Chemistry of Heterocyclic Compounds, Vol. 44, No. 4, 2008

CYCLOCONDENSATION OF 3,3-DIAMINO-1-PHENYLPROPENONE WITH PYRIDINE AND QUINOLINE N-OXIDES CONTAINING AN ELECTROPHILIC GROUP IN POSITION 3*

D. V. Dar'in, S. I. Selivanov, P. S. Lobanov, and A. A. Potekhin*[2]

The cyclocondensation of the N-oxide of the methyl ester of nicotinic acid with 3,3-diamino-1-phenylpropenone and the ethyl ester of 3,3-diaminoacrylic acid in the presence of benzenesulfonyl chloride gives the corresponding 2,7-naphthyridines. The cyclocondensation of 3,3-diamino-1-phenylpropene with the N-oxides of dimethyl 3,5-pyridinedicarboxylate and quinolines containing an electrophilic group at in position 3 yields products of the nucleophilic attack of the carbon nucleophilic site of the enediamine at the 2-pyridine ring position, while the amine group binds to the exocyclic electrophilic group.

Keywords: benzo[*b*]-1,6-naphthyridines, enediamines, 2,7-naphthyridines, pyridine N-oxides, quinoline N-oxides, cyclocondensation.

The N-oxide group permits the facile introduction of substituents into pyridine and quinoline rings [2]. The presence of other reactive substituents in the N-oxide molecule opens a pathway to the construction of condensed heterocycles [3, 4].

In a continuation of an investigation of the reactivity of α-acylacetamidines [5], we have studied the synthetic potential and regioselectivity of the reactions of benzoylacetamidine, which exists in solution as 3,3-diamino-1-phenylpropene (**1a**) with pyridine and quinoline N-oxides containing an electrophilic group in the β-position to the nitrogen atom. In reactions with aromatic aldehydes and esters containing an active halogen atom in the *ortho* position studied in our previous work [5-7], benzoylacetamidine acts as a C,N-dinucleophile. The reactions with aromatic dielectrophiles are chemoselective: the carbon nucleophilic site replaces the halogen atom in the ring, while the amino group reacts with the exocyclic electrophilic group. The formation of regioisomers is also possible in reactions with azine N-oxides having two active positions in the pyridine ring depending on which ring position undergoes nucleophilic attack.

The reactions were carried out under conditions similar to those described by Iwao and Kuraishi [8]. DMF was used as the solvent and benzenesulfonyl chloride was used as the acylating agent. A two-fold excess

* Previous communication, see [1].

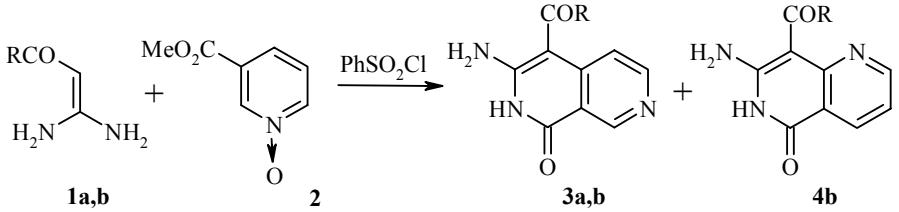
*[2] Deceased.

St. Petersburg State University, 198504 St. Petersburg, Russia; e-mail: pslob@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 578-584, April, 2008. Original article submitted October 16, 2007.

of amidine was taken. Attempts to carry out the reaction with an equimolar amount of the amidine using other bases such as potassium carbonate, 1,4-diazabicyclo[5.4.0]undec-7-ene, triethylamine, and triethylamine acetate led to considerable tar formation and a low product yield.

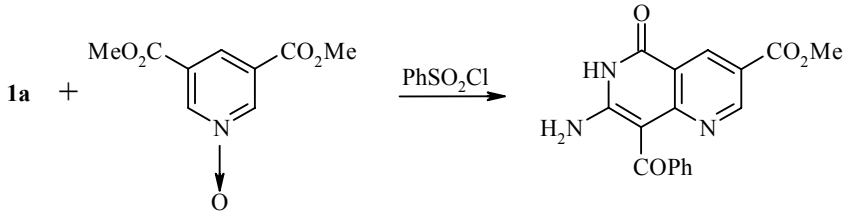
The reaction of N-oxide **2** with **1a** yielded only 2,7-naphthyridine **3a**. The reaction of N-oxide **2** with enediamine **1b** gave a 10:1 mixture of two products in 45% yield. The structures of the major products, 2,7-naphthyridines **3a** and **3b**, were established using ^{1}H and ^{13}C NMR spectroscopy as well as NOESY correlation spectra, in which cross peaks are observed between the signals of the protons of the substituent at the exocyclic carbonyl group (R) and H-5 of the naphthyridine system. The structure of the minor product of the reaction with enediamine **1b** could not be unequivocally established but the ^{1}H NMR spectrum suggested the isomeric 1,6-naphthyridine **4b**.

