Chemistry of Heterocyclic Compounds, Vol. 42, No. 11, 2006

RADICAL-ANIONS IN THE VICARIOUS C-AMINATION REACTIONS OF N-SUBSTITUTED NITROTRIAZOLES

T. I. Vakul'skaya, I. A. Titova, L. I. Larina, O. N. Verkhozina, G. V. Dolgushin, and V. A. Lopyrev

The vicarious nucleophilic substitution of hydrogen in symmetrical and vicinal nitrotriazoles by 1,1,1-trimethylhydrazinium iodide in t-BuOK/DMSO was studied by ESR. In the ESR monitoring of the reactions the primary radical-anions of 4-nitro-2-phenyl-1,2,3-triazole and 1-methyl-3-nitro-1,2,4-triazole were detected and characterized. It was shown by NMR that the amination of 4-nitro-2-phenyl-1,2,3-triazole takes place exclusively in the triazole ring with the formation of 5-amino-4-nitro-2-phenyl-1,2,3-triazole. 1-Methyl-3-nitro-1,2,4-triazole, like 3-nitro-1,2,4-triazole, does not form amination products. A possible mechanism for the vicarious C-amination of nitrotriazoles and the formation of the radical-anions of the substrates is discussed.

Keywords: radical-anions, nitrotriazoles, amination, vicarious nucleophilic substitution of hydrogen, ESR, NMR.

The constant attention of synthetic chemists to the vicarious nucleophilic substitution of hydrogen is reflected in a series of detailed reviews [1-3]. During the vicarious substitution of hydrogen an amino group is readily introduced into nitro aromatic and nitro heteroaromatic compounds [4, 5], and this opens up broad synthetic possibilities (in particular the Sandmeyer reaction) and in itself explains the increased interest in the vicarious nucleophilic substitution of hydrogen. Interest has recently shifted to study of the mechanism of the process [6-9].

Having put forward the idea of possible electron transfer during the vicarious nucleophilic substitution of hydrogen [9] and having confirmed this for the vicarious amination of nitrobenzene and a series of N-methylated nitroazoles [10-12], we assumed that the lower the reduction potential of the nitroazole the more readily the latter should undergo amination in the vicarious nucleophilic substitution of hydrogen. Our papers on the electrochemical reduction of azoles in an aprotic medium [13, 14] show that their first reduction potentials decrease both with the accumulation of nitrogen atoms in the heterocycle and with the introduction of phenylene fragments. Apparently, overlap of the orbitals of the unshared electron pairs of adjacent pyridine nitrogen atoms or increase in the aromaticity of the system help to reduce the energy of the LUMO and facilitate the transfer of an electron to the molecule being reduced.

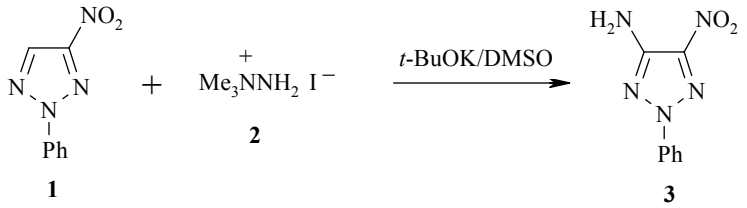
* Dedicated to Academician M. G. Voronkov on his 85th birthday.

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk; e-mail: irk_inst_chem@irioch.irk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1662-1670, November, 2006. Original article submitted July 31, 2006.

However, in spite of the fact that nitroazoles unsubstituted at the nitrogen atom are reduced at the first stage more readily than their N-alkylated derivatives [15-22], mononitro-substituted pyrazoles, imidazoles, and benzimidazoles with unsubstituted nitrogen atoms are not aminated under the conditions of the vicarious nucleophilic substitution of hydrogen [9, 10, 23-25]. This can be explained by the fact that not only the reagent but also the substrate (the mononitroazole) unsubstituted at the nitrogen atom undergoes deprotonation in a highly basic medium, and as a result electron transfer from the anion of the reagent to the anion of the substrate becomes unlikely if not impossible. On the other hand, the presence of a second nitro group in the substrate compensates for the dissociation of the NH bond and, dinitropyrazole unsubstituted at the nitrogen atom, for example, forms an amination product albeit in the form of a crystalline solvate with DMSO [26].

