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# Annelated 4,5-diazaspiro[2.4]hepta-4,6-diene obtained by [3+2] cycloaddition of diazocyclopropane to cyclooctyne

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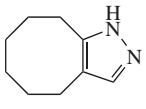
**The 1,3-dipolar cycloaddition of diazocyclopropane generated *in situ* to cyclooctyne at –30 to –25 °C afforded highly reactive spiro(9,10-diazabicyclo[6.3.0]undeca-1(8),9-diene-11,1′-cyclopropane) which can add nucleophiles to the azocyclopropane fragment or undergo oligomerization with three-membered ring opening.**

Diazocyclopropane, which is susceptible to 1,3-dipolar cycloaddition[1–3] similarly to typical aliphatic diazo compounds, is one of the most important intermediates formed upon the decomposition of *N*-nitroso-*N*-cyclopropylurea **1** under the action of strong bases. The addition of diazocyclopropane to 1,3-dienes and the activated double bonds of levoglucosenone[4] and isomeric alantolactones[5] was described. Meantime, the interaction of diazocyclopropane with alkynes was unknown. In this work, we studied for the first time the 1,3-dipolar cycloaddition of diazocyclopropane to the triple bond of cyclooctyne.

We found that diazocyclopropane generated from *N*-cyclopropyl-*N*-nitrosourea **1** under the action of sodium methoxide or potassium carbonate did not give cycloaddition products with usual alkynes, dimethyl acetylenedicarboxylate or phenyl propargyl sulfide. In this connection, we turned to cyclooctyne **2** – an accessible alkyne with a strained triple bond,[6] which is stable at room temperature. Cyclooctyne **2** is known to easily react with diazomethane to form annelated 1*H*-pyrazole **3**.[7] It was assumed that condensed 3*H*-pyrazole **4**, which contains a 4,5-diazaspiro[2,4]heptadiene fragment, can be the product of a reaction between cyclooctyne and diazocyclopropane, since it contains no α-protons in the heterocycle. Compounds with this structure were not described until now, although attempts to generate 4,5-diazaspiro[2,4]heptadiene were undertaken, for example, during dehydrobromination of 5-bromospiro(1-pyrazoline-3,1′-cyclopropane).[8] Structural analogues of the test heterocycle, namely 5,6-diazaspiro[2.4]hepta-4,6-dienes **5a**,**b**, are known, but these compounds were only detected in NMR experiments.[9]



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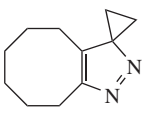

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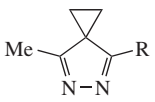
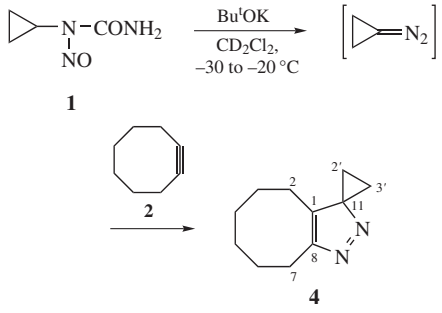


**5a** R = Me
**5b** R = OPr$^i$

Initially, we used the decomposition of nitrosourea **1** with sodium methoxide at a temperature from –40 to –10 °C for the generation of diazocyclopropane in the presence of cyclooctyne. However, elaboration of this reaction in $CD_2Cl_2$ in a NMR tube showed that, under these conditions, different processes occurred to lead to a mixture of compounds; the $^1$H and $^{13}$C NMR spectra of some of these compounds clearly exhibited signals of methoxy groups and isolated 1,2-ethylidene fragments. Nevertheless, in a number of cases at a temperature no higher than –15 °C, low-intensity signals were observed in the $^1$H NMR spectrum, which can be attributed to cycloadduct **4**, and these signals disappeared upon heating the sample above 0 °C. Evidently, the methoxide anion participated in the formation of some reaction products.

