Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2011, **21**, 302–304
Mendeleev Communications

Formation of tetrazoles on diazocyclopropane generation

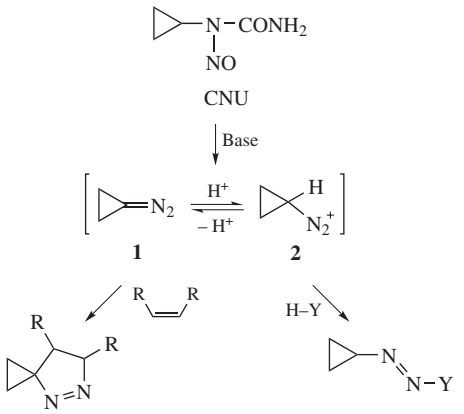
Yury V. Tomilov,* Irina V. Kostyuchenko, Alexander I. Novichkov and Evgeny V. Shulishov

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: tom@ioc.ac.ru

DOI: 10.1016/j.mencom.2011.11.002

Decomposition of *N*-cyclopropyl-*N*-nitrosourea with bases in the absence of agents for trapping of diazocyclopropane and cyclopropyldiazonium leads to 1,5- and 2,5-disubstituted tetrazoles.

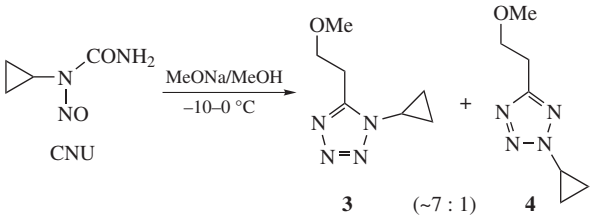
Considerable attention has recently been attracted to the reactivity of diazocyclopropanes and related cyclopropyldiazonium ions, primarily to the reactions which occur with retention of nitrogen atoms in the molecule, in particular, 1,3-dipolar cycloaddition of diazocyclopropane **1** to double bonds to give spirocyclopropanated pyrazolines[1] and azo-coupling of cyclopropyldiazonium **2** with activated arenes and CH-acids to give cyclopropylazoarenes[2] or *N*-cyclopropylhydrazones.[3] It should be noted that generation of cyclopropyldiazonium intermediates, which is generally performed by treatment of *N*-cyclopropyl-*N*-nitrosourea (CNU) with bases,[4] can involve concurrent trapping of both diazocyclopropane and diazocyclopropyldiazonium ions (Scheme 1), depending on the nature of the substrates used.[1(c)]



Scheme 1

In many cases, when generation of intermediates **1** and **2** in the presence of poorly active substrates was performed, we repeatedly detected, in addition to the target products, some side ones formed without any relation to the substrates used but depending on the method employed to decompose the starting CNU. In view of this, we studied CNU decomposition on treatment with a sodium methoxide solution in methanol or an aqueous solution of KOH in the absence of trapping agents for either diazocyclopropane or cyclopropyldiazonium.

In fact, sufficiently rapid mixing of CNU and MeONa/MeOH at –10 to 0 °C results in compounds that were previously observed in NMR spectra as side products only. The amount of the compound isolated after removal of the solvent and volatile reaction products was up to 40% of the original CNU mass. Column chromatography on silica gel allowed us to obtain an analytically pure sample of the major reaction mixture component, to which the structure of 5-(2-methoxyethyl)-1-cyclopropyltetrazole **3** was assigned based on elemental analyses, mass spectrometry and ^{1}H and ^{13}C NMR data, as well as HMBC ^{1}H–^{13}C and ^{1}H–^{15}N two-



Scheme 2

dimensional correlation spectra.† The ^{1}H NMR spectrum of the primary reaction mixture contained, along with the signals of tetrazole **3**, also a second set of similar signals with much lower intensity (ratio ~7:1), which suggested the presence of a second isomer, *viz*., 5-(2-methoxyethyl)-2-cyclopropyltetrazole **4** (Scheme 2). A minor isomer **4** was isolated in enriched form only (up to 80%).