In a continuation of our investigations into the vicarious C-amination of nitroazoles containing two nitrogen atoms in the five-membered ring [9, 10, 12] and the condensed analogs of imidazole (nitrobenzimidazoles) [11] in the present work we present the results from the amination of nitroazoles containing three nitrogen atoms in the five-membered ring, i.e., 3-nitro-1,2,4-triazoles and 4-nitro-2-phenyl-1,2,3-triazole.

The vicarious nucleophilic amination of 4-nitro-2-phenyl-1,2,3-triazole (**1**) with 1,1,1-trimethylhydrazinium iodide (**2**) in *t*-BuOK–DMSO is accompanied by intense coloration of the reaction mixture and leads to the formation of one product from amination in the heterocycle 5-amino-4-nitro-2-phenyl-1,2,3-triazole (**3**), i.e., the phenyl substituent at the nitrogen atom does not prevent amination of the heterocycle but is not itself aminated.



A similar situation was observed during the reaction of 4-nitro-1-phenylimidazole and 2-methyl-1-phenyl-4-nitroimidazole with 4-amino-1,2,4-triazole in the MeONa–DMSO system [27, 28], although in 4-nitropyrazole, which has a *para*-nitrophenyl substituent at position 1, vicarious nucleophilic substitution of hydrogen takes place both in the azole and in the arylene fragments [29].

In the downfield region (7.3-7.6 ppm) the ^{1}H NMR spectra (DMSO-d_6) of compound **3** contain characteristic signals belonging to the *ortho*, *meta*, and *para* protons of the phenyl ring. A broad signal for the protons of the amino group appears in the upfield region (4.5 ppm) on account of exchange with water residues present in the DMSO-d_6. The assignment of the ^{13}C NMR signals was made on the basis of the 2D HSQC-GP ^{1}H–^{13}C and HMBC-GP ^{1}H–^{13}C spectra and published data [30].

During study of the reaction of compound **1** with **2** in an inert atmosphere by ESR a signal in the form of a nitrogen triplet with strongly broadened edge components appeared in the spectrum after only 5 min (Fig. 1a). The intensity of the signal increased for 30 min. The broadening of the lines in the spectrum then disappeared, and it became possible to identify the well resolved signal and assign it to the radical-anion of 4-nitro-2-phenyl-1,2,3-triazole (**4**). The nature of its hyperfine structure (HFS) corresponds to coupling of the unpaired electron with all the magnetic nuclei of the heterocycle and to weak coupling with three protons of the phenyl substituent (Fig. 1b).

The computer simulation corresponds best to the experimental spectrum for the following signals and HFS constants, mT: triplet (N–NO_2, 0.550); doublet (1H, 0.550); triplet (1N, 0.220); triplet (1N, 0.110); triplet (1N, 0.055); doublet (1H-*para*, 0.020); triplet (2H-*ortho*, 0.010) (Fig. 1c).

