Different reactivities of regioisomeric azimines, adducts of phthalimidonitrene with 5-bromospiro[1-pyrazoline-3,1′-cyclopropane]

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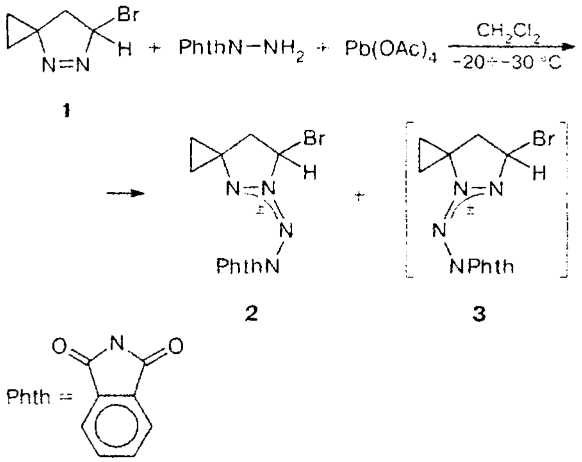
The addition of the phthalimidonitrene fragment, resulting from oxidation of *N*-aminophthalimide by lead tetraacetate at −20 to −30 °C, to the N=N-bond of 5-bromospiro[1-pyrazoline-3,1′-cyclopropane] (**1**) affords, apart from the stable 5-bromo-*N*-{spiro[1-pyrazolinio-3,1′-cyclopropane]}-*N*-phthalimidoamide (azimine **2**), regioisomeric azimine **3**, which is completely transformed into 3-acetoxy-*N*-{spiro[1-pyrazolinio-5,1′-cyclopropane]}-*N*-phthalimidoamide (**4**) under the reaction conditions. The acetoxy group in this product easily undergoes nucleophilic substitution on treatment with MeOH, NaN_3, or the starting bromopyrazoline **1**. The structures of azimines obtained were established using NMR spectra, and the structure of the product of reaction of **4** with **1** was additionally proved by X-ray difraction data.

Key words: 5-bromospiro[1-pyrazoline-3,1′-cyclopropane], 3-substituted *N*-{spiro[1-pyrazolinio-5,1′-cyclopropane]}-*N*-phthalimidoamides (azimines), nucleophilic substitution, NMR spectra, X-ray diffraction analysis.

Previously, we showed[1] that the addition of an *N*-phthalimidonitrene fragment to 5-bromospiro[1-pyrazoline-3,1′-cyclopropane] (**1**) under the conditions of oxidation of *N*-aminophthalimide by lead tetraacetate at −20 to −30 °C affords *N*-{5-bromospiro[1-pyrazolinio-3,1′-cyclopropane]}-*N*-phthalimidoamide (**2**) in ~35% yield. About 30—35% of the starting bromopyrazoline **1** was recovered unchanged, despite some variation of the reaction conditions (the temperature varied from −10 to −30 °C; the time of addition of $Pb(OAc)_4$ was 20 to 90 min; alternating addition of *N*-aminophthalimide and $Pb(OAc)_4$ was used). Judging from the ^1H NMR spectra of the reaction mixtures, in addition to **1** and azimine **2**, the products contained one more compound (**A**) exhibiting a set of signals typical of the three-spin system of a pyrazoline ring. We were unable to isolate and identify this compound, which formed in 15—18% yield. In any case, we could not assign structure **3** to this product because the signal of the methine proton of the CHBr group (δ 6.61) occurred in a lower field than the corresponding signal in azimine **2** (δ 6.44), which is at variance with the spectral data for other regioisomeric azimines.[1,2]

In this work, we attempted to identify compound **A** by converting it into more stable derivatives of spiro[pyrazolinecyclopropane]; one derivative was isolated in the crystalline state and characterized by X-ray diffraction data, along with the ^1H and ^{13}C NMR spectra.



