Addition of diazocyclopropane generated *in situ* to vinyl bromide and chemical transformations of the resulting 5-bromospiro(1-pyrazoline-3,1′-cyclopropane)

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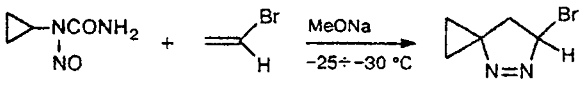
The reaction of diazocyclopropane generated *in situ* with vinyl bromide occurs as regioselective 1,3-dipolar cycloaddition to give 5-bromospiro(1-pyrazoline-3,1′-cyclopropane) in ~60% yield. Reactions of the latter with nucleophilic reagents, which can occur both with retention and opening of the cyclopropane ring, were studied.

Key words: 5-R-spiro(1-pyrazoline-3,1′-cyclopropanes), 3(5)-(2-R-ethyl)pyrazoles, 1,3-dipolar cycloaddition, nucleophilic substitution, NMR spectra.

Unlike the majority of aliphatic diazo compounds, which are sufficiently stable under ordinary conditions, diazocyclopropane (DACP) is an extremely labile compound, which has not been detected in the free state.[1] This restricts considerably the possibility of trapping it by other substrates, in particular by unsaturated compounds. Until now, only strained cyclo- and polycycloalkenes,[2,3] conjugated dienes,[3] and α,β-unsaturated compounds with electron-withdrawing substituents (CN, COR, COOR)[4—6] have been studied as efficient traps for DACP, which react to give products of 1,3-dipolar cycloaddition.

In a continuation of these investigations, we studied the reaction of DACP generated *in situ* with vinyl bromide and found that a product of regioselective 1,3-dipolar cycloaddition, *viz.*, 5-bromospiro(1-pyrazoline-3,1′-cyclopropane) (**1**), is formed rather easily in up to 60% yield. This fact is somewhat unexpected, since noncatalytic reactions of nonsubstituted vinyl halides with other diazo compounds have not been reported.[7]

The reaction was carried out in the usual way. Diazocyclopropane was generated at −25 to −30 °C and trapped by adding *N*-nitroso-*N*-cyclopropylurea (NCU) to a mixture of vinyl bromide and MeONa (molar ratio ~1 : 2 : 1.2). CH_2Cl_2 or toluene with an addition of MeOH (~15%) were used as the solvents. The ^1H NMR spectrum of the residue obtained after aqueous workup of the reaction mixture and removal of organic solvents showed five distinct multiplets (see Experimental) along with weak signals, which were mostly located around δ 2.9—3.8 and 0.9—1.8 and obviously originated from several by-products. The integral intensity of signals of the main compound with respect to the overall intensity of all signals in the spectrum was ~72—75%. The main compound had the structure of a 5-substituted spiro(1-pyrazoline-3,1′-cyclopropane). This followed unambiguously from the presence of a three-spin system of proton signals observed as a doublet of doublets each in addition to the signals of the cyclopropane ring protons and the chemical shifts of signals for protons and carbon atoms in the NMR spectra. The retention of a bromine atom in the pyrazoline formed was established on the basis of chromato-mass spectrometric data. Column chromatography (neutral Al_2O_3, CCl_4 as the eluent) or TLC (silica gel, ether—benzene, 1 : 1, as the eluent) gave pyrazoline **1** of 92—95% purity. These specimens were subsequently used for the study of some chemical transformations of compound **1**.



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For example, the reaction of compound **1** with MeONa/MeOH at 25 °C for 2 h gave 3(5)-(2-methoxyethyl)pyrazole (**2**) and 3(5)-vinylpyrazole (**3**) in a (3—4) : 1 ratio as the main products. Vinylpyrazole **3** was identified by comparison with a previously synthesized sample.[2] Pyrazole **2** was isolated by preparative GLC and characterized by ^1H and ^{13}C NMR spectra.

Monitoring of the reaction of compound **1** with CD_3ONa in a CD_3OD solution by ^1H NMR spectroscopy showed that at temperatures below −20 °C, pyrazoline **1** remained virtually unchanged for 1 h. At −15 to −10 °C, we observed a noticeable decrease in the intensity of the low-field H(5) signal and a change in the multiplicity of signals of geminal protons at C(4), which

