Decomposition of *N*-cyclopropyl-*N*-nitrosourea in the presence of reducing agents as a new way of generating the cyclopropyl radical*

Yu. V. Tomilov, I. V. Kostyuchenko, G. P. Okonnishnikova, I. P. Klimenko, and E. V. Shulishov*

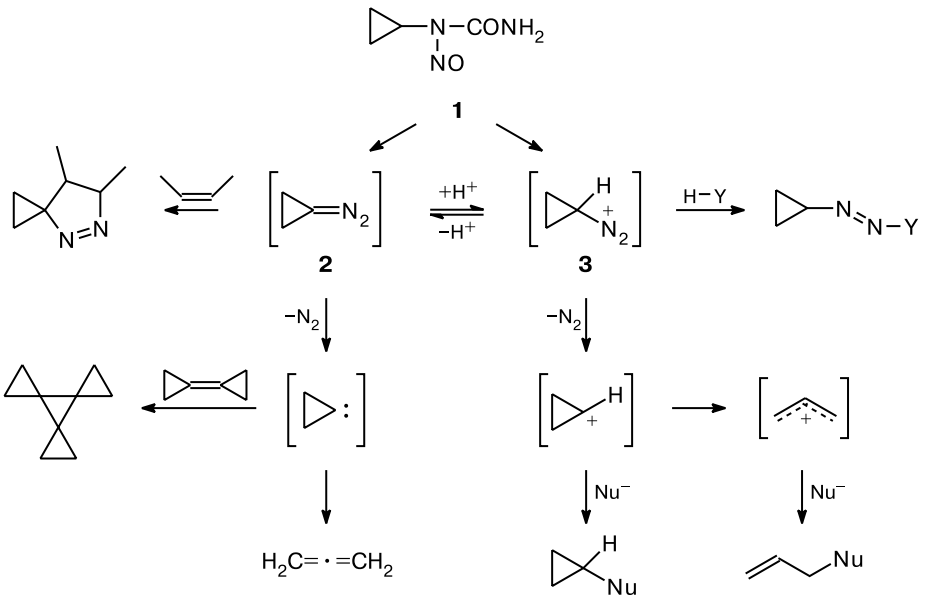
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (495) 135 6390. E-mail: tom@ioc.ac.ru

A new way of generating cyclopropyl radicals in the base-catalyzed decomposition of *N*-cyclopropyl-*N*-nitrosourea in the presence of organic reducing agents (1-phenylpyrazolidin-3-one and 4-methoxyphenol) was developed. The cyclopropyl radical generated under these conditions can not only abstract a proton from the substrate to give cyclopropane but also form C—C or C—Br bonds in reactions with aromatic substrates or polybromomethanes.

Key words: cyclopropylnitrosourea, cyclopropyldiazonium, cyclopropyl radical, cyclopropanes, reducing agents, NMR spectra.

Chemical transformations of *N*-cyclopropyl-*N*-nitrosourea (**1**) have been investigated for more than 70 years;[1] at the moment, this compound is the most suitable source for generation of a number of highly reactive intermediates such as, *e.g.*, diazocyclopropane (**2**) and the cyclopropyldiazonium ion (**3**). Although these intermediates cannot yet be detected by direct physicochemical methods, their formation from compound **1** in the presence of bases is confirmed by chemical methods involving various trapping species (Scheme 1). The most efficient way of trapping of the diazocyclopropane is to use unsaturated compounds, which react with it according to the 1,3-dipolar cycloaddition mechanism;[2,3] in the case of diazonium **3**, azo coupling reactions are em-

Scheme 1



* Dedicated to Academician O. M. Nefedov on the occasion of his 75th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1934—1938, November, 2006.