To increase the concentration of the unknown compound **A**, the reaction mixture (~0.8 g) resulting from the reaction of equimolar amounts of bromopyrazoline **1**, *N*-aminophthalimide, and $Pb(OAc)_4$ was treated with ~10 mL of ether to separate most of azimine **2** as a crystalline product.[1] The filtrate was concentrated and the residue was used for the subsequent chemical trans-

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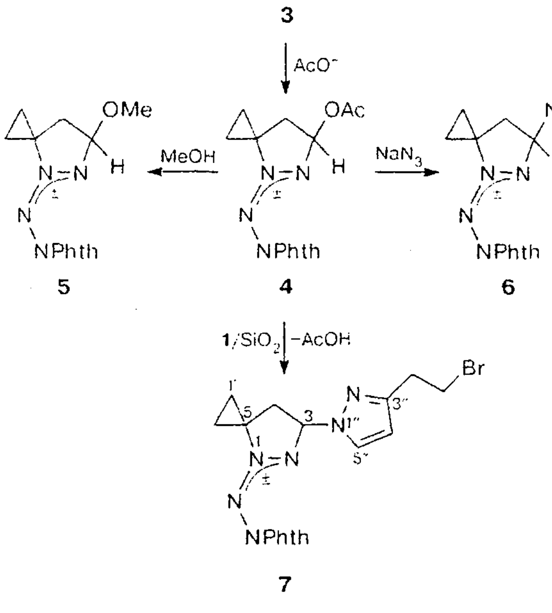
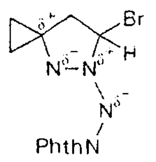
formations. The ^{1}H NMR spectrum of the residue contained a singlet for the acetyl group at δ 2.09 whose integral intensity was correlated with the protons of the pyrazoline ring of compound **A** and which was not observed in our previous experiments on the synthesis of azimines from 5-phenyl-or 5-azidospiro[1-pyrazoline-3,1'-cyclopropanes] structurally related to compound **1**.[1]

Apparently, the addition of the *N*-phthalimidonitrene fragment to pyrazoline **1** gives initially both azimine regioisomers **2** and **3**; however, the latter undergoes easy nucleophilic substitution of an OAc group for the Br atom under the reaction conditions, being thus converted into *N*-{3-acetoxyspiro[1-pyrazolinio-5,1'-cyclopropane]}-*N*-phthalimidoamide (**4**), which is exactly the compound **A** detected in the reaction mixture by NMR. This compound proved to be relatively unstable, which precluded its isolation in a pure state. When the reaction mixture remaining after separation of azimine **2** is treated with MeOH and separated by preparative TLC (Al_2O_3, benzene—AcOEt, 3 : 1), a new compound (R_f 0.46) containing no acetoxy group was isolated instead of acetoxy derivative **4**. The ^{1}H NMR spectrum of the resulting compound also corresponded to the structure of spiro-[1-pyrazolinio-5,1'-cyclopropane]-*N*-phthalimidoamide, but the low-field signal for the methine proton of the pyrazoline ring was substantially shifted and occurred at δ 5.38 (Δδ = 1.06 with respect to the corresponding signal of azimine **4**). In addition, a signal for a methoxy group was detected unambiguously in the ^{1}H and ^{13}C NMR spectra. Apparently, on treatment with MeOH, azimine **4** is transformed according to the same nucleophilic substitution pathway to give more stable methoxy derivative **5**. In addition, in the observed sequence of transformations of azimines, **3** → **4** → **5**, the aminophthalimide substituent remains attached to the N atom of the pyrazoline ring adjacent to the cyclopropane fragment.



Previously,[3] we have shown that the Br atom in pyrazoline **1** can be replaced by the azido group on treatment with NaN_3 in aqueous acetone (20 °C, 18 h). In order to establish the degree of mobility of the substituents in the pyrazolinio-*N*-phthalimidoamide regioisomers, we studied the reaction of NaN_3 with a mixture of azimines **2** and **4** (molar ratio ~3 : 1, according to the ^{1}H NMR spectrum), isolated as a yellow precipitate upon the addition of ~3 mL of ether to the products (~0.8 g) of the reaction of equimolar amounts of bromopyrazoline **1**, *N*-aminophthalimide, and $Pb(OAc)_4$. Analysis of the reaction products by ^{1}H NMR spectroscopy showed that after 3 h at 20 °C, bromine-containing azimine **2** is recovered virtually unchanged, whereas acetoxy derivative **4** is completely converted into azide **6**, identical to the minor product[1] obtained upon the addition of the *N*-phthalimidonitrene fragment to 5-azidospiro[1-pyrazoline-3,1'-cyclopropane] at the N atom remote from the azido group.