To avoid further transformations, we used another base for the decomposition of nitrosourea **1**, namely, potassium *tert*-butoxide, which effectively works at a low temperature and gives less nucleophilic *tert*-butanol. Addition of potassium *tert*-butoxide to a mixture of nitrosourea **1** and cyclooctyne in $CD_2Cl_2$ at –40 °C did not cause noticeable changes. However, the initially yellow colour of the reaction mixture almost completely disappeared upon slow heating to –30...–25°C, with noticeable release of nitrogen having not been observed. $^1$H and $^{13}$C NMR spectra recorded at –25°C showed a significant consumption of the starting reactants **1** and **2** and the appearance of characteristic signals of cycloadduct **4**, whose integral intensities corresponded to the yield of compound **4** of no lower than 75% (Scheme 1).[†] The 2D COSY, HSQC and HMBC spectra confirmed the structure of compound **4**. The key spirocyclopropane fragment manifested itself in the $^{13}$C NMR spectra as signals at $\delta$ 19.8 and 75.2 ppm. The olefin C atoms resonated at $\delta$ 147 and 155 ppm. In the $^1$H NMR spectrum, the nonequivalent protons of a cyclopropane ring appeared as two



**Scheme 1**

[†] *Spiro(9,10-diazabicyclo[6.3.0]undeca-1(8),9-diene-11,1′-cyclopropane)* **4**. Solid Bu$^t$OK (0.09 mmol) was added in one portion to a mixture of *N*-cyclopropyl-*N*-nitrosourea **1** (0.09 mmol) and cyclooctyne **2** (0.08 mmol) in $CD_2Cl_2$ (0.5 ml) at –40 °C, and the reaction mixture was kept at –30 °C for several minutes until the yellow colour disappeared. The main signals in NMR spectra corresponded to compound **4**. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.46–1.52 (m, 4H, $H_2C^4$ and $H_2C^5$), 1.65–1.74 (m, 2H, $H_2C^3$), 1.78–1.85 (m, 2H, $H_2C^6$), 2.02 (m, 2H, $H^{2'}$ and $H^{3'}$), 2.24–2.30 (m, 2H, $H_2C^2$), 2.72 (m, 2H, $H^{2'}$ and $H^{3'}$, directed to the N atoms), 3.01–3.07 (m, 2H, $H_2C^7$). $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$: 19.81 ($C^{2'}$ and $C^{3'}$), 20.92 ($C^2$), 24.42 and 24.90 ($C^4$ and $C^5$), 24.81 ($C^7$), 26.27 ($C^3$), 26.55 ($C^6$), 75.19 ($C^{1'}$), 147.08 ($C^1$), 155.00 ($C^8$).

multiplets looking like quartets at $\delta$ 2.02 and 2.72 ppm, which were downfield shifted by 0.6–0.8 ppm, as compared with the analogous signals of the relative spiro(1-pyrazoline-3,1′-cyclopropanes).[4,5,8] In this case, as in the latter, the signal of vicinal protons in a cyclopropane fragment, oriented towards nitrogen atoms, appeared in a lower field. Note that the experimentally observed chemical shifts of all signals in the $^1$H and $^{13}$C NMR spectra were close to those calculated using the PRIRODA program.[10]

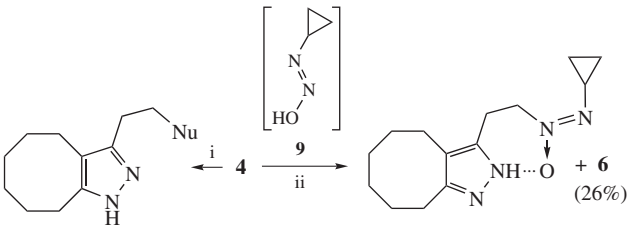
According to NMR-spectroscopic data, 4,5-diazaspiro[2,4]-heptadiene **4** is stable at –15 °C for 1 h. However, the spectrum of the sample became strongly complicated after storage at this temperature for 10–12 h to indicate that it underwent oligomerization.

At the same time, if the reaction mixture obtained at –30 °C, which mainly contained compound **4**, was immediately treated with methanol, stable (2-methoxyethyl)pyrazole **6** was formed in 73% yield (based on nitrosourea after column chromatography) as a result of cyclopropane ring opening in spiro compound **4** with the addition of a methanol molecule (Scheme 2).‡ The position of double bonds in the heterocyclic moiety of product **6** is shown tentatively; in fact, rapid prototropic isomerization occurs as in the majority of HN pyrazoles because the observed line half-width in the $^{13}$C NMR spectrum is 20 Hz for both of the α-C atoms of the pyrazole fragment at 25 °C, whereas it is 2 Hz for the β-C atom.

