*Chemistry of Heterocyclic Compounds, Vol. 45, No. 6, 2009*

# SYNTHESIS OF 2-AROYL-1-HYDROXY-4,5-DIMETHYLIMIDAZOLES BY REACTION OF 3-HYDROXYAMINO-2-BUTANONE OXIME WITH ARYLGLYOXALS*

**S. A. Amitina[1], A. Ya. Tikhonov[1]**, I. A. Grigor'ev[1], Yu. V. Gatilov[1], and B. A. Selivanov[1]**

*Treatment of the acetate of 3-hydroxyamino-2-butanone oxime with arylglyoxals gives α-aroylnitrones which cyclize under acid catalyzed conditions to form principally 2-aroyl-1-hydroxy-4,5-dimethylimidazoles. An X-ray structural analysis of 2-benzoyl-1-hydroxy-4,5-dimethylimidazole has been carried out.*

**Keywords:** arylglyoxals, 2-aroyl-1-hydroxyimidazoles, α-aroyl nitrones, hydroxylamino oxime, pyrazine 1,4-dioxides, X-ray structural analysis.

Imidazoles are an important class of heterocyclic compounds with a broad spectrum of biological activity and practical importance [1]. 1-Hydroxy-2-[(4-phenoxy)benzoyl]-4,5,6,7-tetrahydrobenzimidazole has recently been shown to have antibacterial activity [2]. 2-Aroyl-1-hydroxy-4,5,6,7-tetrahydrobenzimidazoles have previously been prepared by condensation of 2-hydroxyaminocyclohexanone oxime with aryl- and hetarylglyoxals while use of phenylglyoxal gave significant amounts of 5,6,7,8-tetrahydroxyquinoxaline 1,4-dioxide [3]. It should be noted that 4,5-dialkyl-1-hydroxyimidazoles or their tautomeric imidazole N-oxides were not formed upon oxidation of an imidazole ring [4].

In this work we report a study of the condensation of the acetate of the acyclic 3-hydroxyamino-2-butanone oxime **1** with the arylglyoxals hydrates **2a-f** in order to establish the cyclization route. In this case predominant formation of imidazole derivatives rather than pyrazines would be expected because the absence of a methylene bridge should have assisted cyclization of the intermediate nitrones to form the five-membered heterocycle.

---

* Dedicated to Academician Boris Aleksandrovich Trofimov on the occasion of his 70th jubilee.

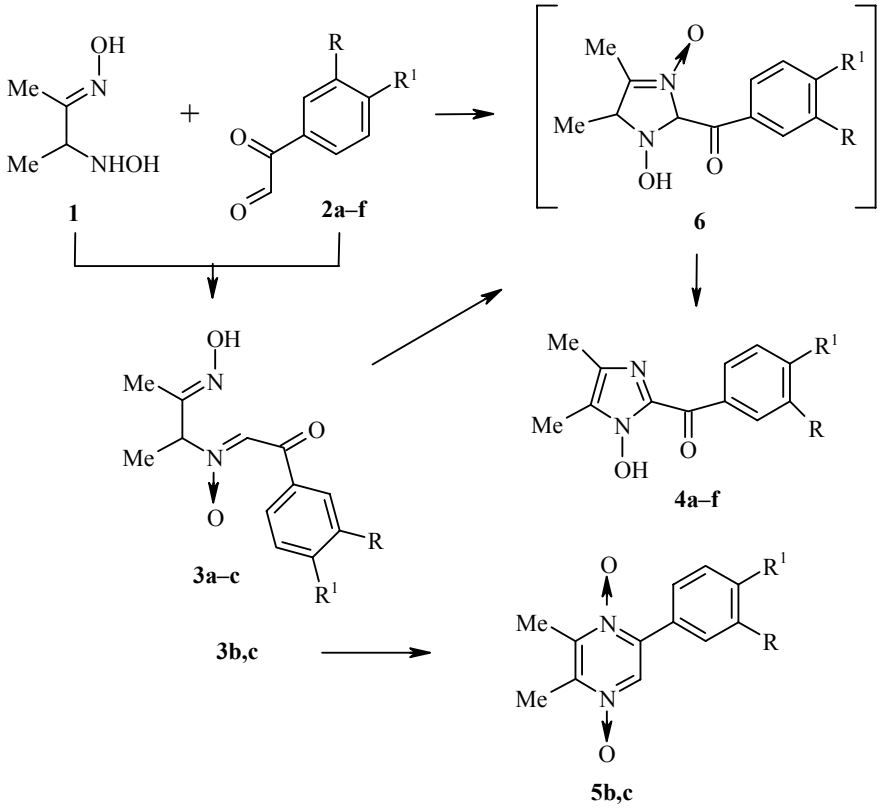
** To whom correspondence should be addressed, e-mail: alyatikh@nioch.nsc.ru.