1066-5285/06/5511-2008

ployed.[4,5] In the absence of appropriate trapping species, intermediates **2** and **3** undergo spontaneous dediazotization accompanied by generation of some more unstable species (cyclopropylidene and cyclopropyl and allyl cations). Cyclopropylidene rearranges itself into allene or cyclopropanates the double bond of bicyclopropylidenes,[6,7] while $C_3H_5^+$ cations react with nucleophiles to give cyclopropyl and allyl derivatives.[8,9]

Apart from the aforementioned intermediates of the base-catalyzed decomposition of compound **1**, the generation of cyclopropyl radical (**4**) is also possible.[10] For instance, the decomposition of compound **1** with amines gives cyclopropane (~2%), while the ^{1}H NMR spectra show the CIDNP effect for the protons of *cyclo*-C_3H_6. Cyclopropane is also detected in the generation of diazonium **3** in the presence of $NaBH_4$ as a reducing agent. However, no transformations of radical **4** into other products (except for cyclopropane itself) in these processes have been reported. Nevertheless, one-electron reduction of cyclopropyldiazonium (or the cyclopropyl cation) to the cyclopropyl radical and its trapping by appropriate substrates seem to be very likely, especially with consideration to some similarity of diazonium **3** with aromatic diazonium salts, for which the reductive generation of aryl radicals is well known.[11]

Results and Discussion

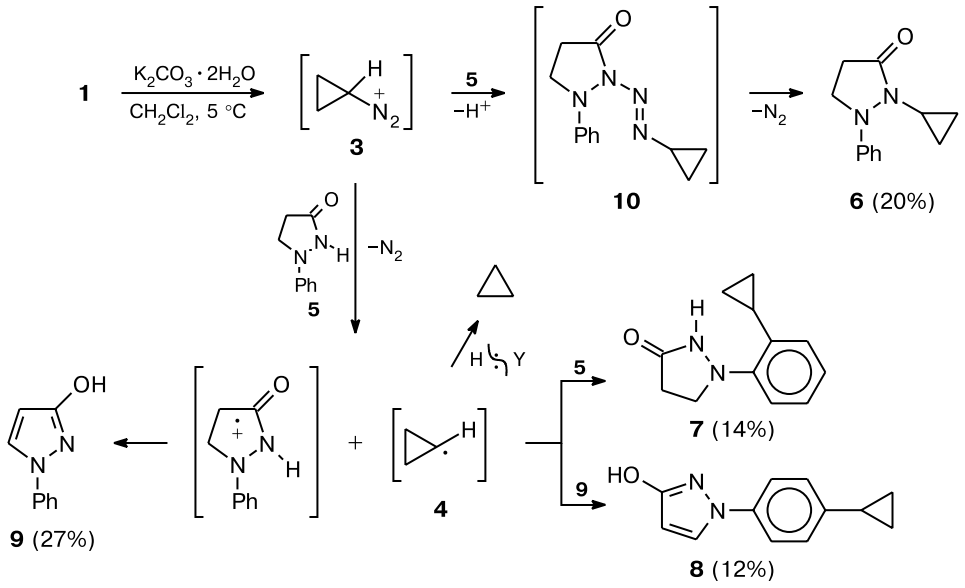
Here we studied the possibility of generating radical **4** in the base-catalyzed decomposition of compound **1** in the presence of organic reducing agents. We have discovered that possibility[12] for 1-phenylpyrazolidin-3-one (**5**) when extensively screening compounds capable of azo coupling with cyclopropyldiazonium ion (**3**).

Compound **1** was decomposed with moist K_2CO_3 in the presence of pyrazolidinone **5** (0.8 equiv.) in CH_2Cl_2 according to a standard procedure.[5] After primary workup of the reaction mixture, the ^{1}H NMR spectrum distinctly showed characteristic signals for the methine protons of the cyclopropane rings in three new compounds; the signals appeared in a sufficiently high field (δ_H 1.9—2.9), which is atypical of compounds with the azocyclopropane fragment (δ_H ~3.7). It is worth noting that the reaction mixture contained no products involving the allyl cation, though they usually form in similar reactions *via* partial dediazotization of ion **3** and isomerization of the cyclopropyl cation. In these reactions, the number of allyl-type compounds was the higher, the less efficient was the trapping species of intermediates **2** and **3** (see Ref. 9).