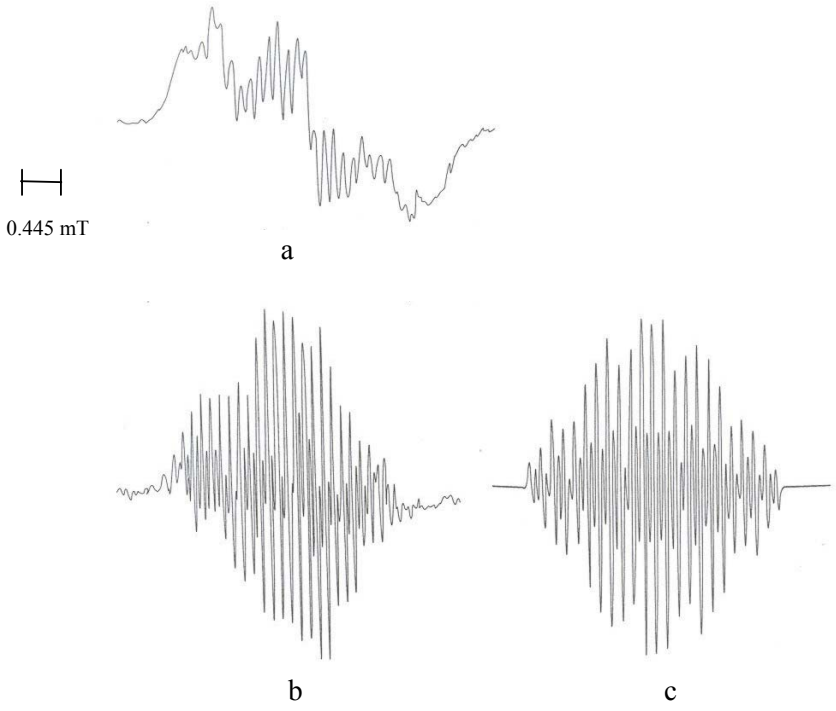


Fig. 1. The ESR spectra of the reaction mixture of compounds **1** and **2** in *t*-BuOK–DMSO 25 min (a) and 45 min (b) after the beginning of the reaction. The simulated spectrum of the radical-anion **4** (c).

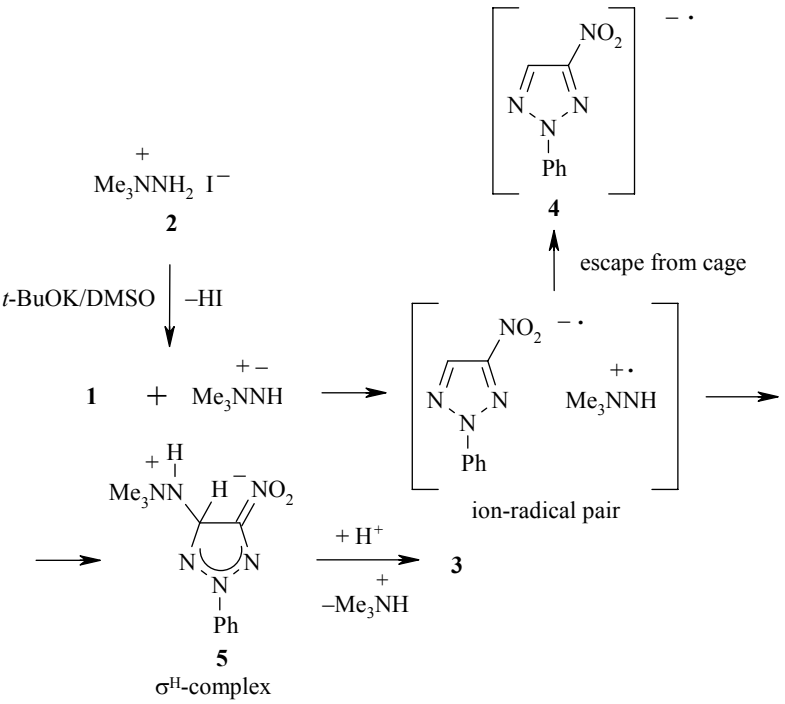
After quantum-chemical calculation of the distribution of the spin density in the radical-anion **4** it was possible to assign the HFS constants of the ring nitrogen atoms. The smallest nitrogen constant belongs to the N-2 atom attached to the phenyl substituent. Incidently, it should be noted that in all the radical-anions of the N-methyl derivatives of nitroazoles that we obtained earlier by electrochemical reduction in acetonitrile the smallest spin density at the nitrogen atoms in all cases corresponded to the pyrrole nitrogen atom [31].