[1]N. N. Vorozhtsov Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Novosibirsk 630090, Russia.

---

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 868-874, June, 2009. Original article submitted May 30, 2008.

Condensation of 3-hydroxyamino-2-butanone oxime **1** acetate with phenylglyoxal hydrate **2a** at room temperature in methanol or in water gave initially the α-benzoylnitrone **3a**. Under the same conditions (methanol) reaction of the **1**·AcOH salt with the arylglyoxal hydrates **2b,c** gave the corresponding α-aroyl nitrones **3b,c**. Chromatography of the reaction mixture after preparation of the benzoylnitrone **3b** gave the benzoylimidazole **4b** and pyrazine 1,4-dioxide **5b**.




**2–5 a–e** R = H; **a** $R^1$ = H, **b** $R^1$ = Cl, **c** $R^1$ = $NO_2$, **d** $R^1$ = OMe, **e** $R^1$ = OEt, f R = R1 = OEt

Heating solutions of the nitrones **3a-c** in methanol in the presence of acetic acid or nitrone **3a** in acetic acid led to formation of the 1-hydroxyimidazoles **4a-c** while TLC showed that the reaction mixture contained the pyrazine 1,4-dioxides **5a-c** isomeric with the 1-hydroxyimidazoles **4a-c**. The pyrazine 1,4-dioxide **5a** was identified by TLC comparison with a known sample which is quantitatively formed by condensation of the *E*-isomer of 2-hydroxyamino-1-phenylethanone oxime with diacetyl [5]. As expected, carrying out the condensation of salt **1**·AcOH with the arylglyoxal hydrates **2d-f** by heating in methanol in the presence of acetic acid led to the 1-hydroxyimidazoles **4d-f**. Typifying the $^1$H NMR spectra of compounds **4a-f** is the presence of a low field hydroxyl group proton signal at 13.7-14.4 ppm and for the pyrazine 1,4-dioxides **5b,c** the signal for the heteroaromatic proton at 8.1-8.7 ppm (Table 1) (cf. [4, 5]).

Formation of the 1-hydroxyimidazoles **4a-f** evidently occurs *via* a ready dehydration reaction of the intermediate 2-aroyl-1-hydroxy-3-imidazoline 3-oxides **6** (see [6]).

The structure and composition of all of the synthesized compounds were supported by their spectroscopic charcteristics (Table 1) and by elemental analytical data (Table 2).

Through studying the structure of the 2-benzoyl-1-hydroxy-4,5-dimethylimidazole **4a** by X-ray analysis it was found that the N(1)–C(7) fragment and atoms O(1), O(2), C(13), and C(14) lie in a single plane in the molecule within ± 0.080 Å. The benzene ring deviates from this plane, the dihedral angle being 14.58(5)º. There is no information in the Cambridge structural database regarding the structure of 1-hydroxyimidazoles containing an