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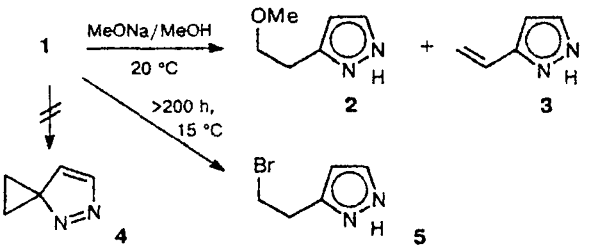
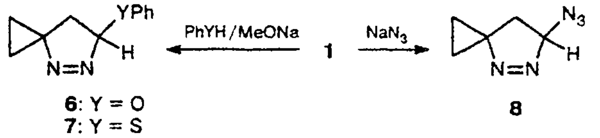
were transformed into two doublets; this indicated that an H—D exchange occurred at the C(5) atom of pyrazoline **1**. At ~20 °C, signals characteristic of pyrazoles **2** and **3** appeared in the ^{1}H NMR spectrum after 1 h. Although weak signals corresponding to by-products were present at δ 2.9—3.9 and δ 1.0—1.8, no signals in the olefin region (except for those of the vinylic protons of compound **3**), which might indicate the possible dehydrobromination of compound **1** into 4,5-diazaspiro[2,4]-heptadiene (**4**), were observed. However, it cannot be ruled out that the formation of pyrazoles **2** and **3** may actually involve unstable pyrazole **4**.



Pyrazoline **1** partly underwent resinification on storage in an inert atmosphere at 15 °C for 8—10 days. However, a considerable fraction of the material solubilized on addition of benzene. TLC of this solution on neutral Al_2O_3 gave the product of isomerization of compound **1**, namely, 3(5)-(2-bromoethyl)pyrazole (**5**), in 57% yield. The reaction of compound **1** with an equimolar amount of Et_3N in CH_2Cl_2 at 15 °C for 6 h resulted mostly in the isomerization of **1** into pyrazole **5** rather than in its dehydrobromination. The yield of product **5** did not exceed 40%, while the **5** : **3** molar ratio was ≈ 5 : 1. The mass spectrum of bromide **5**, unlike the spectrum of the original bromopyrazoline **1**, contained a much more abundant peak of molecular ion. The signals of the CH and CH_2 groups in the ^{1}H NMR spectrum of compound **5** were virtually identical with those of the corresponding protons of pyrazole **2**, which indicates the similarity of the structures of these compounds.

In order to determine whether nucleophilic substitution of the Br atom in pyrazoline **1** occurring with the retention of the spiro(1-pyrazoline-3,1′-cyclopropane) is possible, we studied the reaction of compound **1** with stronger nucleophilic reagents. It was found that the replacement of the Br atom in pyrazoline **1** on treatment with sodium phenoxide or thiophenoxide at 20 °C actually occurs without opening of the cyclopropane ring. Using preparative TLC, 5-phenoxy- and 5-phenylthiospiro(1-pyrazoline-3,1′-cyclopropanes) (**6** and **7**) were isolated in 50—55% yields. The ^{1}H NMR spectra of these compounds contained signals of the same three-spin system of the pyrazoline ring protons as the starting compound **1**. In addition, analysis of the ^{1}H NMR spectra of the reaction mixtures made it possible to conclude that they did not contain compounds analogous to pyrazoles **2** and **5**.

The reaction of pyrazoline **1** with a 1.5-fold molar excess of sodium azide in aqueous acetone for 18 h gave the corresponding 3-azidopyrazoline **8**. The product was found to be a very stable compound, which did not undergo apparent changes on refluxing in CCl_4 and did not react with phenylacetylene at 80 °C (at higher temperatures, azide **8** underwent noticeable resinification).



Thus, DACP generated *in situ* can rather readily enter 1,3-dipolar cycloaddition with vinyl bromide to give relatively stable pyrazoline **1**, which reacts with strong nucleophiles (PhO^-, PhS^-, N_3^-) with replacement of the Br atom and with retention of the spirane structure. However, attempts to perform nucleophilic substitution of the Br atom in pyrazoline **1** using p-$NO_2C_6H_4ONa$, NaCN, $NaCH(COOMe)_2$, and primary amines failed.

Experimental

^{1}H 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% $SiMe_4$ as the internal standard. GC-MS spectra were obtained on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, RSL-200 30 m-long capillary column). IR spectra were recorded in thin films on a Bruker IFS-113v spectrometer.