To explain the weak transfer of spin density to the aromatic fragment we supposed that the phenyl ring was turned away from the plane of the triazole ring. The *ab initio* calculations of the radical-anion **4** actually showed the absence of spin density on the phenyl ring when it is rotated through 90°. In energy, however, the planar molecular structure of the radical-anion proved more favorable (by ~8 kcal/mol) (HF = -673.803 and HF = -673.791 respectively for the planar molecule and for the molecule rotated through 90°). Delocalization of the spin density at the phenyl fragment is probably prevented by ineffective overlap of the orbitals of the pyrrole nitrogen atom and the π system of the ring.

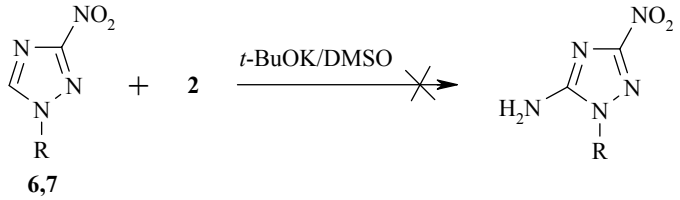
We explain the formation of the radical-anions of the substrate in the above-mentioned vicarious amination reaction by the presence of direct electron transfer from the anion of the reagent, generated in the highly basic medium, to the nitroazole (Scheme 1).

The broadening of the side components of the nitrogen triplet (Fig. 1a) may result from exchange interactions of the radical-ions in the solvent cage, while the strong well-resolved signal of the free radical-anion **4** is observed as it accumulates in the solution as a result of escape from the solvent cage.

Scheme 1



It was not possible to obtain amination products in the vicarious nucleophilic substitution of hydrogen in 3-nitro-1,2,4-triazole (**6**) and 1-methyl-3-nitro-1,2,4-triazole (**7**) by compound **2** in the *t*-BuOK–DMSO medium.



6 R = H, **7** R = Me

As expected, ESR monitoring showed that the reaction mixture of the N-unsubstituted nitrotriazole **6** with the iodide **2** was diamagnetic, and this agrees with the absence both of the blue-violet color in the reaction mixture and of the amination product. It was unexpectedly found that 1-methyltriazole **7**, unlike other N-protected nitroazoles [10-12], also does not form amination products under the conditions of the vicarious nucleophilic substitution of hydrogen, although in this case the reaction mixture was colored, and a signal for the primary radical-anion of 1-methyl-3-nitro-1,2,4-triazole (g = 2.0032) appeared in the ESR spectrum with signals and HFS constants, mT: triplet ($N–NO_2$, 1.178); doublet (1H, 0.440); triplet (1N, 0.160); triplet (1N, 0.120); triplet (1N, 0.050); quartet ($3H–CH_3$, 0.050) (Fig. 2). We obtained the radical-anion **i** with similar constants earlier by the electrochemical reduction of 1-methyl-3-nitro-1,2,4-triazole in an aprotic medium [16, 18].

Why then is the product from amination of 1-methyl-3-nitro-1,2,4-triazole not formed during the vicarious nucleophilic substitution of hydrogen? We found the answer to this question by comparing the results from investigation of the vicarious C-amination of the nitro derivatives of 1,2,3- and 1,2,4-triazoles by ESR and