TABLE 1. Spectroscopic Characteristics for the Compounds Synthesized

| Compound | IR spectrum, ν, $cm^{-1}$ | UV spectrum, $\lambda_{max}$, nm (log ε) | $^1$H NMR spectrum, δ, ppm (*J*, Hz)* |
|---|---|---|---|
| **3a** | 3318, 1649, 1520, 1242, 948 | 309 (4.14) | 1.53 (3H, d, *J* = 6.5, $CH_3$); 1.81 (3H, s, $CH_3$); 5.15 (1H, q, *J* = 6.5, C<u>H</u>–$CH_3$); 7.50-7.59 (3H, m, H-3,4,5 Ar); 7.91 (2H, m, H-2,6 Ar); 8.56 (1H, s, =CH); 11.16 (1H, s, 1-OH) |
| **3b** | 3245, 1651, 1529, 1247, 953 | 314 (4.21) | 1.54 (3H, d, *J* = 6.5, $CH_3$); 1.83 (3H, s, $CH_3$); 5.17 (1H, q, *J* = 6.5, C<u>H</u>-$CH_3$); 7.65 (2H, m, H-3,5 Ar); 7.95 (2H, m, H-2,6 Ar); 8.59 (1H, s, =CH); 11.25 (1H, br. s, OH) |
| **3c** | 1657, 1525, 1347, 1231, 953 | 271 (4.06), 316 (4.15) | 1.52 (3H, d, *J* = 6.9, $CH_3$); 1.80 (3H, s, $CH_3$); 5.18 (1H, q, *J* = 6.9, C<u>H</u>–$CH_3$); 8.09 (2H, m, H-2,6 Ar); 8.34 (2H, m, H-3,5 Ar); 8.63 (1H, s, =CH); 11.21 (1H, br. s, OH) |
| **4a** | 1640, 1467, 1292, 909 | 258 (3.90), 328 (4.06) | 2.28 (6H, s, 4,5-$CH_3$); 7.40–7.60 (3H, m, H-3,4,5 Ar); 8.57 (2H, m, H-2,6 Ar); 14.15 (1H, s, 1-OH) |
| **4b** | 1637, 1587, 1463, 1298, 909 | 265 (3.88), 331 (3.97) | 2.30 (6H, s, 4,5-$CH_3$); 7.49 (2H, m, H-3,5 Ar); 8.60 (2H, m, H-2,6 Ar); 14.06 (1H, s, 1-OH) |
| **4c** | 1608, 1563, 1525, 1472, 1344, 1300, 918 | 268 (4.07), 340 (3.90) | 2.26 (3H, s, 4- or 5-$CH_3$); 2.28 (3H, s, 4- or 5-$CH_3$); 8.30 (2H, m, H-2,6 Ar); 8.74 (2H, m, H-3,5 Ar); 13.71 (1H, s, 1-OH) |
| **4d** | 1603, 1456, 1296, 1259, 1170, 908 | 228 (3.84), 337 (4.45) | 2.24 (6H, s, 4,5-$CH_3$); 3.86 (3H, s, 4-$OCH_3$); 6.97 (2H, m, H-3,5 Ar); 8.66 (2H, m, H-2,6 Ar); 14.39 (1H, s, 1-OH) |
| **4e** | 1606, 1451, 1293, 1254, 1164, 907 | 228 (3.80), 343 (4.18) | 1.42 (3H, t, *J* = 6.9, 4-$OCH_2C\underline{H}_3$); 2.24 (6H, s, 4,5-$CH_3$); 4.09 (2H, q, *J* = 6.9, 4-$OC\underline{H}_2CH_3$); 6.95 (2H, m, H-3,5 Ar); 8.64 (2H, m, H-2,6 Ar); 14.41 (1H, s, 1-OH) |
| **4f** | 1598, 1464, 1274, 1259, 1145, 1041 | 241 (3.91), 357 (4.13) | 1.47 (6H, t, *J* = 7.0, 3,4-$OCH_2C\underline{H}_3$); 2.24 (6H, s, 4,5-$CH_3$); 4.17 (4H, q, *J* = 7.0, 3,4-$OC\underline{H}_2CH_3$); 6.93 (1H, d, *J* = 8.4, H-5 Ar); 8.09 (1H, d, *J* = 1.8, H-2 Ar); 8.50 (1H, dd, *J* = 1.8, 8.4, H-6 Ar); 14.39 (1H, s, 1-OH) |
| **5b** | 1595, 1489, 1354, 1243, 1107, 1091 | 265 (4.37), 314 (4.24) | 2.57 (6H, s, 2,3-$CH_3$); 7.46 (2H, m, H-3,5 Ar); 7.69 (2H, m, H-2,6 Ar); 8.18 (1H, s, H-6) |
| **5c** | 1601, 1516, 1348, 1248, 1105 | 260 sh. (3.15), 294 (4.32) | 2.46 (3H, s, 2- or 3-$CH_3$); 2.47 (3H, s, 2- or 3-$CH_3$); 8.07 (2H, m, H-2,6 Ar); 8.33 (2H, m, H-3,5 Ar); 8.69 (1H, s, H-6) |