In order to fulfil a valid assignment of the cyclopropyltetrazoles obtained as 1- and 2-isomers, we performed a NOESY experiment, which showed that the major isomer **3** truly manifested spatial interaction of the methylene protons in the cyclopropane ring with the protons of the α-methylene group in the 2-methoxyethyl substituent. This effect was not observed for minor isomer **4**.

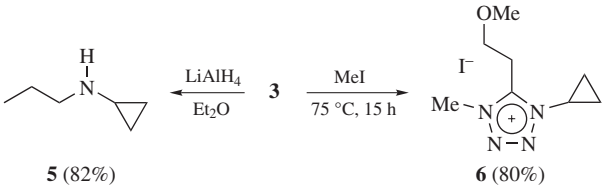
Furthermore, we confirmed the structure of tetrazole **3** by a chemical method. It is known that reduction of disubstituted tetrazoles with complex metal hydrides occurs in different ways

† *1-Cyclopropyl- and 2-cyclopropyl-5-(2-methoxyethyl)tetrazoles* **3** *and* **4**. A solution of MeONa (20 mmol) in methanol (4 ml) was added with stirring to a solution of *N*-cyclopropyl-*N*-nitrosourea (15 mmol) in MeOH (15 ml) at –10 °C. Stirring was continued for 10 min at 0 °C and the solution was concentrated in a vacuum to half of its volume. The reaction mixture was poured into water (15 ml) and extracted with CH_2Cl_2 (2×8 ml). The organic extracts were dried with anhydrous $MgSO_4$ and the solvent was removed in a vacuum. The yellow oily residue (0.90 g), which was generally a mixture of tetrazoles **3** and **4** in a 7:1 ratio, was chromatographed on SiO_2 (CH_2Cl_2–methanol, 10:1) to give 0.69 g (55%) of tetrazole **3** and 0.13 g (10%) of a mixture of **3** and **4** in a ratio of ~1:4.

3: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.22, 1.32 (2m, 2×2H, CH_2CH_2), 3.21 (t, 2H, CH_2, J 7.1 Hz), 3.32 (s, 3H, OMe), 3.58 (tt, 1H, HC, J_{cis} 8.3 Hz, J_{trans} 4.8 Hz), 3.82 (t, 2H, CH_2O, J 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 6.9 (CH_2CH_2), 24.5 (CH_2), 28.2 (CH), 59.0 (OMe), 69.7 (OCH_2), 154.8 (C=N). MS, *m*/*z* (%): 168 (2) $[M]^+$, 153 (3) $[M – Me]^+$, 95 (17), 45 (100). Found (%): C, 49.64; H, 6.79; N, 33.40. Calc. for $C_7H_{12}N_4O$ (%): C, 50.00; H, 7.14; N, 33.33.

4: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20, 1.43 (2m, 2×2H, CH_2CH_2), 3.12 (t, 2H, CH_2, J 7.0 Hz), 3.36 (s, 3H, OMe), 3.79 (t, 2H, CH_2O, J 7.0 Hz), 4.14 (tt, 1H, HC, J_{cis} 8.4 Hz, J_{trans} 4.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 7.4 (CH_2CH_2), 26.4 (CH_2), 34.6 (CH), 58.8 (OMe), 70.2 (OCH_2), 153.4 (C=N).

for 1,5- and 2,5-disubstituted tetrazoles. In fact, one secondary amine is formed from 1,5-disubstituted tetrazoles, whereas a mixture of two primary amines is formed from 2,5-disubstituted ones.[5] It was found that reduction of the major isomer with lithium aluminium hydride, along with the heterocycle reduction, also involved cleavage of the ether bond to give known *N*-cyclopropyl-*N*-propylamine **5**.[6] The formation of secondary amine **5**, which was isolated as a hydrochloride,‡ additionally confirms that the major isomer has the structure of 1,5-disubstituted tetrazole **3** (Scheme 3).