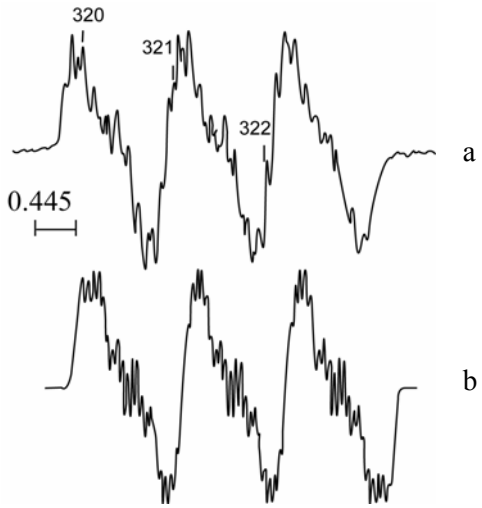
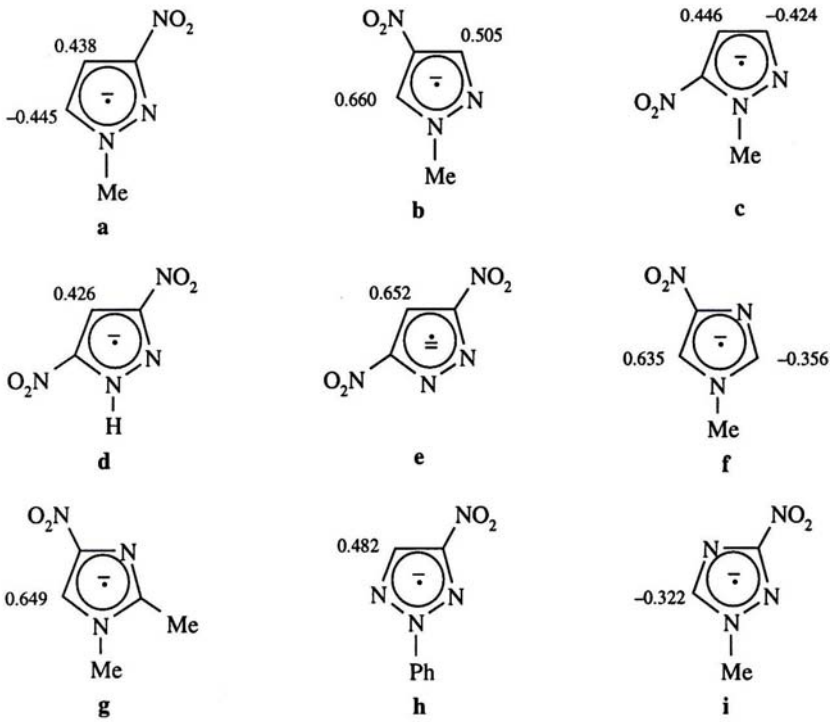


Fig. 2. The ESR spectrum of the reaction mixture of compounds **7** and **2** in *t*-BuOK–DMSO (a) and the simulated spectrum of the radical-anion of compound **7** (b).

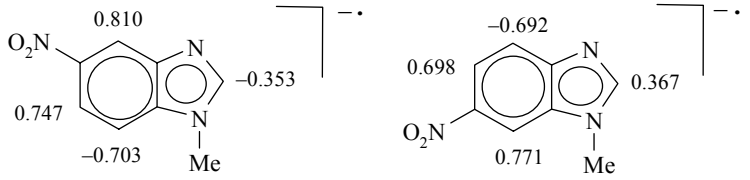
the analogous results that we obtained earlier for 1-methyl-4-nitropyrazole [12], 1-methyl-4-nitroimidazole [9, 10], and 1-methyl-5- and 1-methyl-6-nitrobenzimidazoles [11] with the data from quantum-chemical calculations of the spin density distribution in the radical-anions of the substrates **a**-**i**. It was found that the

The calculated spin density at the CH carbon atoms in the radical-ions of nitroazoles



amination of all the above-mentioned compounds takes place exclusively at carbon atoms with sufficiently high *positive* spin density in their radical-anions. In particular, in the radical-anion of compound **7** at the only position 5 at which amination could occur the spin density has a negative sign **i**.

The vicarious amination of 1-methyl-5- and 1-methyl-6-nitrobenzimidazoles is important from this standpoint [11]. Whereas the former forms a single product, i.e., 4-amino-1-methyl-5-nitrobenzimidazole, the latter forms two products 7-amino-6-nitrobenzimidazole and 2-amino-6-nitrobenzimidazole in a ratio of 2:1 during amination. In the radical-anion of 1-methyl-5-nitrobenzimidazole **A** maximum positive spin density is concentrated at position 4, while in the radical-anion of 1-methyl-6-nitrobenzimidazole **B** it is concentrated at position 7. But then position 2 in **A** is characterized by negative and that in **B** by fairly high positive spin density.