* The $^1$H NMR spectra were recorded in DMSO-$d_6$ (compounds **3a-c** and **5c**) or $CDCl_3$ (compounds **4a-f** and **5b**).

aroyl or acetyl group at position 2 of the heterocycle. Table 3 shows selected bond lengths for the **4a** molecule and those calculated by the DFT/PBE/3z method for the isolated molecule **4a**. The high uniformity of bond lengths for the imidazole ring in the crystal with those calculated should be noted. The parameters for the intramolecular hydrogen bond O(1)–H(1)···O(2) are: O–H 1.03(3), H···O 1.60(3), O···O 2.536(2) Å and O–H···O 150(2)º. In the crystal of compound **4a** stacs of the molecules are formed along the *a* axis thanks to π-stacking interaction between the imidazole rings (intercentroid and interplanar distances 3.488(1) and 3.410 Å) and also between the C=O group and the imidazole ring (distances centroid-C(6) 3.477, interplanar 3.356 Å).

TABLE 2. Characteristics of the Compounds Synthesized

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C* | Yield*[2], % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **3a** | $C_{12}H_{14}N_2O_3$ | 61.72<br>61.52 | 6.06<br>6.02 | 11.80<br>11.96 | 153-154<br>(decomp.) | 62<br>(60) |
| **3b** | $C_{12}H_{13}ClN_2O_3$*[3] | 54.10<br>53.64 | 4.85<br>4.88 | 10.68<br>10.43 | 132<br>(decomp.) | 41 |
| **3c** | $C_{12}H_{13}N_3O_5$ | 51.65<br>51.61 | 4.75<br>4.69 | 14.83<br>15.05 | 149<br>(decomp.) | 72 |
| **4a** | $C_{12}H_{12}N_2O_2$ | 66.65<br>66.65 | 5.84<br>5.59 | 12.97<br>12.96 | 62-64 | 84<br>(84) |
| **4b** | $C_{12}H_{11}ClN_2O_2$*[4] | 57.40<br>57.49 | 4.34<br>4.42 | 11.43<br>11.18 | 111-112 | 76 |
| **4c** | $C_{12}H_{11}N_3O_4$ | 54.94<br>55.17 | 4.03<br>4.24 | 16.03<br>16.09 | 149-150 | 55 |
| **4d** | $C_{13}H_{14}N_2O_3$ | 63.58<br>63.40 | 5.73<br>5.73 | 11.33<br>11.38 | 103-104 | 57 |
| **4e** | $C_{14}H_{16}N_2O_3$ | 64.52<br>64.60 | 6.21<br>6.20 | 10.73<br>10.76 | 92-93 | 46 |
| **4f** | $C_{16}H_{20}N_2O_4$ | 63.48<br>63.14 | 6.72<br>6.62 | 9.16<br>9.21 | 116-117 | 63 |
| **5b** | $C_{12}H_{11}ClN_2O_2$*[4] | 57.94<br>57.49 | 4.27<br>4.42 | 10.99<br>11.18 | 192-193 | 8 |
| **5c** | $C_{12}H_{11}N_3O_4$ | 55.36<br>55.17 | 4.45<br>4.24 | 16.19<br>16.09 | 249<br>(decomp.) | 12 |

* Solvent for crystallization: MeOH (compounds **3c, 4c,f, 5b,c**), hexane (compounds **4a,b**) or ether (compounds **4d,e**).