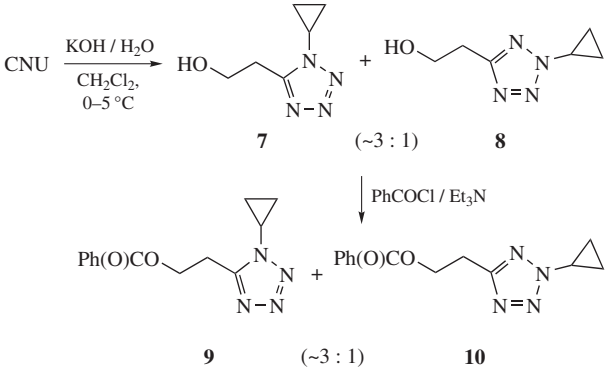


5 (82%) **6** (80%)

Scheme 3

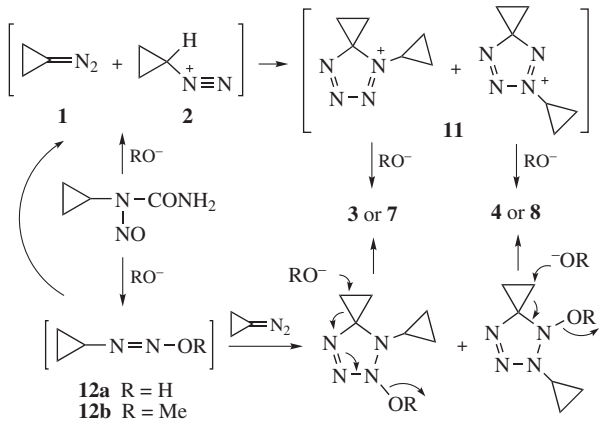
Similarly to other tetrazoles, cyclopropyltetrazole **3** can be alkylated with iodomethane; however, unlike *e.g.* 1,5-dimethyltetrazole,[7] the reaction requires more drastic conditions (sealed tube, 75 °C, 15 h). Nevertheless, even under these conditions the conversion of the starting tetrazole to tetrazolium iodide **6** was incomplete and amounted to 80%. ^{1}H and ^{13}C NMR spectra showed that all signals of the starting tetrazole were preserved (while some of them were shifted downfield) and one more methyl group signal appeared.§ A NOESY experiment revealed that the protons of the α-methylene moiety in the 2-methoxyethyl substituent correlate with protons of both the cyclopropane ring and the methyl group, which suggests that it is located at 4-position of the tetrazole ring (Scheme 3).

Further on, in order to find out whether other analogous tetrazoles can be obtained, we studied CNU decomposition on treatment with aqueous solutions of potassium hydroxide as well as potassium and cesium carbonates. Our experiments demonstrated that considerable yield of tetrazoles can be achieved only on using strong bases. In fact, rapid addition of a 30% aqueous solution of KOH to CNU in CH_2Cl_2 at 0–5 °C resulted in the corresponding 1- and 2-cyclopropyltetrazoles **7** and **8** (isomer ratio ~3:1) containing a 2-hydroxyethyl substituent at 5-position of the heterocycle (Scheme 4).¶ Under these conditions (with a rapid mixing of reagents) allene and allyl alcohol were by-products, and the overall yield of tetrazoles **7** and **8** amounted to 50–55%. Hydroxyethyl-substituted tetrazoles were found to be less stable than methoxy derivatives **3** and **4**, and we failed to isolate them in individual form. In view of this, the resulting mixture of tetrazoles **7** and **8** was treated with benzoyl chloride in the presence of triethylamine. The benzoates **9** and **10** were separated by column chromatography on silica gel.



