NMR, IR spectra, chromato-mass spectra, UV spectra were recorded and the melting point for the obtained pyrazoles was determined.

Main body

Previously, we obtained nitrosation of β-diketones **1 (a-c)** followed by cyclocondensation of the resulting polyfluorinated oximes **2 (a-c)** for the first time nitrosopyrazoles **3 (a-c)** [11] (Scheme 1).



1, 2, 3 a – R = 2-thienyl, b – R = Ph, c – R = 2-naphthyl

Scheme 1. Nitrosation of polyfluorinated β-diketones

The obtained compounds **3 (a-c)** are green and blue-green coloured crystals.

The UV spectra of the synthesised 4-nitrosopyrazoles **3 (a-c)** contain absorption bands in the region of 713-716 nm, characteristic of the *n-π** transition of the nitroso group.

Compounds **3 (a-c)** are characterised by three tautomeric forms **A**, **B,** and **C** (Scheme 1). At the same time, *E*,*Z*-isomerisation is possible for the hydroxyimine tautomer **C** (Fig. 1).

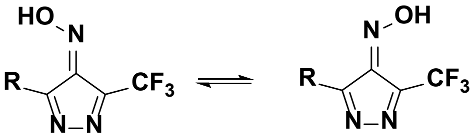


Fig. 1. *E*,*Z*-isomery of the hydroxyimine tautomer **C** of compounds **3 (a-c)**

The existence of dimers of 4-nitrosopyrazoles **3 (a-c)** was confirmed by IR spectroscopy. Characteristic nitroso group absorption bands for the *cis*-dimer in the region of 1414-1390 cm^{-1} are observed in the IR spectra of the obtained compounds **3 (a-c)**; the corresponding bands of the *trans* form at 1300-1250 cm^{-1} are absent. The hydroxyimine group of compounds **3 (a-c)** corresponds to the peaks at 3512-3501 cm^{-1} (NOH), 956-936 cm^{-1} (N-O). At the same time, the signal of nitroso group was recorded in the region 1606-1601 cm^{-1}. This also proves the presence of 4-nitrosopyrazoles **3** in three tautomeric forms (Scheme 1).

The spectra obtained by LCMS showed *m/z* peaks for compound **3a** - 494.01, **3b** - 482.09, **3c** - 582.12 with an intensity of 100% corresponding to the dimers of the obtained nitrosopyrazoles (Figure 2).

The presence of the dimer in the form (**I**) is possible due to the presence of an undivided electron pair on the nitrogen atom of compound **3** nitroso group. However, the reaction temperature (75 °C) is low to break the N=N multiple bond with an energy of 420 kJ/mol. Also, nitrogen-oxygen bonds are semipolar, i.e. each nitrogen atom should have a full positive charge; the formation of a multiple covalent bond is unlikely. Thus, the dimer structure has been assigned the form (**II**) shown in Fig. 2.

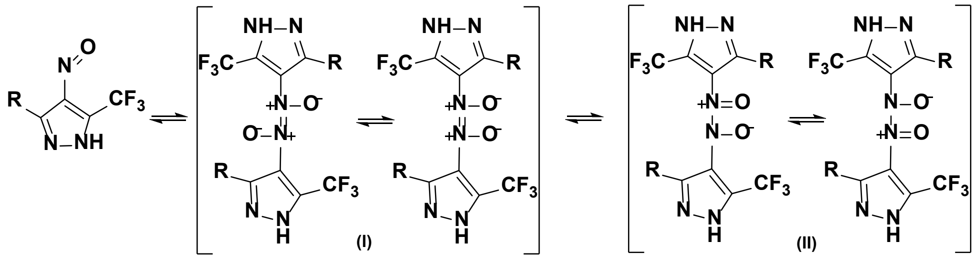


Fig. 2. Dimers of obtained nitrosopyrazoles **3**

The molecular ions of all synthesised 4-nitrosopyrazoles were recorded by gas chromatography - mass spectrometry. Fig. 3 shows the putative fragmentation decomposition of compounds **3 (a, b)**; they can proceed in three directions for each of the indicated compound.