The compounds obtained were isolated in the individual state by column chromatography on SiO_2 with benzene—ethyl acetate (3 : 1) as an eluent and characterized by data from elemental analysis, mass spectrometry, and ^{1}H and ^{13}C NMR spectroscopy. The assigned structures were 2-cyclopropyl-1-phenylpyrazolidin-3-one (**6**), 1-(2-cyclopropylphenyl)pyrazolidin-3-one (**7**), and 1-(4-cyclopropylphenyl)-3-hydroxypyrazole (**8**). Along with compounds **6**—**8**, the starting pyrazolidinone **5** (~10%) was recovered and 3-hydroxy-1-phenylpyrazole (**9**) was obtained (Scheme 2).

Compound **9** was identified by comparing the ^{1}H and ^{13}C NMR spectra with the literature data.[13] In the ^{1}H and ^{13}C NMR spectra of pyrazole **8**, the signals for the pyrazole ring are virtually identical with those in the spectra of compound **9**; however, the signals for the corresponding

Scheme 2



atoms of the benzene ring unambiguously indicate the presence of the *para*-cyclopropyl substituent in the system (see Experimental). In contrast to pyrazoles **8** and **9**, the ^1H and ^{13}C NMR spectra of pyrazolidinones **6** and **7** are similar to those of the starting pyrazolidinone **5**. The difference is that the ^1H NMR spectrum of compound **6** shows no low-field signal for the NH proton but exhibits signals for the cyclopropyl protons (for the methine proton, δ 2.92); in contrast, ^1H NMR spectrum of the structurally isomeric compound **7** contains a signal for the NH proton at δ 9.1 but the range of signals for aromatic protons shows a four-spin system typical of the *ortho*-substituted benzene ring and the signal for the methine proton of the cyclopropane ring appears at δ 2.18.

To confirm the formation of pyrazole **9** directly during the reaction rather than during chromatographic separation of the reaction mixture, we decomposed compound **1** in the tube of an NMR spectrometer (CD_2Cl_2, 0 °C). Under these conditions, stirring is insufficient and the reaction was catalyzed by Cs_2CO_3, which is a stronger base than K_2CO_3. This experiment proved the formation of hydroxypyrazole **9** during the course of the reaction and additionally revealed two important results. The ^1H NMR spectrum of the reaction mixture contains a very intense singlet at δ 0.24 that indicates the formation of cyclopropane in ~35% yield (estimated from the integral intensities of the signals). In addition, the ^1H NMR spectrum shows another distinct signal (δ 3.42, tt) characteristic of the methine proton of the cyclopropane fragment (most likely, (*cyclo*-C_3H_5)—N=N). Immediately after the reaction was completed, this signal was dominant in contrast to analogous signals for compounds **7** and **8** and especially to the signal for the methine proton of *N*-cyclopropylpyrazolidinone **6**. However, this signal gradually disappeared with time (1—20 h, 20 °C), which was accompanied by a simultaneous increase in the intensities of the signals due to compound **6**; the intensities of the other signals remained unchanged.

The results obtained suggest that the spectroscopically detected intermediate is 2-(cyclopropylazo)-1-phenylpyrazolidin-3-one (**10**) formed *via* addition of diazonium **3** to the NH group of the starting pyrazolidinone **5**. An analogous process leading to cyclopropyltriazenes has been observed earlier in the generation of ion **3** in the presence of ethyl- and dimethylamines.[10] Subsequent spontaneous dediazotization of *N*-azopyrazolidinone **10** is probably sufficiently selective, yielding compound **6**.

The results obtained (on the one hand, the presence of products of oxidation of the saturated heterocycle into hydroxypyrazoles **8** and **9** and, on the other hand, a sufficiently rare example of insertion of the cyclopropyl fragment into the C—H bond of the phenyl substituent[14] and the formation of cyclopropane itself) provide strong evidence for the generation of the cyclopropyl radical during the decomposition of compound **1** with bases in the presence of pyrazolidinone **5**, which ensures the electron transfer to cyclopropyldiazonium **3**. A specific attack of the cyclopropyl radical on the phenyl substituent* (*ortho*-substitution for 1-phenylpyrazolidine **5** and *para*-substitution for 1-phenylpyrazole **9**) is probably due to various effects of conjugation of the phenyl substituent with those heterocycles.