*[2] Yield in brackets given for method B.

*[3] Found, %: Cl 13.19. Calculated, %: Cl 13.20.

*[4] Found, %: Cl 14.15. Calculated, %: Cl 14.15.

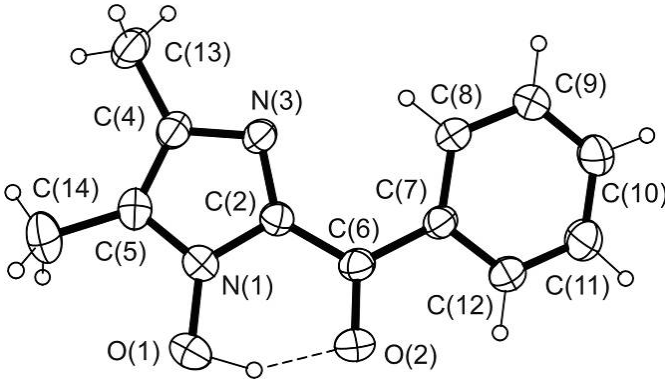



Fig. 1. Molecular structure and atomic numbering for compound **4a**. The thermal ellipsoids are shown at the 30% probability level.

According to the DFT/PBE/3z calculated for the gaseous phase the possible tautomer of compound **4a** as 2-benzoyl-4,5-dimethyl-1H-imidazole 3-oxide is 8.0 kcal/mol less stable and the alternative tautomer 2-(1-hydroxy-1-phenylmethylidene)-4,5-dimethyl-2H-imidazole 1-oxide is not a local minimum and crosses to **4a** without a barrier.

TABLE 3. Selected Bond Lengths (l) in the Compound **4a** Molecule

| Bond | *l*, Å | DFT/PBE/3z | Bond | *l*, Å | DFT/PBE/3z |
|---|---|---|---|---|---|
| N(1)–C(2) | 1.374(2) | 1.391 | N(1)–O(1) | 1.376(2) | 1.370 |
| C(2)–N(3) | 1.338(2) | 1.353 | C(2)–C(6) | 1.442(2) | 1.443 |
| N(3)–C(4) | 1.353(2) | 1.353 | C(6)–O(2) | 1.249(2) | 1.272 |
| C(4)–C(5) | 1.387(2) | 1.416 | C(6)–C(7) | 1.484(2) | 1.485 |
| C(5)–N(1) | 1.344(2) | 1.354 | | | |

Hence the α-benzoylnitrones formed by condensation of the acyclic 1,2-hydroxylamino oxime with arylglyoxals undergo cyclization to form principally the 2-aroyl-1-hydroxyimidazoles and these can be prepared in a single stage without separation of the α-benzoylnitrones.

## EXPERIMENTAL

IR spectra for KBr tablets were recorded on a Bruker Vector 22 spectrophotometer and UV spectra on a Hewlett Packard 8453 spectrophotometer using ethanol. $^1$H NMR spectra were taken on a Bruker AC-300 instrument (300 MHz) with residual solvent as internal standard ($CDCl_3$ at 7.24 ppm and DMSO-$d_6$ at 2.50 ppm). Monitoring of the reaction course and the purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates with chloroform–methanol (10:1) as eluent.

The acetate of the hydroxylamino oxime **1** was obtained by method [8] and the arylglyoxals *via* the Riley reaction [9]. The melting points of the arylglyoxal hydrates **2a-f** agreed with those given in the literature [10–12].