Note that compound **6** was also formed when MeONa/MeOH was used to decompose nitrosourea **1** in the presence of cyclooctyne in our preliminary experiments.

Similar addition of thiophenol to diazaspiroheptadiene **4**, which was obtained at –30 °C, in the course of heating the reaction mixture gave (2-phenylthioethyl)pyrazole **7** (Scheme 2).‡

An unexpected result was obtained when an excess of cyclopropylnitrosourea **1** was used in a reaction with cyclooctyne **2**. Thus, upon the slow heating (from –30 to 20 °C) of the reaction mixture containing compounds **1** and **2**, MeONa and MeOH in a molar ratio of 2.5 : 1 : 4 : 4, compound **8** bearing a cyclopropyl-oxodiazene fragment was produced in addition to methoxy derivative **6** (Scheme 2).§ Compound **8** resulted from the generation of cyclopropyldiazohydroxide **9** at a step of nitrosourea **1** decomposition and its addition to the unstable molecule of **4** in a temperature range from –20 to 20 °C. Note that the decomposition of nitrosourea **1** under the action of Bu$^t$OK does not lead to the noticeable formation of oxodiazene **8**, which can be related to a low probability of the generation of free diazohydroxide **9** in the absence of methanol.




**6** Nu = OMe (73%)
**7** Nu = SPh (65%)

**8** (58%)

**Scheme 2** *Reagents and conditions*: i, NuH, $CD_2Cl_2$, –20→20 °C; ii, **1**, MeONa/MeOH, $CD_2Cl_2$, –20→20 °C.

The presence of an azoxy group in compound **8** was detected based on the $^{14}$N NMR spectrum and confirmed by mass-spectrometric data. The chemical shifts of all of the four nitrogen atoms were identified by 2D {$^1$H–$^{15}$N}HMBC NMR. The set of $^{13}$C and $^{15}$N NMR-spectroscopic data also indicates that azoxy derivative **8** is formed as a single isomer, and the line broadening of the quaternary carbon atoms in its $^{13}$C NMR spectrum is much lower ($\Delta\nu$ 4 Hz for α-C atoms) than that in pyrazole **6**, which may be due to the formation of an intramolecular hydrogen bond.

To conclude, we were the first to detect substituted 4,5-diaza-spiro[2.4]hepta-4,6-diene **4**, which was formed by the trapping of *in situ* generated diazocyclopropane by cyclooctyne, with the aid of low-temperature NMR spectroscopy. The discovered high reactivity of this species makes it promising for the preparation of new unusual derivatives as well as for general knowledge of polycyclic compound chemistry.

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‡ *11-(2-Methoxyethyl)-9,10-diazabicyclo[6.3.0]undeca-1(8),10-diene* **6**. To a mixture containing compound **4**, which was obtained as described above, methanol (10 mg) was added at –25 °C, and the mixture was allowed to warm to room temperature. Compound **6** was isolated by chromatography on silica gel (eluent, EtOAc) in 73% yield as yellowish thick oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.40–1.50 (m, 4H, 2$CH_2$), 1.55–1.63 and 1.65–1.73 (2m, 2×2H, 2$CH_2$), 2.49–2.54 and 2.70–2.75 (2m, 2×2H, $H_2C^2$ and $H_2C^7$), 2.82 (t, 2H, $CH_2$, *J* 6.6 Hz), 3.38 (s, 3H, MeO), 3.60 (t, 2H, $OCH_2$, *J* 6.6 Hz), 8.00 (br.s, 1H, NH). $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$: 21.25, 24.75, 25.33, 25.63, 25.65, 29.38 and 29.76 (all $CH_2$), 58.77 (MeO), 71.93 ($OCH_2$), 115.15 ($C^1$), 141.6 and 148.2 (br., $\Delta\nu$ 20 Hz, $C^8$ and $C^{11}$). $^{15}$N NMR ($CDCl_3$, 30.4 MHz, $MeNO_2$ as a standard) $\delta$: –134 and –157. HRMS, *m/z*: 209.1652, 231.1463 (calc. for $C_{12}H_{20}N_2O$: 209.1648 $[M+H]^+$, 231.1468 $[M+Na]^+$).