The possibility of easy nucleophilic substitution of the functional groups in regioisomeric azimines **3** or **4** (unlike that in azimine **2**) is in good agreement with the electron density distribution in the 3-X-1-pyrazolinio-*N*-phthalimidoamide system present in compounds **3—6**, according to which the substituted N(1) atom of the pyrazoline ring bears a partial positive charge, while negative charge can be transferred on the leaving group located in position 3.



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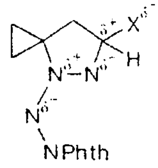

3—6

An attempted isolation of the hypothetical azimine **4** by TLC on SiO_2 without pre-treatment of the reaction mixture with methanol led to an unexpected result. This gave several chromatographic zones containing, in particular, the initial bromopyrazoline **1**, stable regioisomeric bromoazimine **2**, and the products of transformation of *N*-aminophthalimide, which are formed inevitably during its oxidation by $Pb(OAc)_4$ (see Ref. 4). However, none of these zones exhibited ^{1}H NMR signals corresponding to azimine **4**. Instead, a new crystalline compound (benzene—AcOEt, 3 : 1, R_f 0.26) was isolated. In addition to the spiro[1-pyrazolinecyclopropane] and phthalimide fragments, it contained the (2-bromoethyl)pyrazole fragment, as indicated by two triplets at δ 3.19 and δ 3.61 and two doublets at δ 6.17 and δ 7.54.

In order to determine unambiguously the structure of the obtained compound, *N*-{3-[3-(2-bromoethyl)pyrazol-1-yl]spiro[1-pyrazolinio-5,1'-cyclopropane]}-*N*-phthalimidoamide (**7**), it was studied by X-ray diffraction analysis (Fig. 1). The main geometric parameters of the molecule are presented in Table 1. First, it should be noted that the resulting compound is an azimine derivative in which the PhthN substituent is attached to the N atom of the pyrazoline ring closest to the cyclopropane fragment, *i.e.*, this compound contains the same group as azimines **4**—**6**. Comparison of the geometric parameters of molecule **7** with the X-ray diffraction data obtained previously[1] for molecule **2** shows that the most substantial difference between the substituted pyrazoline fragments is in the N—C(substituent) bond lengths. Whereas the N(2)—C(13) bond length in compound **7**, equal to 1.469 Å, corresponds to a single bond, the corresponding bond in compound **2** is substantially lengthened and equals 1.520(10) Å. It is noteworthy that in azimines **7** and **2**, the influence of the *N*-phthalimidoamide substituent on the N—C(spiro) bond length is much less pronounced (1.477(7) and 1.460(10) Å, respectively).

The azimine system in compound **7**, like that in **2**, is virtually planar: the N(2)N(1)N(3)N(4) torsional angle is equal to zero to within the detemination error. The N(2)—N(1) and N(1)—N(3) bond lengths (1.285(7) and 1.293(7) Å, respectively) points to electron density delocalization over the N(2)N(1)N(3) fragment due to the conjugation of the N(2)—N(1) double bond with the lone electron pair of N(3). The pyrazoline fragment is markedly flattened; the root-mean-square deviation of atoms from the heterocycle plane is ~0.03 Å. The plane of the pyrazole substituent is rotated through 93° relative to the plane of the pyrazoline fragment.