**N-(2-Hydroxyimino-1-methylpropyl)-α-aroyl nitrones 3a-c**. **(General Method)** A. The acetate of hydroxylamino oxime **1** (5 mmol) was dissolved with heating in MeOH (7 ml) and cooled to room temperature. The arylglyoxals **2a-c** (5 mmol) were added with stirring and full solubility occurred. The solution turned yellow after 5-10 min, a precipitate was formed, and the mixture was allowed to stand overnight. The precipitated aroyl nitrones **3a-c** filtered off, washed with MeOH, and dried.

The filtrate after separation of the benzoyl nitrone **3b** was evaporated and the residue was treated with water and then $NaHCO_3$ to neutrality and extracted with chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, solvent was evaporated, and the residue was chromatographed on a silica gel column (eluent chloroform) to give the aroylimidazole **4b** (0.45 g, 36%). Elution with chloroform–MeOH (10:1) then gave the pyrazine **5b** (0.1 g, 8%).

**N-Benzoylmethylidene-N-(2-hydroxyimino-1-methylpropyl)amine N-Oxide (3a)**. B. The phenylglyoxal **2a** (1.6 g, 10.5 mmol) was added portionwise, as solubility allowed, to a solution of the hydroxylamino oxime acetate (1.78 g, 10 mmol) in water (7 ml). After 5-7 min the solution became turbid and a yellow precipitate began to form. The reaction mixture was left overnight at room temperature and then cooled to 5ºC. The precipitate formed was filtered off, washed on the filter with water, and dried in air to give compound **3a** (1.4 g, 60%).

**2-Aroyl-1-hydroxy-4,5-dimethylimidazoles 4a-c**. **(General Method)**. A. The aroyl nitrones **3a-c** (5 mmol) were heated at 80-90ºC in a mixture of MeOH (10 ml) and glacial AcOH (3 ml). The solution was evaporated and the residue was mixed with water, neutralized with $NaHCO_3$, and extracted with chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, and the solvent was evaporated. Crystallization of the residue from hexane gave the imidazoles **4a,b**. In the case of cyclization of aroylnitrone **3c** cooling of the reaction mixture gave the pyrazine **5c** and the filtrate after dilution with water gave the imidazole **4c**.

**2-Benzoyl-1-hydroxy-4,5-dimethylimidazole (4a)**. B. The benzoyl nitrone **3a** (1.03 g, 4.4 mmol) was dissolved with heating in AcOH (12 ml) and held overnight at room temperature. Solvent was evaporated and the residue was dissolved in EtOAc. The solution was washed with a 3% solution of sodium bicarbonate and water, dried over $MgSO_4$, and the solvent was evaporated. Chromatography of the residue on a silica gel column with pentane–ether as eluent gave compound **4a** (0.8 g, 84%).

**2-Aroyl-1-hydroxy-4,5-dimethylimidazoles (4d-f) (General Method)**. The arylglyoxal **2d-f** (10 mmol) was added to a solution of the hydroxylamino oxime **1** acetate (10.5 mmol) in a mixture of MeOH (20 ml) and glacial AcOH (3 ml). The solution obtained was heated for 2 h at 80-90ºC. Solvent was evaporated and the residue was washed with water, neutralized with $NaHCO_3$, and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and the solvent was evaporated. Treatment of the crystalline residue with ether gave the imidazoles **4d-f** in 30-60% yield. The ether solution was evaporated and the residue was chromatographed on a silica gel column using chloroform eluent to give additional amounts of the imidazoles **4d-f**.