The only product of the reaction of N-oxide **5** with enediamine **1a** was 1,6-napthyridine **6**, which was isolated in 28% yield. The structure of this product was established by ^{1}H and ^{13}C NMR spectroscopy. The major indication for nucleophilic attack at C-2 was found in the values of the direct coupling constants $^{1}J_{C\text{-}H}$ = 182 Hz for C-2 and $^{1}J_{C\text{-}H}$ = 167 Hz for C-4, which depend strongly on the arrangement of the nitrogen atom and C-H fragment and are 178 and 162 Hz for C-2 and C-4, respectively, in quinoline [9].



1a,b **2** **3a,b** **4b**

a R = Ph 49% 0%
b R = OEt 41% (4%)*



5 **6** 28%

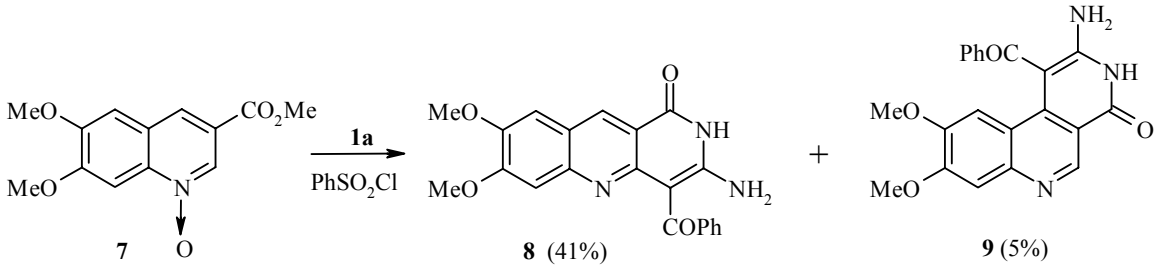
This finding indicates that the protons remaining in the pyridine ring are in the α- and γ-positions relative to the nitrogen atom. The chemical shift of the carbon atom of the ring carbonyl group (161.6 ppm) indicates that this group is bound to the nitrogen atom. In the case of the isomeric product, the signal for the carbonyl carbon atom would have been shifted toward higher field by ~10 ppm.

Thus, the literature data indicate that the chemical shifts of the carbonyl group carbon atom in 2- and 4-pyridones are 162.3 and 175.7 ppm, respectively [10].

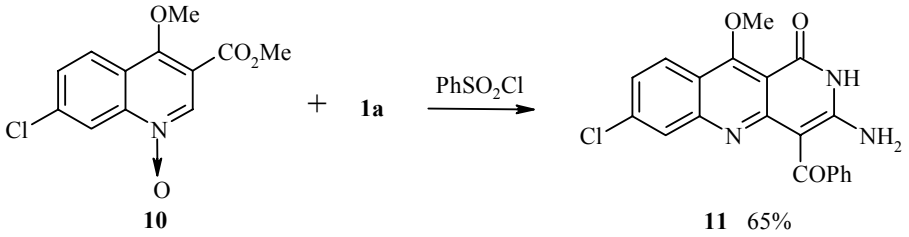
The reaction of N-oxide **7** with enediamine **1a** gives an 8:1 mixture of benzonaphthyridines **8** and **9**. The major product **8** was isolated in 41% yield. The minor product could not be isolated as a pure compound and its structure was suggested from the ^{1}H NMR spectrum of the reaction mixture.

---

* Here and subsequently, the yields of the products observed in the reation mixture by ^{1}H NMR spectroscopy and not isolated as individual substances are indicated in the brackets.