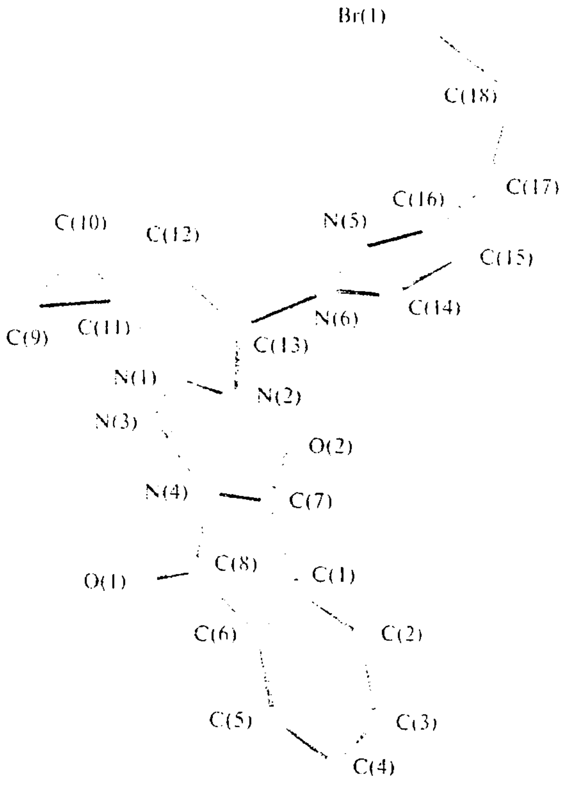

Fig. 1. General view of molecule **7**.

Table 1. Main geometric parameters of molecule **7**

Bond	*d*/Å	Bond	*d*/Å
C(9)—C(11)	1.524(8)	N(1)—N(2)	1.285(7)
C(9)—C(10)	1.533(9)	N(1)—N(3)	1.293(7)
C(10)—C(11)	1.522(8)	N(1)—C(11)	1.477(7)
C(11)—C(12)	1.468(9)	N(2)—C(13)	1.469(7)
C(12)—C(13)	1.546(8)	N(5)—C(16)	1.321(8)
C(14)—C(15)	1.357(8)	N(5)—N(6)	1.383(7)
C(15)—C(16)	1.440(8)	N(6)—C(14)	1.322(7)
C(5)—C(6)	1.387(8)	N(6)—C(13)	1.460(7)

Angle	ω/deg	Angle	ω/deg
N(2)—N(1)—N(3)	126.6(5)	C(14)—N(6)—N(5)	112.5(5)
N(2)—N(1)—C(11)	115.4(5)	C(14)—N(6)—C(13)	129.3(5)
N(3)—N(1)—C(11)	118.0(5)	N(5)—N(6)—C(13)	117.9(4)
N(1)—N(2)—C(13)	107.4(5)	C(12)—C(11)—N(1)	105.4(4)
N(1)—N(3)—N(4)	111.2(5)	N(2)—C(13)—C(12)	107.9(5)
C(16)—N(5)—N(6)	104.6(4)	C(11)—C(12)—C(13)	103.3(5)

The formation of compound **7** during chromatography on SiO_2 seems to be due to the easy heterolysis of the C—O bond in acetoxyazimine **4** and to the addition of the electrophilic part of the molecule to the N(1) atom of the starting bromopyrazoline **1**, which is present in a sufficient amount in the reaction mixture. As follows from the data on acylation and protonation of bromopyrazoline **1** (see Ref. 5), migration of the Br atom and cyclopropane ring opening giving rise to a bromoethylpyrazole fragment occur simultaneously in this compound, which ultimately yields compound **7**.

Thus, attachment of the *N*-phthalimidoamide substituent to different nitrogen atoms of the pyrazoline ring results in azimine regioisomers, in particular, bromo derivatives **2** and **3**, in which the mobility of the substituent (bromine) located in the α-position relative to the endocyclic N—N bond is appreciably different. Unlike azimine **2**, in azimine **3**, nucleophilic substitution of Br by an acetoxy group takes place even under conditions of its synthesis (−30 °C). The subsequent replacement of the OAc group in the resulting azimine **4** on treatment with MeOH and NaN_3 in aqueous acetone or with pyrazoline **1** on the SiO_2 surface proceeds equally easily. It should be noted that azimine **2** does not enter into nucleophilic substitution reactions of this type under the same conditions.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 (200 and 50.3 MHz) and Bruker AM-300 (300 MHz) spectrometers for solutions in $CDCl_3$ containing 0.05% Me_4Si as the internal standard. Mass spectra were run on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct injection). IR spectra were measured on a Bruker IFS-113v spectrometer in thin films. The starting 5-bromospiro[1-pyrazoline-5,1′-cyclopropane] (**1**) and *N*-aminophthalimide were prepared by procedures described previously;[3,6] lead tetraacetate was recrystallized from AcOH and dried in a vacuum desiccator prior to use. The solvents were distilled. The preparative TLC was carried out on 20 × 20 cm plates with a nonfixed layer of the adsorbent (silica gel L 40/100 μm Chemapol, layer thickness 2 mm).