A **B**

Thus, in our work on the vicarious nucleophilic substitution of hydrogen in azoles the reaction mechanism was examined for the case of the vicarious C-amination of nitroazoles from the standpoint of possible electron transfer for the first time. A reaction scheme involving successive stages with electron transfer, the formation of a σ^H complex, and the formation of the amination product was proposed. Observation of the primary radical-anions of the nitroazoles in the vicarious C-amination reactions shows that electron transfer takes place quickly, while the next stage with the formation of the σ^H complex is a slow stage. This makes it possible for the radical particles to escape from the solvent cage before their "collapse" into the σ^H complex and by virtue of their stability to accumulate in the solution. Amination here takes place at carbon atoms with sufficiently high and only positive spin density in the radical-anions of the substrate.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DPX-400 and Bruker AV-400 spectrometers (400 and 101 MHz respectively). The ^1H and ^{13}C chemical shifts were measured with reference to TMS with an accuracy of 0.01 and 0.02 ppm respectively. The spin–spin coupling constants (J_{CH}) were determined with an accuracy of 0.1 Hz. The HSQC-GP (heteronuclear single quantum correlation gradient pulse) [32] and HMBC-GP (heteronuclear multiple bond correlation gradient pulse) [33] methods were used to obtain the 2D ^1H–^{13}C spectra.

The ESR spectra were obtained in special cells in an atmosphere of dry argon on an SE/X-2547 spectrometer (Radiopan, Poland) with a resolving power of not less than 0.06 mT (controlled by the radical-cation of perylene) and a sensitivity of $5 \cdot 10^{11}$ c*P*/mT, equipped with a magnetometer and a high-frequency meter. All the starting materials and the solvents were submitted to thorough purification. Each component of the reaction mixture was checked for the absence of paramagnetism. Control tests were carried out in the required order, where one of the components was omitted from the reaction mixture in turn. Each reaction mixture was monitored continuously for several hours by ESR.

The ESR signals of the radical-anions of the 1-methylnitroazoles were identified by alternative synthesis under the conditions of electrochemical generation and computer simulation of the ESR spectra using the Bruker WINEPR SimFonia 1.26 1966 software.

The quantum-chemical calculations of the spin density distribution in the radical-anions and radical-dianions were performed with the GAUSSIAN-98 software package [34].

The nitrotriazoles **1**, **6**, and **7** were prepared by the methods described in [35-37] and purified by recrystallization or vacuum sublimation just before use.

5-Amino-4-nitro-2-phenyl-1,2,3-triazole (3). 4-Nitro-2-phenyl-1,2,3-triazole **1** (4.0 g, 0.021 mmol) was dissolved in absolute DMSO (40 ml) with stirring, and 1,1,1-trimethylhydrazinium iodide **2** (4.85 g, 0.024 mmol) was then added. When the latter had completely dissolved potassium *t*-butoxide (5.38 g, 0.048 mmol) was added. The reaction mass acquired a saturated red-black color. The mixture was stirred at room temperature for 10 h, poured into water, and acidified to pH 6 with 10% hydrochloric acid. The orange precipitate was filtered off, washed with cold water, and recrystallized from aqueous ethanol; mp 165°C. Yield 4 g (93% on the unrecrystallized product). IR spectrum, ν, cm^{-1}: 3500, 3390 (NH_2); 1575, 1320, 1270 (NO_2); 1485, 1210, 765 (C_6H_5); 1635 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.53 (2H, d, *J* = 7.6, H-*p* Ph); 7.46 (2H, t, *J* = 7.6, H-*m* Ph); 7.26 (1H, t, *J* = 7.6, H-*p* Ph); 4.00 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 146.21 (C-4); 143.48 (C-*ipso* Ph); 141.20 (C-5); 129.64 (C-*m* Ph); 126.47 (C-*p* Ph); 117.77 (C-*o* Ph). Chromato-mass spectrum, found: *m*/*z* 205 $[M]^+$. $C_8H_7N_5O_2$. Calculated, %: M = 205.18. Found %: C 46.32; H 3.64; N 34.27. $C_8H_7N_5O_2$. Calculated %: C 46.83; H 3.44; N 34.13.