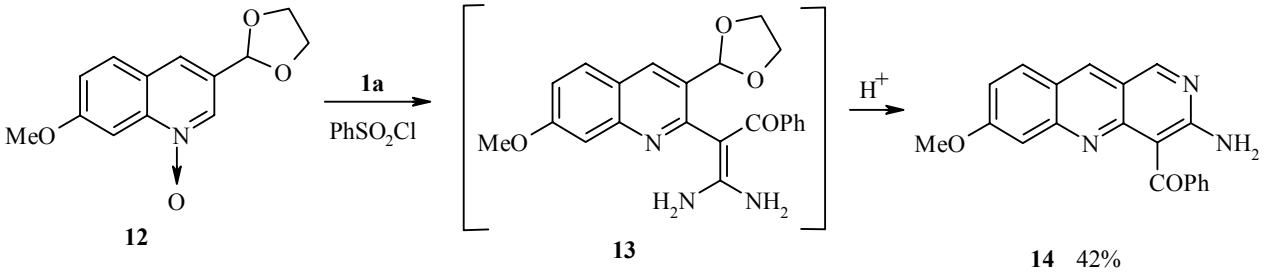


It is known [1] that the presence of electron-donor substituents in the ring of the N-oxide, especially, alkoxy groups in pyridines, markedly enhances the yields of the substitution products in comparison with the analogous substrates lacking electron-donor substituents. This effect may be related to the increased nucleophilicity of the N-oxide oxygen atom and increased rate of the acylation step. In order to check this tendency, we carried out the reaction of enediamine **1a** with N-oxide **10**, which has a methoxy group directly attached to the pyridine ring. This reaction gave benzonaphthyridine **11** in a yield indeed somewhat higher.



Considerable interest is found in the N-oxides of 3-azinecarbaldehydes. At present, we have obtained only one such compound, N-oxide **12**. The reaction of N-oxide **12**, which has the synthetic equivalent of the formyl group at C-3, with enediamine **1a** gives a mixture of two products, one of which is benzonaphthyridine **14**. ^{1}H NMR spectroscopy was used to ascribe the structure of the intermediate product of substitution in the quinoline system with an unaffected dioxolane group (**13**) to the second compound, which could not be isolated in pure form. In order to check the conversion of intermediate **13** into cyclization product **14**, the reaction mixture was treated with picric acid in ethanol. Product **14** was isolated chromatographically after completion of the cyclization reaction and treatment with potassium carbonate.

Thus, in all cases, the cyclocondensation proceeds with the same selectivity as the reaction with *ortho*-halocarbonyl dielectrophiles. Specifically, the carbon nucleophilic site participates in the nucleophilic attack of the aromatic ring, while the enediamine nitrogen atom forms a bond with the exocyclic electrophilic group. In regard to the direction of the reaction relative to the activated positions of the pyridine ring, we should note that the cyclocondensation proceeds selectively with the participation of C-4 only in the case of methyl nicotinate N-oxide **2**. On the other hand, attack of the carbon nucleophilic site of the enediamine at C-2 is preferred for dimethyl pyridinedicarboxylate N-oxide **5**, methyl 6,7-dimethoxy-3-quinolinecarboxylate N-oxide (**7**), and 7-methoxy-3-(1,3-dioxolan-3-yl)quinoline N-oxide (**12**).



EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 300 spectrometer at 300 and 75 MHz with DMSO-d_6 as the solvent. The residual signals of the solvent δ 2.50 (for the ^{1}H nuclei) and δ 39.7 ppm (for the ^{13}C nuclei) were used as the internal standards. The coupling constants in the ^{1}H NMR spectra were measured to a first order approximation. The elemental analysis was carried out on a Hewlett-Packard HP-185B CHN analyzer. The purity of the products and the reaction course were monitored by thin-layer chromatography on Silufol UV-254 plates.

3-Amino-4-benzoyl-2,7-naphthyridin-1(2H)-one (3a). A solution of benzenesulfonyl chloride (0.36 g, 2 mmol) in DMF (2 ml) was added dropwise over 20 min with stirring and ice cooling to a mixture of methyl nicotinate N-oxide (**2**) (0.3 g, 2 mmol), enediamine **1a** [12] (0.65 g, 4 mmol), and DMF (2 ml). The mixture was then left for 24 h at -10°C. The precipitate of benzoylacetamidine hydrochloride was filtered off. The filtrate was poured into water (30 ml) and potassium carbonate (0.2 g) was added. The crystalline precipitate was filtered off and recrystallized from acetonitrile to give compound **3a** (0.26 g, 49%); mp 321-324°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.44 (1H, d, *J* = 5.6, H-5); 7.39-7.58 (5H, m, C_6H_5); 7.88 (2H, s, NH_2); 8.07 (1H, d, *J* = 5.6, H-6); 9.01 (1H, s, H-8); 11.38 (1H, s, NH). Found, %: C 67.59; H 4.23; N 15.78. $C_{15}H_{11}N_3O_2$. Calculated, %: C 67.92; H 4.18; N 15.84.