The crystals of **7** were monoclinic. At 110 K, $a = 8.571(1)$ Å, $b = 8.408(1)$ Å, $c = 12.759(1)$ Å, $V = 898.7(1)$ Å^3, $Z = 2$, $d_{calc} = 1.586$ g cm^{-3}, space group *Pn*. The unit cell parameters and the intensities of the 8158 reflections were measured on a Bruker 1K SMART CCD automated diffractometer (Mo$K\alpha$ radiation, ω scanning, $2\theta_{max} = 60°$). The data were processed using the SAINT program package.[7] Absorption corrections were applied by means of the SADABS program package.[8] The structure was solved by the direct method and refined by the full-matrix least-squares method in the anisotropic approximation. The hydrogen atoms in the molecule are arranged geometrically and included in refinement in terms of the "riding" model. The final discrepancy factors: $wR_2 = 24.11\%$ over all the 4391 independent reflections and $R_1 = 8.45\%$ over 3306 reflections with $I > 2\sigma(I)$. All the crystal structure calculations were performed using the SHELXS-97 program package.[9]

***N*-{3-Acetoxyspiro[1-pyrazolinio-5,1′-cyclopropane]}-*N*-phthalimidoamide (4)** was identified using ^{1}H and ^{13}C NMR spectra of two samples taken from the reaction mixture formed upon the reaction of equimolar amounts (2.5 mmol) of bromopyrazoline **1**, *N*-aminophthalimide, and Pb(OAc)$_4$ by the procedure described previously.[1]

Sample A. The organic residue (~0.8 g) resulting from the removal of the solvents was treated with ~10 mL of ether; the major part of azimine **2** was separated as a crystalline product,[1] the filtrate was concentrated, and the residue (~0.56 g) was analyzed by spectroscopy and used in subsequent transformations. According to ^{1}H NMR spectrum, the molar ratio of compounds **1**, **2**, and **4** was ~1.8 : 0.3 : 1.

Sample B. Ether (~3 mL) was added with stirring to the residue (~0.8 g) obtained after the reaction and removal of the organic solvents, and the precipitate (0.28 g) consisting mainly of azimines **2** and **4** in ~3 : 1 molar ratio was separated.

Compound 4. ^{1}H NMR (CDCl$_3$), δ: 1.29 and 2.07 (both m, *cyclo*-C$_3$H$_4$); 2.09 (s, Me); 2.37 and 2.93 (both dd, H(4), $^2J = 13.2$ Hz); 6.61 (dd, H(3), $^3J = 6.7$ and 2.8 Hz); 7.70 and 7.84 (both m, *o*-C$_6$H$_4$). ^{13}C NMR (CDCl$_3$), δ: 14.2 and 16.4 (CH$_2$CH$_2$); 21.2 (Me); 35.6 (C(4)); 56.1 (C(5)); 88.9 (C(3)); 123.5, 131.1 and 134.0 (C$_6$H$_4$); 163.6 (CO); 169.9 (COO).

***N*-{3-Methoxyspiro[1-pyrazolinio-5,1′-cyclopropane]}-*N*-phthalimidoamide (5)**. Methanol (2.0 mL) was added to sample A (0.30 g) (see above) containing ~27% azimine **4**. The mixture was kept for 8 h at 20 °C and separated by preparative TLC (Al$_2$O$_3$, benzene—AcOEt, 3 : 1) to give 60 mg (~85% based on azimine **4**) of methoxy derivative **5** ((R_f 0.46) as a yellow finely crystalline powder, m.p. 147—150 °C. ^{1}H NMR (CDCl$_3$), δ: 1.22 and 2.08 (both m, each 2 H, *cyclo*-C$_3$H$_4$); 2.32 and 2.73 (both dd, each 1 H, H(4), $^2J = 13.0$ Hz); 3.42 (s, 3 H, OMe); 5.38 (dd, 1 H, H(3), $^3J = 6.6$ and 2.9 Hz); 7.72 and 7.85 (both m, each 2 H, *o*-C$_6$H$_4$). ^{13}C NMR (CDCl$_3$), δ: 14.1 and 16.2 (CH$_2$CH$_2$); 35.7 (C4)); 55.8 (OMe); 56.2 (C(5)); 95.8 (C(3)); 123.4, 131.2 and 134.0 (C$_6$H$_4$); 164.0 (CO).