The work was carried out with financial support from the Department of Chemistry and Science of Materials, Russian Academy of Sciences (grant 4.1.7.).

REFERENCES

1. M. Makosza, *Usp. Khim.*, **58**, 1298 (1989).
2. M. Makosza, *Izv. Akad. Nauk. Ser. Khim.*, 531 (1996).
3. O. N. Chupakhin and D. G. Beresnev, *Usp. Khim.*, **71**, 803 (2002).
4. A. R. Katritzky and K. S. Laurenzo, *J. Org. Chem.*, **53**, 3978 (1988).
5. O. V. Donskaya, G. V. Dolgushin, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 435 (2002). [*Chem. Heterocycl. Comp*., **38**, 371 (2002)].
6. M. Makosza and A. Kwast, *J. Phys. Org. Chem*., **11**, 341 (1998).
7. M. Makosza, T. Lemek, A. Kwast, and F. Terrier, *J. Org. Chem.*, **67**, 394 (2002).
8. T. Lemek, M. Makosza, D. S. Stephenson, and H. Mayr, *Angew. Chem., Int. Ed. Engl.*, **42**, 2793 (2003).
9. O. V. Donskaya, V. N. Elokhina, T. I. Vakul'skaya, A. V. Vokin, L. I. Larina, and V. A. Lopyrev, in: *Abstracts of International Conference "Reaction Mechanisms and Organic Intermediates"*, St. Petersburg, Russia (2001), p. 96.
10. O. V. Donskaya, V. N. Elokhina, A. S. Nakhmanovich, T. I. Vakul'skaya, L. I. Larina, A. V. Vokin, A. I. Albanov, and V. A. Lopyrev, *Tetrahedron Lett.*, **43**, 6613 (2002).
11. I. A. Titova, T. I. Vakul'skaya, L. I. Larina, M. I. Mizandrontsev, V. A. Volkov, G. V. Dolgushin, and V. A. Lopyrev, *Zh. Org. Khim.*, **41**, 1331 (2005).
12. T. I. Vakul'skaya, I. A. Titova, G. V. Dolgushin, and V. A. Lopyrev, *Magn. Reson. Chem.*, **43**, 1023 (2005).
13. V. A. Lopyrev, T. G. Ermakova, T. N. Kashik, L. E. Protasova, and T. I. Vakul'skaya, *Khim. Geterotsikl. Soedin.*, 315 (1986). [*Chem. Heterocycl. Comp.*, **22**, 253 (1986)].
14. T. G. Ermakova, A. I. Gritsa, N. M. Deriglazov, L. A. Tatarova, V. V. Keiko, T. I. Vakul'skaya, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 408 (1980). [*Chem. Heterocycl. Comp.*, **16**, 313 (1980)].
15. V. A. Shagun, T. I. Vakul'skaya, L. I. Larina, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 193 (2000). [*Chem. Heterocycl. Comp.*, **36**, 157 (2000)].