Scheme 4

Apparently, the formation of tetrazoles **3** and **4** or **7** and **8** formally involves interaction of two diazocyclopropane molecules and one methanol or water molecule. The formation of tetrazoles in 12 and 24% yields in the reaction of diazomethane with 4-nitrophenyl- and 3-pyrazolyldiazonium salts, respectively, has been reported;[8] however, the application of this scheme in our case would assume the reaction of two highly reactive intermediates, diazocyclopropane **1** and a cyclopropyldiazonium ion **2**, followed by opening of the spiro coupled cyclopropane moiety in heterocyclic intermediates **11** (Scheme 5).



Scheme 5

‡ N-*Cyclopropyl*-N-*propylamine* **5**. A solution of tetrazole **3** (1 mmol) in Et_2O (3 ml) was added dropwise to a solution of $LiAlH_4$ (2 mmol) in Et_2O (5 ml) at 5 °C and the reaction mixture was stirred until the starting tetrazole disappeared in a treated aliquot of reaction mixture (GLC). After that, a small amount of water was added and the organic layer was treated with HCl. The solvent was removed and the residue was dried in a vacuum. The yield of amine **5** hydrochloride was 0.10 g (82%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.70 and 0.88 (2m, 2×2H, CH_2CH_2), 0.93 (t, 3H, Me, J 7.3 Hz), 1.65 (m, 2H, CH_2), 2.63 (m, 1H, CH), 2.90 (m, 2H, CH_2N), 4.47 (br. s, 2H, NH_2^+). ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ: 2.3 (cyclo-CH_2CH_2), 10.4 (Me), 18.2 (CH_2), 28.8 (CH), 48.4 (NCH_2). Amine **5** has been previously obtained from cyclopropylamine and propyl bromide,[6] but its NMR spectra were not published.

§ *1-Cyclopropyl-4-methyl-5-(2-ethoxyethyl)tetrazolium iodide* **6**. A solution of tetrazole **3** (0.6 mmol) and methyl iodide (2 mmol) in acetone (1 ml) was heated at 70 °C in a sealed tube for 15 h. The reaction mixture was cooled; recrystallization from an acetone–diethyl ether mixture (1:1) gave product **6** as pale brown crystals in 80% yield, mp 124–125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 and 1.78 (2m, 2×2H, CH_2CH_2), 3.33 (s, 3H, MeO), 3.87 and 3.98 (2m, 2×2H, OCH_2CH_2N), 4.14 (tt, 1H, CH, J_{cis} 7.6 Hz, J_{trans} 4.3 Hz), 4.40 (s, 3H, MeN^+). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 7.46 (CH_2CH_2), 27.1 (CH_2N), 32.3 (CH), 38.5 (MeN^+), 59.3 (MeO), 67.8 (CH_2O), 155.2 (C=N).

¶ *1-Cyclopropyl- and 2-cyclopropyl-5-(2-hydroxyethyl)tetrazoles* **7** *and* **8**. A 30% aqueous solution of KOH (9 mmol) was added in one portion to a solution of *N*-cyclopropyl-*N*-nitrosourea (4 mmol) in CH_2Cl_2 (10 ml) at 5 °C and the reaction mixture was stirred for 20 min at this temperature. Then water (10 ml) was added and the mixture was extracted with CH_2Cl_2 (4×5 ml). The combined organic layers were dried with anhydrous $MgSO_4$; removal of the solvent gave a mixture of tetrazoles **7** and **8** in 3:1 ratio as a yellowish oil in ~50–55% yield.

1-Cyclopropyl- and 2-cyclopropyl-5-(2-benzoyloxyethyl)tetrazoles **9** *and* **10**. A solution of benzoyl chloride (1 mmol) in CH_2Cl_2 (3 ml) was added at 5 °C to a solution of tetrazoles **7** and **8** obtained in the previous experiment and triethylamine (1.6 mmol) in CH_2Cl_2 (8 ml). The reaction mixture was stirred for 2 h and water (10 ml) was added. The organic layer was washed with water (6 ml) and evaporated in a vacuum. The residue was treated with column chromatography [SiO_2, benzene–AcOEt (10:1)] to furnish pure compounds **9** (58%) and **10** (19%).