The cyclopropyl radical mainly generated by thermolysis or photolysis of biscyclopropanoyl peroxide is known[14,15] to be a highly reactive species; its reactivity is one to two orders of magnitude higher than most primary aliphatic radicals. According to quantum-chemical calculations,[16] the energy barrier to an electrocyclic transformation of this species into an allyl system is appreciably higher than that for the cyclopropyl cation; the allyl radical usually isomerizes under photolysis conditions.[17] The high hydrogen affinity of the cyclopropyl radical has also been reported.[18] The above data explain well the absence of allyl derivatives among the reaction products and the sufficiently high yield of cyclopropane.

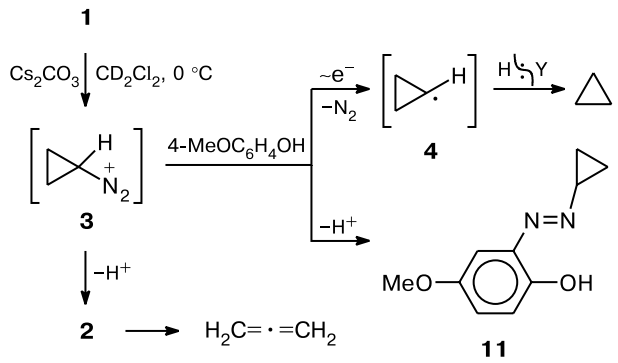
We tried to extend the range of reagents capable of generating the cyclopropyl radical in the decomposition of compound **1** and, as far as possible, obtain derivatives of the cyclopropane series. Experiments were carried out in the tube of the NMR spectrometer at 20 °C, by adding a double amount of Cs_2CO_3 to a mixture of the reagents in CD_2Cl_2. Hydroquinone could be a good reducing agent for diazonium **3**; however, it is poorly soluble in dichloromethane and thus is unfit for NMR experiments. Instead, we used 4-methoxyphenol, which also exhibits reductive properties.

Addition of Cs_2CO_3 and 4-methoxyphenol to a solution of compound **1** caused gas evolution; cyclopropane, allene, and 2-(cyclopropylazo)-4-methoxyphenol (**11**) as an azo adduct were detected already during the first minutes of the process, despite poor recording conditions (Scheme 3). It should be noted that the CIDNP effect for the signal of cyclopropane was observed during the reaction. After the reaction was completed (20—25 min), the molar ratio of **11** : cyclopropane : allene was ~1.6 : 1.8 : 1.0. To isolate and identify the earlier unknown azo compound **11**, we carried out this reaction in a reaction vessel with equimolar amounts of compound **1** and 4-methoxyphenol and K_2CO_3 as a base (see Experimental).

The presence of cyclopropane in the reaction mixture suggests the generation of the cyclopropyl radical under these conditions; therefore, radical **4** can also be trapped by other substrates. It turned out that addition of Cs_2CO_3 and 4-methoxyphenol to a solution of compound **1** containing a small excess of CBr_4 gives rise, along with azo adduct **11** and allene, to cyclopropyl bromide (**12**) and

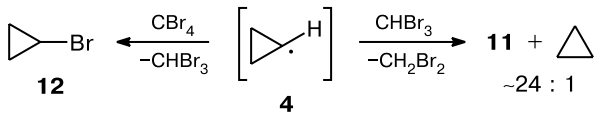
* We do not exclude the possible formation of *para*-isomer **7** and *ortho*-isomer **8**; however, their amounts are too small for reliable identification.

Scheme 3



bromoform; the spectrum of the reaction mixture contained no signal for cyclopropane. After the reaction was completed, the integral intensities of the nonoverlapping signals for bromide **12**, azo adduct **11**, bromoform, and allene corresponded to their molar ratio ~8 : 6 : 2 : 1.

Scheme 4



Under analogous conditions, the use of bromoform instead of CBr_4 also afforded cyclopropyl bromide **12**; the CIDNP effect was observed in the spectrum recorded two minutes after the beginning of the reaction. The final reaction mixture contained bromide **12**, azo adduct **11**, CH_2Br_2, allene, and cyclopropane in the molar ratio 24 : 15 : 6 : 4.5 : 1 (see Schemes 3, 4).