16. T. I. Vakul'skaya, L. I. Larina, O. B. Nefedeva, and V. A. Lopyrev, 523 (1982). [*Chem. Heterocycl. Comp.*, **18**, 400 (1982)].
17. T. I. Vakul'skaya, T. N. Rakhmatulina, M. S. Pevzner, T. P. Kofman, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 343 (1987). [*Chem. Heterocycl. Comp.*, **23**, 287 (1987)].
18. V. A. Lopyrev, L. I. Larina, L. Kh. Baumane, E. F. Shibanova, R. A. Gavar, S. M. Ponomareva, T. I. Vakul'skaya, and Ya. P. Stradyn', *Khim. Geterotsikl. Soedin.*, 1246 (1984). [*Chem. Heterocycl. Comp.*, **20**, 1021 (1984)].
19. V. A. Lopyrev, L. I. Larina, T. I. Vakul'skaya, E. F. Shibanova, I. A. Titova, and M. G. Voronkov, *Magn. Reson. Chem.*, **23**, 305 (1985).
20. V. A. Lopyrev, L. I. Larina, I. M. Sosonkin, T. I. Vakul'skaya, G. L. Kalb, and E. F. Shibanova, *Khim. Geterotsikl. Soedin.*, 827 (1985). [*Chem. Heterocycl Comp.*, **21**, 688 (1985)].
21. T. I. Vakul'skaya, L. I. Larina, O. B. Nefedova, L. P. Petukhov, M. G. Voronkov, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 1398 (1979). [*Chem. Heterocycl. Comp.*, **15**, 1127 (1979)].
22. V. A. Lopyrev, L. I. Larina, T. N. Rakhmatulina, E. F. Shibanova, T. I. Vakul'skaya, and M. G. Voronkov, *Dokl. Akad. Nauk*, **242**, 142 (1978).
23. V. A. Lopyrev, V. N. Elokhina, O. V. Krylova, A. S. Nakhmanovich, L. I. Larina, M. S. Sorokin, and A. I. Vokin, *Khim. Geterotsikl. Soedin.*, 1254 (1999). [*Chem. Heterocycl. Comp.*, **35**, 1109 (1999)].
24. V. N. Elokhina, O. V. Krylova, L. I. Larina, A. S. Nakhmanovich, M. S. Sorokin, K. A. Volkova, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 551 (2000). [*Chem. Heterocycl. Comp.*, **36**, 476 (2000)].
25. M. K. Bernard, *Polish J. Chem.*, **69**, 1120 (1995).
26. R. D. Schmidt, G. S. Lee, P. F. Pagoria, A. R. Mitchell, and R. Gilardi, *J. Heterocycl. Chem.*, **38**, 1227 (2001).
27. J. Suwinski, K. Swierczek, and T. Glowiak, *Tetrahedron*, **49**, 5339 (1993).
28. J. Suwinski, K. Swierczek, and T. Glowiak, *Tetrahedron Lett.*, **33**, 7941 (1992).
29. M. K. Bernard, M. Makosza, B. Szafran, and U. Wrzeciono, *Liebigs Ann. Chem.*, 545 (1989).
30. L. I. Larina and V. A. Lopyrev, *Topics in Heterocyclic Systems - Synthesis, Reactions and Properties*, **1**, 187 (1996).
31. L. I. Larina, V. M. Dubnikov, F. S. Lur'e, T. I. Vakul'skaya, N. M. Vitkovskaya, V. A. Lopyrev, and M. G. Voronkov, *Zh. Strukt. Khim.*, **21**, 203 (1980).
32. A. Bax and S. Subramanian, *J. Magn. Reson.*, **67**, 565 (1986).
33. A. Bax and S. Subramanian, *J. Am. Chem. Soc.*, **108**, 2093 (1986).
34. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, *Gaussian 98*, Revision A. 6, Gaussian Inc., Pittsburgh, PA (1998).
35. H. A.-G. Farbwerke, German Patent 1168437; *Chem. Abstr.*, **61**, 1873 (1964).
36. L. I. Bagal, M. S. Pevzner, A. N. Frolov, and N. I. Sheludyakova, *Khim. Geterotsikl. Soedin.*, 259 (1970). [*Chem. Heterocycl. Comp.*, **6**, 240 (1970)].
37. L. I. Bagal, M. S. Pevzner, N. I. Sheludyakova, and V. M. Kerusov, *Khim. Geterotsikl. Soedin.*, 265 (1970). [*Chem. Heterocycl. Comp.*, **6**, 245 (1970)].