**X-ray Structural Investigation**. Single crystals of compound **4a** (hexane). The size of the crystal in the X-ray diffraction experiment was 0.56×0.44×0.32 mm and the work was carried out on a Bruker P4 diffractometer (graphite monochromator, $\lambda(MoK\alpha)$ = 0.71073 Å, temperature 296 K, $\theta/2\theta$ scanning to $2\theta_{max}$ = 55º). Crystallographic data for compound **4a**: $C_{12}H_{12}N_2O_2$, triclinic crystal system, space group $P\bar{1}$, $a$ = 7.4321(5), $b$ = 8.0943(6), $c$ = 9.6860(7) Å, $\alpha$ = 90.999(6), $\beta$ = 107.164(5), $\gamma$ = 98.264(6)º, $V$ = 549.85(7) Å$^3$, $Z$ = 2, $M_r$ = 216.24, $D_x$ = 1.306 g/cm$^3$, $\mu$ = 0.091 mm$^{-1}$. Calculation of the absorption was carried out from the azimuthal scanning experimental curve ($T_{min}/T_{max}$ = 0.9262/0.9693). The structure was solved by a direct method. The positions and thermal parameters for the atoms were calculated in the anisotropic-isotropic (for H atoms) approximation using full matrix least squares analysis. The hydrogen atoms were localized from difference synthesis. The refinement parameters were: $wR_2$ = 0.1400, $S$ = 1.041 for all 2535 independent reflections, $R$ = 0.0463 for 1895 observed reflections with $I > 2\sigma(I)$. All of the calculations were carried out using the SHELX-97 program package [13]. The data obtained was deposited in the Cambridge structural data bank (deposit No CCDC 688298).

DFT/PBE/3z quantum-chemical calculations were carried out using the PRIRODA program [14].

## REFERENCES


1. M. R. Grimmett, in: O. Meth-Cohn and A. R. Katritzky (editors), *Best Synthetic Methods*, Academic Press, London, San Diego (1997).
2. L. M. Junker and J. Clardy, *Antimicrob. Agents Chemother.*, **51**, 3582 (2007).
3. L. N. Grigor'eva, S. A. Amitina, and L. B. Volodarskii, *Khim. Geterotsikl. Soedin.*, 1387 (1983). [*Chem. Heterocycl. Comp.*, **19**, 1104 (1983)].
4. M. R. Grimmett, in: A. R. Katritzky and C. W. Rees (editors), *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*, Vol. 5, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt (1984), p. 405.
5. L. N. Grigor'eva, A. Ya. Tikhonov, S. A. Amitina, L. B. Volodarskii, and I. K. Korobeinicheva, *Khim. Geterotsikl. Soedin.*, 331 (1986). [*Chem. Heterocycl. Comp.*, **22**, 268 (1986)].
6. N. V. Dulepova, D. G. Mazhukin, A. Ya. Tikhonov, and L. B. Volodarskii, *Khim. Geterotsikl. Soedin.*, 1060 (1986). [*Chem. Heterocycl. Comp.*, **22**, 856 (1986)].
7. Cambridge Structural Database. Version 5.29. University of Cambridge, UK.
8. L. N. Grigor'eva, L. B. Volodarskii, and A. Ya. Tikhonov, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.*, No. 3, 125 (1989).

9. N. N. Mel'nikov in: S. S. Nametkin, V. M. Rodionov, and N. N. Mel'nikov (editors), *Reactions and Methods in the Study of Organic Compounds* [in Russian], Vol. 1, Goskhimizdat, Moscow, Leningrad (1951), p. 99.
10. Beilstein, *Handbuch der Organischen Chemie*, 4. Aufl. Springer-Verlag, Berlin, Heidelberg, New York (1969); Vol. 7, E III 3433, 3451; and (1970) Vol. 8, E III, 2325.
11. L. Steinbach and E. J. Becker, *J. Am. Chem. Soc.*, **76**, 5808 (1954).
12. B. J. McLoughlin, UK Patent 975291*; Chem. Abstr.*, **62**, 2737 (1965).
13. G. M. Sheldrick, SHELXL-97, release 97-2, University of Göttingen, Germany (1998).
14. D. N. Laikov, *Chem. Phys. Lett.*, **281**, 151 (1997).