Ethyl Ester of 3-Amino-1-oxo-1,2-dihydro-2,7-naphthyridine-4-carboxylic Acid (3b). A solution of benzenesulfonyl chloride (0.44 g, 2.5 mmol) in DMF (2 ml) was added dropwise over 20 min with stirring and ice cooling to a solution of enediamine **1b** [6] (0.65 g, 5 mmol) and compound **2** (0.38 g, 2.5 mmol) in DMF (3 ml). The mixture was maintained for 25 h at room temperature and then poured into water (25 ml). Potassium hydroxide (0.16 g, 2.8 mmol) was added. The crystalline precipitate was filtered off and dried to give 2,7-naphthyridine **3b** with a 9% impurity of the ethyl ester of 7-amino-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxylic acid (**4b**). The yield of **3b** was 0.26 g (45%); mp 271-274°C (dec.). An analytical sample of **3b** was obtained by recrystallization from 1:1 ethanol–acetonitrile. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (3H, t, *J* = 8.2, CH_3); 4.33 (2H, q, *J* = 7.3, CH_2); 7.72 (2H, s, NH_2); 8.25 (1H, d, *J* = 5.9, H-5); 8.49 (1H, d, *J* = 5.9, H-6); 9.06 (1H, s, H-8); 11.28 (1H, s, NH). Found, %: C 56.46; H 4.72; N 18.05. $C_{11}H_{11}N_3O_3$. Calculated, %: C 56.65; N 4.75; N 18.02. The signals for 1,6-naphthyridine **4b** were observed in the ^{1}H NMR spectrum of the mixture, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 8.2, CH_3); 7.12 (1H, dd, *J* = 4.5 and *J* = 7.8, H-3); 7.25 (2H, s, NH_2); 8.71 (1H, d, *J* = 4.5, H-2).

Methyl Ester of 7-Amino-8-benzoyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylic Acid (6). A solution of benzenesulfonyl chloride (0.3 g, 1.7 mmol) in DMF (2 ml) was added dropwise over 30 min with stirring and ice cooling to a mixture of dimethyl 3,5-pyridinedicarboxylate N-oxide (**5**) [13] (0.315 g, 1.5 mmol), enediamine **1a** (0.5 g, 3.1 mmol), and DMF (2 ml). The mixture was stirred for 23 h at room temperature and then poured into a solution of NaOH (0.08 g) in water (25 ml). The oil formed crystallized after 24 h. The crystals were filtered off, heated at reflux in 10 ml methanol, cooled, filtered off, and dried to give compound **6** (0.135 g, 28%); mp 250-260°C (dec.). An analytical sample was obtained by recrystallization from 1:1 methanol–acetonitrile. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (3H, s, OCH_3); 7.32 (2H, t, *J* = 8.2, *m*-C_6H_5); 7.41-7.52 (3H, m, *o*-C_6H_5, *p*-C_6H_5); 7.67 (2H, s, NH_2); 8.62 (2H, s, H-2, H-4); 11.48 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 52.5 (OCH_3); 95.2 (C-8); 114.8 (C-4a); 118.9 (C-3); 128.1 (*m*-C_6H_5); 129.7 (o-C_6H_5); 131.2 (*p*-C_6H_5); 136.2 (C-4); 142.6 (*ipso*-C_6H_5); 152.9 (C-2); 155.2 (C-7); 157.4 (C-8a); 161.6 (C-5); 165.0 ($\underline{C}O_2CH_3$); 194.5 ($\underline{C}OC_6H_5$). Found, %: C 63.24; H 4.13; N 12.94. $C_{17}H_{13}N_3O_4$. Calculated %: C 63.16; H 4.05; N 13.00.