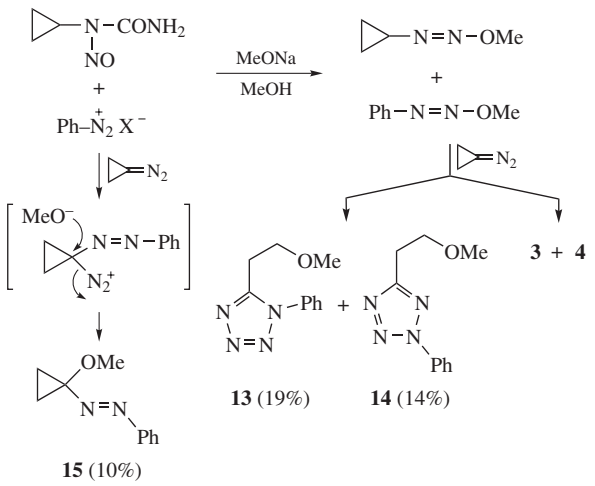
For characteristics of compounds **7**–**10**, see Online Supplementary Materials.

However, another reaction pathway is possible, in which the generation of CNU on treatment with NaOH/MeOH or KOH/H_2O is preceded by the formation of cyclopropyldiazenes **12a** or **12b**. Subsequent addition of diazocyclopropane to intermediates **12** followed by transformation of the spirane system would also produce the target tetrazoles **3** and **4** or **7** and **8** (Scheme 5). The regioselectivity of compound **1** addition to the N=N bond of diazenes **12a** and **12b** can vary, thus giving different ratios of isomeric tetrazoles in the case of methoxy and hydroxy derivatives.

Though the mechanisms of this transformation is still in question, the discovered possibility to obtain tetrazole derivatives in a reaction of two unstable intermediates is rather unique. Obviously, increasing the yield of tetrazoles requires raising the concentration of cyclopropyldiazonium intermediates in the solution, in particular, the latter may be enhanced by accelerating the CNU decomposition.

Based on the possible concepts of the tetrazole formation mechanism, it appeared interesting to perform the reactions of cyclopropyldiazonium with other diazo compounds or diazocyclopropane with aryldiazonium salts. We initially attempted to carry out the reactions of diazomethane or phenyldiazomethane with cyclopropyldiazonium intermediates **1** and **2** generated upon CNU decomposition on treatment with potassium or cesium carbonates or MeONa, at temperatures from –10 to 5 °C. However, the ^{1}H NMR spectra of the reaction mixtures were found to be very complex and non-informative; furthermore, the majority of the signals suggested the predominance of allylic compounds formed upon dediazotization of ion **2**.

Conversely, the reaction of a pre-synthesized phenyldiazonium salt with cyclopropyldiazonium intermediates generated *in situ* was more successful. In fact, addition of CNU and a methanolic solution of phenyldiazonium sulfate to a sodium methoxide solution in methanol at –15 °C gave not only cyclopropyltetrazoles **3** and **4** but also phenyltetrazoles **13** and **14**, as well as cyclopropylazobenzene **15** (Scheme 6).[††] Isomeric tetrazoles **13** and **14** were identified using ^{1}H and ^{13}C NMR spectra; a NOESY experiment revealed correlation between *ortho*-protons of the phenyl substituent with the α-methylene protons of the 2-methoxyethyl moiety in 1,5-isomer **13**.



Scheme 6

The formation of tetrazoles **13** and **14** containing a 2-methoxyethyl moiety apparently follows a scheme similar to the formation of tetrazoles **3** and **4**; again, it is probable that in this case diazocyclopropane **1** would add to *N*-methoxyphenyldiazene that is generated under the reaction conditions on treatment of a phenyldiazonium salt with MeONa. The formation of compound **15** can be attributed to the reaction of the phenyldiazonium salt itself with diazocyclopropane, followed by nucleophilic elimination of a nitrogen molecule.