Thus, the base-catalyzed decomposition of *N*-cyclopropyl-*N*-nitrosourea in the presence of reducing agents such as 1-phenylpyrazolidin-3-one (**5**) or 4-methoxyphenol allows generation of the cyclopropyl radical, which can not only abstract proton from a substrate to give cyclopropane but also alkylate the benzene ring or form C—Br bonds in reactions with polybromomethanes.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75.5 MHz, respectively) in $CDCl_3$, CD_3OD, or CD_2Cl_2 all containing 0.05% Me_4Si as the internal standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct inlet probe). For chromatography, silica gel 60 (0.040—0.063 mm; Merck) was used. 1-Phenylpyrazolidin-3-one (Reakhim), 4-methoxyphenol, cyclopropyl bromide, tetrabromomethane, bromoform, and cesium carbonate (Merck) were used as purchased. *N*-Cyclopropyl-*N*-nitrosourea (**1**) was prepared according to a known procedure.[1]

Decomposition of compound 1 in the presence of 1-phenylpyrazolidin-3-one (5). *N*-Cyclopropyl-*N*-nitrosourea (**1**) (0.62 g, 4.8 mmol) was added in small portions at 5 °C to a stirred mixture of 1-phenylpyrazolidin-3-one (**5**) (0.65 g, 4.0 mmol) and moist K_2CO_3 (1.32 g; ~20% water) in CH_2Cl_2 (45 mL). The reaction mixture was stirred at this temperature for 3 h and filtered. The dark red filtrate was concentrated and the residue was separated by column chromatography on SiO_2 with benzene—AcOEt (3 : 1) as an eluent. After the removal of the solvents, the starting pyrazolidinone **5** (0.064 g, ~10%) was recovered and compounds **6**—**9** were obtained.

2-Cyclopropyl-1-phenylpyrazolidin-3-one (6). The yield was 0.16 g (20%). Found (%): C, 70.95; H, 6.87; N, 13.71. $C_{12}H_{14}N_2O$. Calculated (%): C, 71.26; H, 6.98; N, 13.85. ^1H NMR ($CDCl_3$), δ: 0.80 (m, 4 H, CH_2CH_2); 2.50 (t, 2 H, $H_2C(4)$, J = 7.4 Hz); 2.92 (m, 1 H, CH); 3.75 (t, 2 H, $H_2C(5)$, J = 7.4 Hz); 7.35 and 7.05 (both m, 2 + 3 H, Ph). MS, m/z (I_{rel} (%)): 202 $[M]^+$ (39), 187 (16), 145 (82), 117 (100), 77 (92).

1-(2-Cyclopropylphenyl)pyrazolidin-3-one (7). The yield was 0.11 g (14%), m.p. 152—153 °C. Found (%): C, 71.03; H, 6.90; N, 13.69. $C_{12}H_{14}N_2O$. Calculated (%): C, 71.26; H, 6.98; N, 13.85. ^1H NMR ($CDCl_3$), δ: 0.74 and 1.03 (both m, 2 H each, CH_2CH_2); 2.18 (m, 1 H, CH); 2.55 (t, 2 H, $H_2C(4)$, J = 7.6 Hz); 3.87 (t, 2 H, $H_2C(5)$, J = 7.6 Hz); 6.85 (dd, 1 H, H(3′), J = 1.6 Hz, J = 7.3 Hz); 7.10 and 7.18 (both m, 1 H each, H(4′) and H(5′); 7.28 (dd, 1 H, H(6′), J = 1.6 Hz, J = 7.6 Hz). ^{13}C NMR (CD_3OD), δ: 9.36 (CH_2CH_2), 11.88 (CH), 30.33 (C(4)), 56.35 (C(5)), 117.70 (C(6′)), 125.56 and 125.71 (C(4′) and C(5′)), 126.84 (C(3′)), 136.40 (C(2′)), 151.77 (C(1′)), 177.71 (C=O). MS, m/z (I_{rel} (%)): 202 $[M]^+$ (24), 173 (68), 131 (100), 119 (27), 91 (27), 77 (39), 55 (35).