5-Bromo(1-pyrazoline-3,1′-cyclopropane) (1). *N*-Nitroso-*N*-cyclopropylurea (1.5 g, 11 mmol) was added in small portions over a period of 20 min at −30 to −25 °C to a vigorously stirred mixture of MeONa (0.81 g, 15 mmol) and vinyl bromide (2.45 g, 23 mmol) in MeOH (3 mL) and CH_2Cl_2 (20 mL). The mixture was stirred for 10 min, slowly warmed to 10 °C, and treated with saturated aqueous NH_4Cl (30 mL). The organic layer was dried with Na_2SO_4, the solvents were removed *in vacuo*, and the residue (1.22 g) was purified by column chromatography (neutral Al_2O_3, CCl_4 as the eluent) to give pyrazoline **1** as a yellowish liquid, yield ~60%, purity 92—95% (according to the ^{1}H NMR spectral data). ^{1}H NMR, δ: 6.39 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 3.0 Hz, H-5); 2.50 (dd, 1 H, J_1 = 8.0 Hz, J_3 = 14.5 Hz, H-4a); 2.12 (dd, 1 H, J_2 = 3.0 Hz, J_3 = 14.5 Hz, H-4b); 1.84 and 1.27 (both m, 2×2 H, CH_2CH_2). ^{13}C NMR, δ: 78.6 (C-5); 68.2 (C-3); 35.3 (C-4); 14.8 and 12.9 (CH_2CH_2). MS (in part), m/z (I_{rel} (%)): 176 (0.7) and 174 (0.7) $[M]^+$, 95 (12), 81 (10), 67 (100).

3(5)-(2-Methoxyethyl)pyrazole (2). MeONa (0.103 g, 1.9 mmol) was added to a stirred solution of pyrazoline **1** (0.144 g, 1.3 mmol) in MeOH (2 mL), and stirring was continued for 2 h at 20 °C. Then the MeOH was removed *in vacuo*, CH_2Cl_2 (6 mL) was added to the residue, the precipitate was filtered off, and the solution was concentrated *in vacuo*. According to GLC and ^{1}H NMR spectroscopic data, the residue (0.11 g) consisted of a ~3 : 1 mixture of methoxyethyl- and vinylpyrazoles. Pyrazole **3** was identified by comparison with an authentic sample. Pyrazole **2** was isolated in a pure state by preparative GLC (SE-30, 150 °C). ^{1}H NMR, δ: 9.2 (br.s, 1 H, NH); 7.50 (d, 1 H, $J = 2.0$ Hz, H-5(3)); 6.12 (d, 1 H, $J = 2.0$ Hz, H-4); 3.64 (t, 2 H, $J = 6.5$ Hz, OCH_2); 3.41 (s, 3 H, OMe); 2.94 (t, 2 H, $J = 6.5$ Hz, CH_2). ^{13}C NMR, δ: 147.1 (C-3(5)); 135.0 (C-5(3)); 104.6 (C-4); 73.1 (OCH_2); 58.8 (OMe); 28.4 (CH_2). MS (in part), *m/z* (I_{rel} (%)): 126 (11) $[M]^+$, 111 (13), 96 (19), 95 (13), 94 (27), 81 (22), 45 (100).

3(5)-(2-Bromoethyl)pyrazole (5). A specimen of bromopyrazoline **1** (0.085 g) was kept for 8 days at 20 °C. The product was extracted with benzene (2 mL), and the solution was concentrated *in vacuo*. Purification by preparative TLC on Al_2O_3 (ether—benzene, 1 : 2) gave 0.049 g (57%) of compound **5** (purity ~93%). ^1H NMR, δ: 8.90 (br.s, 1 H, NH); 7.54 (d, 1 H, $J = 2.0$ Hz, H-5(3)); 6.21 (d, 1 H, $J = 2.0$ Hz, H-4); 3.62 (t, 2 H, $J = 6.5$ Hz, CH_2Br); 3.27 (t, 2 H, $J = 6.5$ Hz, CH_2). ^{13}C NMR, δ: 147.5 (C-3(5)); 132.2 (C-5(3)); 104.5 (C-4); 31.3 (the signals of CH_2Br and CH_2 coincided; in C_6D_6, the signals of these groups are recorded at δ 31.33 and 31.23). MS (in part), *m/z* (I_{rel} (%)): 176 (10) and 174 (10) $[M]^+$, 95 (100), 81 (63).

5-Phenoxyspiro(1-pyrazoline-3,1′-cyclopropane) (6). MeONa (0.054 g, 1 mmol) and pyrazoline **1** (0.158 g, 0.9 mmol) in benzene (2 mL) were added to a solution of phenol (0.094 g, 1 mmol) in MeOH (1 mL), and the mixture was stirred for 6 h. Preparative TLC (silica gel, ether—benzene, 1 : 2.5, $R_f = 0.70$) gave 0.085 g (~50%) of pyrazoline **6** as a viscous yellowish liquid. ^1H NMR, δ: 7.32 (dd, 2 H, $^3J =$ 6.6 Hz, $^4J = 1.4$ Hz, *o*-CH); 7.08 (tt, 1 H, $^3J = 6.6$ Hz, $^4J =$ 1.4 Hz, *p*-CH); 6.86 (m, 2 H, *m*-CH); 6.40 (dd, 1 H, $J_1 =$ 7.7 Hz, $J_2 = 5.4$ Hz, H-5); 2.18 (dd, 1 H, $J_1 = 7.7$ Hz, $J_3 =$ 13.4 Hz, H-4a); 1.88 (dd, 1 H, $J_2 = 5.4$ Hz, $J_3 = 13.4$ Hz, H-4b); 1.77 and 1.24 (both m, 2×2 H, CH_2CH_2). Found (%): C, 70.02; H, 6.78; N, 14.57. $C_{11}H_{12}N_2O$. Calculated (%): C, 70.19; H, 6.43; N, 14.88.