3-Amino-4-benzoyl-7,8-dimethoxybenzo[*b*]-1,6-naphthyridin-1(2H)-one (8). A solution of benzenesulfonyl chloride (0.23 g, 1.3 mmol) in DMF (2 ml) was added dropwise over 20 min with stirring and ice cooling to a mixture of methyl 6,7-dimethoxy-3-quinolinecarboxylate N-oxide (**7**) (0.32 g, 1.2 mmol),

enediamine **1a** (0.39 g, 2.4 mmol), and DMF (2 ml). The mixture was left for 20 h at room temperature and then poured into a solution of NaOH (0.06 g) in water (30 ml). The crystalline precipitate was filtered off, heated at reflux in 1:1 methanol–acetonitrile (10 ml), cooled and filtered off to give benzonaphthyridine **8** (80 mg). Crystals precipitated overnight from the aqueous filtrate, which were filtered off, heated at reflux in acetonitrile (10 ml), cooled, and filtered off to give an additional benzonaphthyridine **8** (0.105 g). The total yield of **8** was 0.185 g (41%); mp 285-290°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (3H, s, 7-OCH_3); 3.83 (3H, s, 8-OCH_3); 6.22 (1H, s, H-6); 7.25-7.41 (6H, m, C_6H_5, H-9); 7.85 (2H, s, NH_2); 8.69 (1H, s, H-10); 11.12 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 55.8 (7-OCH_3); 56.0 (8-OCH_3); 93.9 (C-4); 106.0 (C-9); 106.6 (C-6); 113.7 (C-10a); 119.9 (C-9a); 127.6 (*m*-C_6H_5); 127.9 (*o*-C_6H_5); 129.4 (*p*-C_6H_5); 134.4 (C-10, $^1J_{C\text{-}H}$ = 164.4); 144.2 (*ipso*-C_6H_5); 147.2 (C-5a); 148.8 (C-8); 151.4 (C-4a); 154.6 (C-3); 154.8 (C-7); 162.2 (C-1); 194.9 ($\underline{C}O_2C_6H_5$). Found, %: C 67.15; H 4.57; N 11.13. $C_{21}H_{17}N_3O_4$. Calculated %: C 67.13; H 4.56; N 11.19. A crystalline precipitate settled from the aqueous mother liquor after several days, which was filtered off, heated to reflux in acetonitrile (5 ml), cooled, and filtered off to give a 2:1 mixture of benzonaphthyridine **8** (0.07 g, 16%) and 2-amino-1-benzoyl-8,9-dimethoxybenzo[*c*]-2,7-naphthyridin-4(3H)-one (**9**). The signals for benzonaphthyridine **9** were found in the ^{1}H NMR spectrum, δ, ppm: 3.54 (3H, s, 9-OCH_3); 3.84 (3H, s, 8-OCH_3); 6.79 (1H, s, H-7 or H-10); 9.12 (1H, s, H-5); 11.43 (1H, s, NH).

3-Amino-4-benzoyl-7-chloro-10-methoxybenzo[*b*]-1,6-naphthyridin-1(2H)-one (11). A solution of benzenesulfonyl chloride (0.23 g, 1.3 mmol) in DMF (2 ml) was added dropwise with stirring and ice cooling over 30 min to a mixture of enediamine **1a** (0.4 g, 2.5 mmol), methyl 7-chloro-4-methoxy-3-quinoline-carboxylate N-oxide (**10**) (0.32 g, 1.2 mmol), and DMF (3 ml). The mixture was stirred for 48 h at room temperature and mixed with water (30 ml). Sodium hydroxide (0.06 g, 1.5 mmol) was added. The crystals formed were filtered off, heated to reflux in 2:1 methanol–acetonitrile (20 ml), cooled, filtered off, and dried to give compound **11** (0.295 g, 65%); mp 238-245°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.12 (3H, s, OCH_3); 6.81 (1H, s, H-6); 7.25-7.46 (6H, m, C_6H_5, H-8); 7.80 (2H, s, NH_2); 8.08 (1H, d, *J* = 8.4, H-9); 11.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 63.9 (OCH_3); 94.1 (C-4); 107.5 (C-10a); 119.1 (C-9a); 124.9, 125.77, 125.80, (C-6, C-8, C-9); 127.7 (*m*-C_6H_5); 127.8 (*o*-C_6H_5); 129.7 (*p*-C_6H_5); 137.3 (C-7); 144.1 (*ipso*-C_6H_5);150.6 (C-5a); 154.8 (C-3); 156.8 (C-4a); 159.9 (C-1); 166.9 (C-10); 195.2 ($\underline{C}O_2C_6H_5$). Found, %: C 61.52; H 3.60; N 10.78. $C_{20}H_{14}N_3O_3$. Calculated, %: C 63.25; H 3.72; N 11.06.