1-(4-Cyclopropylphenyl)-3-hydroxypyrazole (8). The yield was 0.096 g (12%), m.p. 168—170 °C. Found (%): C, 71.72; H, 6.00; N, 13.75. $C_{12}H_{12}N_2O$. Calculated (%): C, 71.98; H, 6.04; N, 13.99. ^1H NMR ($CDCl_3$), δ: 0.72 and 1.00 (both m, 2 H each, CH_2CH_2); 1.92 (m, 1 H, CH); 5.88 (d, 1 H, H(4), J = 2.5 Hz); 7.14 and 7.42 (both m, 2 H each, *para*-C_6H_4); 7.62 (d, 1 H, H(5), J = 2.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 9.29 (CH_2CH_2), 15.06 (CH), 93.83 (C(4)), 118.97 (C(2′) and C(6′)), 126.05 (C(3′) and C(5′)), 129.07 (C(5)), 137.33 (C(4′)), 142.11 (C(1′)), 163.86 (C(3)). MS, m/z (I_{rel} (%)): 200 $[M]^+$ (100), 165 (26), 117 (69), 91 (25), 77 (29), 63 (28).

3-Hydroxy-1-phenylpyrazole (9) was identified by comparison with the literature data.[13] The yield was 0.17 g (27%).

2-(Cyclopropylazo)-4-methoxyphenol (11). Potassium carbonate (2.76 g) containing water (~20%) was added to a solution of 4-methoxyphenol (0.62 g, 5 mmol) and compound **1** (0.65 g, 5 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at 2—5 °C for 6 h and filtered. The filtrate was concentrated *in vacuo* and the residue was separated by column chromatography on SiO_2 with benzene—ether (70 : 1) as an eluent. The isolated fractions contained the starting 4-methoxyphenol (0.35 g, ~55%) and azo adduct **11** (0.36 g, 37%).

2-(Cyclopropylazo)-4-methoxyphenol (11), m.p. 57—58 °C. Found (%): C, 62.63; H, 6.40; N, 14.29. $C_{10}H_{12}N_2O_2$. Calculated (%): C, 62.49; H 6.29; N, 14.57. ^1H NMR (CD_2Cl_2), δ: 1.32 and 1.45 (both m, 2 H each, CH_2CH_2); 3.68 (tt, 1 H, CH, J = 3.3 Hz, J = 7.0 Hz); 3.75 (s, 3 H, OMe); 6.95 (dd, 1 H, H(6), J_{para} = 0.6 Hz, J_{ortho} = 9.0 Hz); 6.90 (dd, 1 H, H(5), J_{meta} = 2.8 Hz, J_{ortho} = 9.0 Hz); 7.29 (dd, 1 H, H(3), J_{meta} = 2.8 Hz,

J_{para} = 0.6 Hz); 11.0 (br.s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 10.77 (CH_2CH_2), 49.33 (CH), 55.96 (OMe), 113.66 (C(3)), 118.40 (C(5)), 119.44 (C(6)), 135.85 (C(2)), 146.46 (C(1)), 152.70 (C(4)). MS, m/z (I_{rel} (%)): 192 $[M]^+$ (43), 177 $[M - Me]^+$ (8), 165 (75), 122 (26), 108 (42), 95 (22), 79 (22), 68 (18), 52 (26), 41 (49), 39 (100).

Reactions in the tube of an NMR spectrometer (general procedure). A solution of compound **1** (10 mg, 0.077 mmol) in CD_2Cl_2 (0.4 mL) and 1-phenylpyrazolidin-3-one (**5**) or 4-methoxyphenol (0.07 mmol) were placed in the tube. In experiments with polyhalomethanes, CBr_4 or $CHBr_3$ (0.1 mmol) was also added. Then Cs_2CO_3 (50 mg, 0.153 mmol) was added in one portion at 0 °C and the tube was placed in the probe of the NMR spectrometer. Spectra were recorded at regular periods of time (*e.g.*, 2, 10, 30 min, *etc.*). The spectra were compared with each other and with the spectra of known compounds; the ratio of the products was determined from the integral intensities of the nonoverlapping signals.

A. Cesium carbonate was added to a solution of compound **1** and pyrazolidinone (**5**). After 1 h, compounds **6**—**10** and cyclopropane itself were detected in the molar ratio ~1 : 2 : 2 : 6 : 4 : 3. After a 20-h exposure at 20 °C, the ratio of compounds **6**—**9** was ~5 : 2 : 2 : 6, while compound **10** was virtually absent.