In summary, we have found a new reaction, namely, straightforward conversion of cyclopropyldiazonium intermediates into disubstituted tetrazoles, which brings more insight into chemistry of highly reactive linear compounds with N–N bonds.

This study was supported by the Division of Chemistry and Materials Science of the Russian Academy of Sciences (Programme for Basic Research ‘Theoretical and Experimental Study of the Nature of Chemical Bond and Mechanisms of the Most Important Chemical Reactions and Processes’).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.11.002.

References

1 (*a*) Yu. V. Tomilov, I. V. Kostyuchenko and O. M. Nefedov, *Usp. Khim.*, 2000, **69**, 507 (*Russ. Chem. Rev.*, 2000, **69**, 461); (*b*) Yu. V. Tomilov and I. V. Kostyuchenko, in *Sovremennye problemy organicheskoi khimii* (*Modern Problems of Organic Chemistry*), St. Petersburg State University, St. Petersburg, 2001, issue 13, p. 113 (in Russian); (*c*) I. P. Klimenko, Yu. V. Tomilov and O. M. Nefedov, *Izv. Akad. Nauk, Ser. Khim*., 2004, 226 (*Russ. Chem. Bull., Int. Ed*., 2004, **53**, 236); (*d*) E. V. Guseva, N. V. Volchkov, E. V. Shulishov, Yu. V. Tomilov and O. M. Nefedov, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1265 (*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1318).

2 (*a*) Yu. V. Tomilov, I. V. Kostyuchenko, E. V. Shulishov and O. M. Nefedov, *Mendeleev Commun.*, 2002, 104; (*b*) Yu. V. Tomilov, G. P. Okonnishnikova, E. V. Shulishov and O. M. Nefedov, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 640 (*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 671); (*c*) I. P. Klimenko, V. A. Korolev, Yu. V. Tomilov and O. M. Nefedov, *Zh. Org. Khim.*, 2006, **42**, 1299 (*Russ. J. Org. Chem.*, 2006, **42**, 1320).

3 (*a*) 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); (*b*) G. P. Okonnishnikova, I. V. Kostyuchenko, E. V. Shulishov and Yu. V. Tomilov, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 2151 (*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 2233).

4 W. Kirmse and H. Schütte, *Chem. Ber.*, 1968, **101**, 1674.

5 V. V. Semenov, V. S. Bogdanov, B. S. El’yanov, L. G. Mel’nikova, S. A. Shevelev, V. M. Zhulin and A. A. Fainzil’berg, *Khim. Geterotsikl. Soedin.*, 1982, 1118 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1982, **18**, 859].

6 Y. Maeda and K. U. Ingold, *J. Am. Chem. Soc.*, 1980, **102**, 328.

7 M. W. Dunker, E. R. Starkey and G. L. Jenkins, *J. Am. Chem. Soc.*, 1936, **58**, 2308.

8 (*a*) H. Zollinger, *Diazo Chemistry II. Aliphatic, Inorganic and Organometallic Compounds*, VCH, Weinheim, 1995, Sect. 6.5, p. 234; (*b*) H. Reimlinger, G. S. D. King and M. A. Peiren, *Chem. Ber.*, 1970, **103**, 2821.

[††] *Decomposition of CNU with MeONa in the presence of phenyldiazonium sulfate*. A mixture of *N*-cyclopropyl-*N*-nitrosourea (4 mmol) and phenyldiazonium sulfate obtained preliminarily (8 mmol) in methanol (6 ml) was added in small portions at –20 °C to a solution of MeONa and additionally stirred for 20 min. Then water (15 ml) was added and the reaction mixture was extracted with CH_2Cl_2 (4×5 ml). After removing the solvent, the residue was treated with column chromatography [SiO_2, benzene–AcOEt (5:1)] to give phenyltetrazoles **13** and **14** and 1-(1-methoxycyclopropyl)-2-phenyldiazene **15**.

For NMR spectra of compounds **13**–**15**, see Online Supplementary Materials.

Received: 1st April 2011; Com. 11/3712