***N*-{3-Azidospiro[1-pyrazolinio-5,1′-cyclopropane]}-*N*-phthalimidoamide (6)**. A solution of NaN$_3$ (0.08 g, 1.2 mmol) in 1 mL of water was added to a solution of sample **B** (0.25 g) (see above) containing ~0.2 mmol of azimine **4** in 2 mL of acetone and the mixture was stirred for 3 h at 20 °C. Acetone was removed *in vacuo*, the residue was extracted with CH$_2$Cl$_2$, the solvent was evaporated, and the resulting solid material was separated by preparative TLC (SiO$_2$, benzene—ether, 3 : 1) to give the starting azimine **2** (0.18 g) (R_f 0.37) unreacted with NaN$_3$ and azido derivative **6** (0.05 g) (R_f 0.46) (~80% based on azimine **4**) as a yellow finely crystalline powder, m.p. 143—145 °C. The ^{1}H and ^{13}C NMR spectra of compound **6** were fully identical to those of the minor isomer identified previously[1] upon the addition of *N*-phthalimidonitrene to 5-azidospiro[1-pyrazoline-3,1′-cyclopropane].

***N*-{3-(2-Bromoethyl)pyrazol-1-ylspiro[1-pyrazolinio-5,1′-cyclopropane]}-N-phthalimidoamide (7).** Sample **A** (0.18 g) containing ~27% azimine **4** and ~48% starting bromopyrazoline **1** was applied onto a 20 × 20 cm plate with SiO$_2$ and eluted with a 3 : 1 benzene—AcOEt mixture to give 42 mg (~65% based on azimine **4**) of compound **7** (R_f 0.26) as a yellowish beige fine crystals, m.p. 158—160 °C. ^{1}H NMR, δ: 1.15—1.35 (m, 2 H, H(1′) and H(2′) directed away from the N atom of the heterocycle); 2.02—2.20 (m, 2 H, H(1′) and H(2′) oriented toward the N atom of the heterocycle); 2.68 (dd, 1 H, H(4), $^2J = 13.0$ Hz, $J = 3.5$ Hz); 3.01 (dd, 1 H, H(4), $^2J = 13.0$ Hz, $J = 7.5$ Hz); 3.19 (t, 2 H, CH$_2$, $J = 7.1$ Hz); 3.61 (t, 2 H, CH$_2$Br, $J = 7.1$ Hz); 6.16 (d, 1 H, H(4″), $J = 2.4$ Hz); 6.38 (dd, 1 H, H(5), $J = 7.6$ Hz, $J = 3.5$ Hz); 7.53 (d, 1 H, H(5″), $J = 2.4″$); 7.70 and 7.82 (both m, 2+2 H, C$_6$H$_4$). ^{13}C NMR, δ: 13.9 and 16.2 (C(1′) and C(2′)); 31.4 and 32.3 (BrCH$_2$CH$_2$); 36.4 (C(4)); 56.5 (C(5)); 80.7 (C(3)); 105.7 (C(4″)); 128.8 (C(5″)); 123.5, 131.2, and 134.1 (C_γ, C_α and C_β atoms of the benzene ring); 150.9 (C(3″)); 163.8 (2 CO). Partial MS, *m/z* (I_{rel} (%)): 430 and 428 (0.3) [M]+, 307 and 305 (3), 292 (11), 104 (100). Found (%): N, 19.12. C$_{18}$H$_{17}$BrN$_6$O$_2$. Calculated (%): N, 19.58. X-Ray diffraction data are listed in Table 1. The complete tables of the atomic coordinates, thermal parameters, bond lengths, and bond angles were deposited with the Cambridge Structural Database

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