B. Cesium carbonate was added to a solution of compound **1** and 4-methoxyphenol (**5**). After 2 min, the ^{1}H NMR spectrum showed a strong emission of the signal for cyclopropane (CIDNP effect). After the reaction was completed, azo adduct **11**, cyclopropane, and allene were detected in the molar ratio 1.8 : 1.6 : 1.0.

C. Cesium carbonate was added to a solution of compound **1**, 4-methoxyphenol, and CBr_4. After the reaction was completed, azo adduct **11**, cyclopropyl bromide, bromoform, and allene were detected in the molar ratio ~6 : 8 : 2 : 1. Cyclopropane was virtually absent from the reaction mixture.

D. Cesium carbonate was added to a solution of compound **1**, 4-methoxyphenol, and $CHBr_3$. After 2 min, the ^{1}H NMR spectrum showed a CIDNP effect for the signals of cyclopropane and cyclopropyl bromide. After the reaction was completed, azo adduct **11**, cyclopropyl bromide, CH_2Br_2, allene, and cyclopropane were detected in the molar ratio ~15 : 24 : 6 : 4 : 1.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 06-03-33149).

References

1. V. P. Gol´mov, *Zh. Obshch. Khim.*, 1935, **5**, 1562 [*Chem. Zentralbl.*, 1936, **107 (II)**, 1905].
2. Yu. V. Tomilov, I. V. Kostyuchenko, and O. M. Nefedov, *Usp. Khim.*, 2000, **69**, 507 [*Russ. Chem. Rev.*, 2000, **69**, 461 (Engl. Transl.)].
3. Yu. V. Tomilov and I. V. Kostyuchenko, *Sovremennye problemy organicheskoi khimii* [*Modern Problems of Organic Chemistry*], St.-Petersburg State University, St.-Petersburg, 2001, Issue 13, 113 (in Russian).
4. Yu. V. Tomilov, I. V. Kostyuchenko, E. V. Shulishov, and O. M. Nefedov, *Mendeleev Commun.*, 2002, 104.
5. Yu. V. Tomilov, I. V. Kostyuchenko, E. V. Shulishov, and G. P. Okonnishnikova, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 941 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 993].
6. L. Fitjer and J. Conia, *Angew. Chem.*, 1973, **85**, 349.
7. A. de Meijere and S. I. Kozhushkov, *Chem. Rev.*, 2000, **100**, 93.
8. W. Kirmse and H. Schütte, *Chem. Ber.*, 1968, **101**, 1674.
9. I. P. Klimenko, V. A. Korolev, Yu. V. Tomilov, and O. M. Nefedov, *Zh. Org. Khim.*, 2006, **42**, 1320 [*Russ. J. Org. Chem.*, 2006, **42**, 1299].
10. W. Kirmse and U. Seipp, *Chem. Ber.*, 1974, **107**, 745.
11. H. Zollinger, *Diazo Chemistry I*, Weinheim, VCH Verlagsgesellschaft, 1994, **1**, 188.
12. Yu. V. Tomilov, I. V. Kostyuchenko, I. P. Klimenko, and G. P. Okonnishnikova, *Abstrs VII Conf. on the Chemistry of Carbenes and Related Intermediates*, Kazan, 2003, 22.
13. H. H. Adam, B. D. Baigrie, and T. A. Joslin, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1287.
14. T. Shono and I. Nishiguchi, *Tetrahedron*, 1974, **30**, 2183.
15. L. J. Johnston, J. C. Scaiano, and K. U. Ingold, *J. Am. Chem. Soc.*, 1984, **106**, 4877.
16. D. J. Mann and W. L. Hase, *J. Am. Chem. Soc.*, 2002, **124**, 3208.
17. (a) G. Maier and S. Senger, *Angew. Chem., Int. Ed.*, 1994, **33**, 558; (b) K. B. Wiberg and C. G. Österle, *J. Org. Chem.*, 1999, **64**, 7756.
18. I. G. Green and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1597.

Received September 22, 2006;
in revised form October 11, 2006