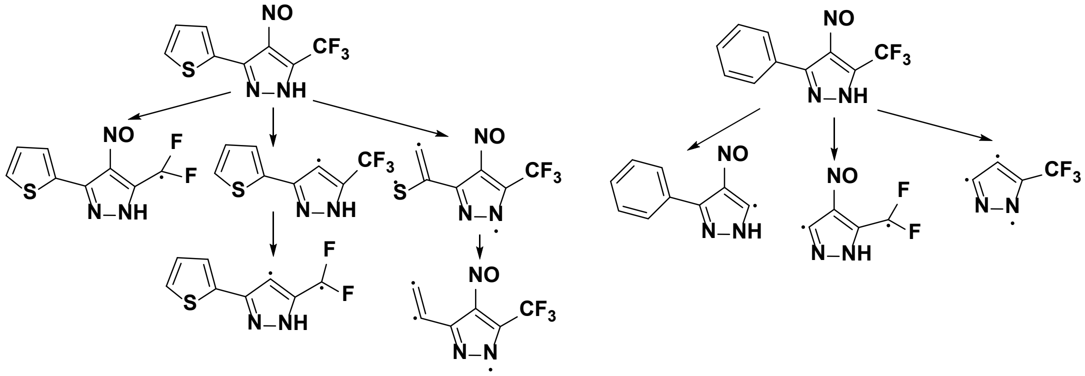


Fig. 3. Expected fragmentation decomposition of compounds **3 (a, b)**

When determining the structure of fragmentation ions, it was assumed that the decomposition of compounds is accompanied by aziridine rearrangement (Fig. 4) [10].

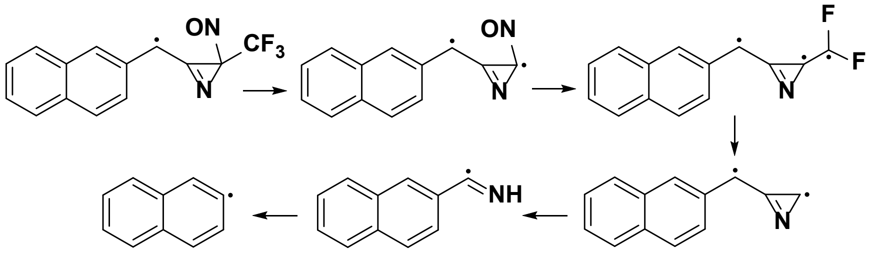


Fig. 4. Aziridine rearrangement of 3(5)-(naphthalene-2-yl)-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole **3c**

^{1}H NMR and ^{13}C NMR spectra were recorded to prove the structure of the obtained substances. The hydrogen atom signals of the aromatic rings, belonging to thienyl, phenyl and naphthalene groups, were recorded, respectively in the ^{1}H NMR spectra of 3(5)-(thiophen-2-yl)-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole **3a**, 3(5)-phenyl-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole **3b**, 3(5)-(naphthalene-2-yl)-4-nitroso-5(3)-(trifluoromethyl)-1*H*-pyrazole **3c** in the region 7.03-8.83 ppm. Signals of hydrogen atoms of the pyrazole cycle were detected in a weaker field in the region from 8.83 m.d. to 15.15 ppm. The theoretical location of the proton signals is consistent with the data obtained. Indeed, a 4-fold increase in the number of protons was detected in each spectrum. It is associated with the possibility of ring-chain tautomerism.

The signals of all carbon atoms located in the obtained molecules of organic compounds were detected in the NMR ^{13}C spectrum of synthesised substances **3 (a-c)**. The peaks related to quaternary carbon atoms have the largest chemical shifts.

Two sets of signals referred to the optical isomers of the compounds are present in all ^{1}H-^{13}C HSQC spectra of 4-nitrosopyrazoles **3**.

To investigate the properties of the obtained compounds, it is necessary to determine their acidity constants (*pKa*).

A number of synthesised trifluorine-containing oximes of *β*-diketones **2** and 4-nitrosopyrazoles **3** were investigated for their acidity by spectrophotometric method at 25±0.1 °C in phosphate buffer solutions for compounds **2** and in citrate buffer solutions for structures **3** [12-15]. The optical density of the solutions was determined on a spectrophotometer in the wavelength range 320-510 nm. The working concentration of alcohol solutions of the studied compounds is 10^{-4} mol/l.

To determine the analytical wavelengths of compounds **2** and **3**, we obtained a dependence diagram of optical density (D) on wavelength (λ) on a spectrophotometer. After that we prepared a series of buffer solutions; their value of optical density was determined by wavelength with $D_{\max}$ in 0.2N NaOH (λ=325 nm).