5-Phenylthiospiro(1-pyrazoline-3,1′-cyclopropane) (7). MeONa (0.165 g, 3 mmol) and pyrazoline **1** (0.480 g, 2.7 mmol) in benzene (6 mL) were added at 15 °C to a solution of freshly distilled thiophenol (0.328 g, 3 mmol) in MeOH (2 mL). The mixture was stirred for 6 h. Removal of the solvents and column chromatography of the reaction mixture (silica gel, benzene as the eluent) gave 0.303 g (55%) of pyrazoline **7** as slightly yellowish crystals, m.p. 28—30 °C. ^1H NMR, δ: 7.58 and 7.30 (both m, 2 H + 3 H, Ph); 5.76 (dd, 1 H, $J_1 = 9.5$ Hz, $J_2 = 5.3$ Hz, H-5); 2.23 (dd, 1 H, $J_1 =$ 9.5 Hz, $J_3 = 13.4$, H-4a); 1.67 (dd, 1 H, $J_2 = 5.3$ Hz, $J_3 =$ 13.4 Hz, H-4b); 1.72, 1,37, 1.04 and 0.68 (all m, 4×1 H, CH_2CH_2). ^{13}C NMR, δ: 134.3 (*m*-Ph); 131.5 (*i*-Ph); 129.1 (*o*-Ph); 128.6 (*p*-Ph); 88.2 (C-5); 68.7 (C-3); 30.6 (C-4); 14.5 and 14.3 (CH_2CH_2). MS (in part), *m/z* (I_{rel} (%)): 204 (100) $[M]^+$, 189 (14), 126 (16), 109 (50). Found (%): C, 64.23; H, 6.10; N, 13.41, S, 15.92. $C_{11}H_{12}N_2S$. Calculated (%): C, 64.67; H, 5.92; N, 13.72; S, 15.69.

5-Azidospiro(1-pyrazoline-3,1′-cyclopropane) (8). A solution of NaN_3 (0.10 g, 1.5 mmol) in water (0.5 mL) was added at 20 °C to a solution of pyrazoline **1** (0.21 g, 1.2 mmol) in acetone (1 mL), and the mixture was stirred for 18 h. The acetone was evaporated *in vacuo*, and the residue was treated with 3 mL of a benzene—hexane mixture (1 : 1). The mixture was filtered, and the filtrate was dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue (0.13 g) was analyzed by NMR spectroscopy. The yield of azide **8** was ~65%, its purity was ~90%. ^1H NMR, δ: 5.81 (dd, 1 H, $J_1 =$ 8.7 Hz, $J_2 = 5.5$ Hz, H-5); 2.09 (dd, 1 H, $J_1 = 8.7$ Hz, $J_3 =$ 13.4 Hz, H-4a); 1.61 (dd, 1 H, $J_2 = 5.5$ Hz, $J_3 = 13.4$ Hz, H-4b); 1.80 and 1.19 (both m, 2×2 H, CH_2CH_2). ^{13}C NMR, δ: 96.0 (C-5); 69.6 (C-3); 30.6 (C-4); 14.6 and 14.3 (CH_2CH_2).

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References

1. W. Kirmse and H. Schutte, *Chem. Ber.*, 1968, **101**, 1674.
2. Yu. V. Tomilov, E. V. Shulishov, and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1057 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 939 (Engl. Transl.)].
3. Yu. V. Tomilov, E. V. Shulishov, G. P. Okonnishnikova, and O. M. Nefedov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2199 [*Russ. Chem. Bull.*, 1995, **44**, 2105 (Engl. Transl.)].
4. Yu. V. Tomilov, I. V. Kostyuchenko, E. V. Shulishov, and O. M. Nefedov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 532 [*Russ. Chem. Bull.*, 1997, **46**, 511 (Engl. Transl.)].
5. P. Bladon, D. R. Rae, and A. D. Tait, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1468.
6. P. Bladon and D. R. Rae, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2240.
7. M. Regitz and H. Heydt, *1,3-Dipolar Cycloaddition Chemistry*, Ed. A. Padwa, Wiley Interscience, New York, 1984, **1**, p. 393.

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