3-Amino-4-benzoyl-7-methoxybenzo[*b*]-1,6-naphthyridine (14). A solution of benzenesulfonyl chloride (0.23 g, 1.3 mmol) in DMF (1.5 ml) was added dropwise with stirring and ice cooling over 1 h to a mixture of 7-methoxy-3-(1,3-dioxolan-2-yl)quinoline N-oxide (**12**) (0.296 g, 1.2 mmol), enediamine **1a** (0.39 g, 2.4 mmol), and DMF (2 ml). The mixture was stirred at room temperature for 24 h. The solvent was distilled off in vacuum at 55-60°C over 2.5 h. The residue was added to water (30 ml) and thoroughly triturated. Then, potassium carbonate (0.4 g, 3 mmol) was added and the mixture was left for 72 h at 6°C. The crystalline precipitate was filtered off and dissolved in ethanol (20 ml). Then, picric acid (0.8 g, 3.5 mmol) was added and the mixture was stirred at room temperature for 20 h. The solvent was evaporated off. The residue was added to aqueous potassium carbonate (30 ml, 5%) and thoroughly extracted with methylene chloride. The organic layer was dried over sodium sulfate. The solvent was evaporated off. The residue was subjected to column chromatography using chloroform as the eluent to give compound **14** (0.164 g, 42%); mp 213-216°C. An analytical sample was obtained by recrystallization from acetonitrile. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 (3H, s, OCH_3); 6.67 (1H, d, *J* = 2.3, H-6); 7.04 (2H, s, NH_2); 7.07 (1H, dd, *J* = 2.3 and *J* = 9.4, H-8); 7.40 (2H, t, *J* = 8.4, *m*-C_6H_5); 7.54 (1H, t, *J* = 8.4, *p*-C_6H_5); 7.64 (2H, d, *J* = 8.4, *o*-C_6H_5); 7.93 (1H, d, *J* = 9.4, H-9); 8.91 (1H, s, $^1J_{C\text{-}H}$ = 163.2, H-10); 9.28 (1H, s, $^1J_{C\text{-}H}$ = 180.7, H-1). Found %: C 73.06; H 4.63; N 12.96. $C_{19}H_{15}N_3O_2$. Calculated %: C 72.94; H 4.59; N 12.76.

REFERENCES

1. D. V. Dar'in, S. I. Selivanov, P. S. Dobanov, and A. A. Potekhin, *Vestn. St. Peterb. Gos. Univ., Ser. 4, Fiz. Khim.*, No. 1, 112 (2005).
2. M. Hamana, *Khim. Geterotsikl. Soedin.*, 1155 (1973), Masatomo Hamana, *J. Heterocycl. Chem.,* S-51 (1970)
3. Y. Miura, S. Takaku, Y. Fujimura, and M. Hamana, *Heterocycles*, **34**, 1055 (1992).
4. Y. Miura, M. Yoshida, and M. Hamana, *Heterocycles*, **36**, 1005 (1993).
5. D. V. Dar'in, S. I. Selivanov, P. S. Lobanov, and A. A. Potekhin, *Khim. Geterotsikl. Soedin.*, 1036 (2004). [*Chem. Heterocycl. Comp.*, **40**, 888 (2004)].
6. S. G. Ryazanov, D. V. Dar'in, S. I. Selivanov, P. S. Lobanov, and A. A. Potekhin, *Vestn. St. Peterb. Gos. Univ., Ser. 4, Fiz. Khim.*, No. 2, 138 (2005).
7. D. V. Dar'in, S. G. Ryazanov, S. I. Selivanov, P. S. Lobanov, and A. A. Potekhin, *Khim. Geterotsikl. Soedin.*, 589 (2008). [*Chem. Heterocycl. Comp.*, **44**, 461 (2008)].
8. M. Iwao and T. Kuraishi, *J. Heterocycl. Chem.*, **15**, 1425 (1978).
9. H.-O. Kalinowsky, S. Berger, and S. Braun, *^{13}C-NMR Spektroskopie*, Georg Thieme Verlag, Stuttgart, New York (1984), p. 455.
10. T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles*, Georg Thieme Verlag, Stuttgart, New York (1995), p. 311.
11. H. Yamanaka, S. Niitsuma, Y. Bannai, and T. Sakamoto, *Chem. Pharm. Bull.*, **23**, 2591 (1975).
12. B. Roth and J. M. Smith, *J. Am. Chem. Soc.*, **71**, 616 (1949).
13. B. Nowak-Wydra and M. Szafran, *Roczniki Chem.*, **51**, 593 (1977).