Table 1 shows the obtained *pKa* of compounds **2** and **3**; the following compounds are included for comparison: acetylacetone, trifluoroacetylacetone, compounds **1 (a, b)**, unsubstituted 1*H*-pyrazole, 3,5-dimethyl-4-nitroso-1*H*-pyrazole, and 3-(naphthalene-1-yl)-4-nitroso-1*H*-pyrazole [16-21].

Table 1. Acidity constants

Compound	R^{1}	R^{2}	R^{3}	pK_a
Acetylacetone	-	-	-	8.93
Trifluoroacetylacetone	-	-	CF_3	6.79
1a	thiophene-2-yl	-	CF_3	6.35±0.03
2a	thiophene-2-yl	NOH	CF_3	5.61±0.05
1b	phenyl	-	CF_3	6.54
2b	phenyl	NOH	CF_3	5.61±0.03
2c	naphthalene-2-yl	NOH	CF_3	5.87±0.06
Pyrazole	-	-	-	14.21
Dimethylnitrosopyrazole	CH_3	NO	CH_3	9.14
3a	thiophene-2-yl	NO	CF_3	3.50±0.04
3b	phenyl	NO	CF_3	3.52±0.04
Naphthalene-nitrosopyrazole	naphthalene-1-yl	NO	-	8.41±0.01
3c	naphthalene-2-yl	NO	CF_3	3.74±0.04

We obtained the values of ionisation ratio I during the experiment. They represent the ratios of nitrosopyrazolate ion concentration to the concentration of the undissociated form depending on the pH values of the solutions. We then calculated lgI values at each pH value of the buffer solutions at least 5-6 times. They overlapped the region with the half nitrosopyrazoles ionisation.

The dependence of lgI on pH was found to be linear on the diagram for 3-(thiophen-2-yl)-4-nitroso-5-(trifluoromethyl)-1*H*-pyrazole with the tangent of the slope of the straight line close to one. Consequently, we observe the process of molecules ionisation. This process is described by the equation: $lgI = \text{pH} - pKa$.

Since the value of pKa is almost numerically equal to the pH value of the solution, one can conclude the presence of the protonated and deprotonated forms of compounds **2** and **3** in equal concentrations.

Pyrazole is an amphoteric compound with the N atom is the majority centre and the NH group is the acidity centre. However, the pKa value of unsubstituted pyrazole is 14.21. This indicates a greater occurrence of acidic properties. Therefore, by comparing the pKa values, the acidity of fluorine-containing compounds is increased compared to their non-fluorinated analogues. For example, the introduction of a trifluoromethyl substituent into the naphthalene nitrosopyrazole molecule significantly reduces pKa from 8.41 to 3.74. The introduction of a hydroxyimino group into compounds **1(a, b)** increases the acidity of structures **2(a, b)** by ≈ 1.

Conclusion

We have studied the effect of perfluorinated substituent on the acidity constant of compounds: introduction of a fluorine-containing substituent into the molecule increases the acidity of the substance. The structure of the synthesised compounds **3 (a-c)** has been determined for the first time, the presence of isomeric forms with respect to the nitroso group and substituents at the 3 and 5 positions has been established.

Experimental part

The ^{1}H, ^{13}C NMR and ^{1}H-^{13}C HSQC spectra were recorded at the Krasnoyarsk Regional Centre for Collective Use of Federal Research Center Krasnoyarsk Scientific Center of the Siberian Branch of the RAS on a Bruker Avance III 600 MHz (150.9 MHz) FTIR spectrometer equipped with sensitive helium probes with diameters of 5 mm and 1.7 mm. TMS has been applied as an internal standard.

Chromato-mass spectra were obtained on ISQ 7610 Single Quadrupole GC-MS and Shimadzu LC/MS-2020 instruments. Methyl alcohol was used as mobile phase. The method of ionisation is electronic impact (EI).

We recorded the IR spectra on a SIMEX FT-801 (FT-801) FT-IR spectrometer with a spectral range of 450 to 5700 cm^{-1}.

We recorded UV spectra on a HELIOS OMEGA spectrophotometer equipped with a wolfram-halogen lamp in 1 cm diameter quartz cuvettes at a concentration of 1-10^{-4} mol/L for 200-400 nm and a concentration of 1-10^{-2} mol/L for 400-800 nm in ethanol.

We determined melting temperatures in open capillaries on a PTP instrument (TU25-11-1144-76).

Nitrosopyrazoles with perfluoroalkyl substituent **3 (a-c)** were obtained previously [10].

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