*11-(2-Phenylthioethyl)-9,10-diazabicyclo[6.3.0]undeca-1(8),10-diene* **7**. Similarly, to a mixture containing compound **4**, thiophenol (10 mg) was added at –25 °C, and the mixture was allowed to warm to room temperature. New compound **7** was isolated by chromatography on silica gel (benzene–EtOAc, 1:1) in 65% yield as yellowish thick oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.39–1.50 (m, 4H, 2$CH_2$), 1.55–1.64 and 1.68–1.76 (2m, 2×2H, 2$CH_2$), 2.45–2.52 and 2.76–2.82 (2m, 2×2H, $H_2C^2$ and $H_2C^7$), 2.95 (t, 2H, $CH_2$, *J* 7.5 Hz), 3.26 (t, 2H, $SCH_2$, *J* 7.5 Hz), 7.18 (m, 1H, *p*-$H_{Ph}$), 7.38 (m, 2H, *m*-$H_{Ph}$), 7.36 (m, 2H, *o*-$H_{Ph}$), 12.5 (br.s, 1H, NH). $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$: 21.06, 24.38, 25.44, 25.48, 29.07, 29.52 (all $CH_2$), 25.30 ($CH_2CH_2S$), 33.13 ($CH_2S$), 126.31 (*p*-CH), 129.06 (*m*-CH), 129.56 (*o*-CH), 116.57 (C1), 135.71 (*i*-C), 143.82 and 146.38 ($C^8$ and $C^{11}$). $^{15}$N NMR ($CDCl_3$, 30.4 MHz, $MeNO_2$ as a standard) $\delta$: –158 and –166. HRMS, *m/z*: 287.1579, 309.1400 (calc. for $C_{17}H_{22}N_2S$: 287.1576 $[M+H]^+$, 309.1396 $[M+Na]^+$).

§ *1-Oxo-1-[2-(4,5,6,7,8,9-hexahydro-1*H*-cycloocta[c]pyrazolyl)ethyl]-2-cyclopropyldiazene* **8**. Dry MeONa (4 mmol) was added to a mixture of **1** (2.5 mmol), cyclooctyne (1 mmol) and methanol (4 mmol) in dichloromethane (4 ml) with stirring at –30 °C, and the reaction mixture was allowed to warm to room temperature for 15 min. Then, water was added, the organic layer was dried with $Na_2SO_4$, and the solvent was removed *in vacuo*. Column chromatography on silica gel (eluent, AcOEt) gave methoxy derivative **6** (26%) and diazene oxide **8** (58%) as yellowish thick oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 0.85–0.94 and 0.97–1.06 (2m, 2×2H, $CH_2CH_2$), 1.39–1.50 and 1.55–1.73 (2m, 2×4H, 4$CH_2$), 2.49–2.55 and 2.69–2.75 (2m, 2×2H, $H_2C^2$ and $H_2C^7$), 3.22 (t, 2H, $CH_2$, $^3J$ 7.4 Hz), 3.83 (m, 1H, CH), 4.37 (t, 2H, $NCH_2$, *J* 7.4 Hz), 8.60 (br.s, 1H, NH). $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$: 8.15 ($CH_2CH_2$), 21.22 ($CH_2C$=), 24.31, 24.78, 25.56, 25.61, 29.38, 29.69 (6$CH_2$), 33.96 (CH), 69.46 ($NCH_2$), 115.66 (C=*C*–C), 142.41 and 145.55 (–C=N and =C–N). $^{14}$N NMR ($CDCl_3$, 21.7 MHz, $MeNO_2$ as a standard) $\delta$: –41 (N=*N*→O, $\Delta\nu$ 450 Hz). $^{15}$N NMR ($CDCl_3$, 30.4 MHz, $MeNO_2$ as a standard) $\delta$: –25 (*N*=N→O), –46 (N=*N*→O), –131 (N=*N*–H), –154 (*N*=N–H). HRMS, *m/z*: 263.1861 (calc. for $C_{14}H_{22}N_4O$: 263.1866 $[M+H]^+$).

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