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REACTION OF 3,3-DIMETHYL- AND 3-SPIROCYCLOHEXYL-TETRAHYDROISOQUINOLINES WITH ALKYNES*

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It has been found that 2,3,3-trimethyl-1-phenyl- and 1,2-dimethyl-3-spirocyclohexyltetrahydroisoquinolines react with activated alkynes in methanol with cleavage of the tetrahydropyridine ring to give methoxybenzyl- and methoxyethylbenzenes, and in boiling acetonitrile form N-butenoyl derivatives from N-methylspirocylohexyltetrahydroisoquinoline by its reaction with acetylacetylene.

Keywords: tetrahydroisoquinoline, cleavage of the tetrahydropyridine ring, *N*-demethylation, tandem transformations.

The tandem expansion of aryl- and hetaryl-fused tetrahydropyridine rings under the influence of activated alkynes allows the synthesis in high yields of the corresponding fused azocines [1]. In methanol, this reaction is frequently accompanied by cleavage of the tetrahydropyridine fragment with participation of the solvent molecule which leads to the formation of methoxymethyl(alkyl, benzyl)-substituted arenes and heterocycles [2]. Sometimes, this process becomes predominant [3]. It was shown recently that 1-phenyl-2-R- and 1-aryl-2-R-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines under the influence of dimethyl acetylenedicarboxylate (DMAD), methyl propiolate, and acetylacetylene in acetonitrile and in methanol give 1-aryl-2-R-8,9-dimethoxy-tetrahydrobenzo[*d*]azocines as a result of the tetrahydropyridine ring expansion. Only in methanol under the influence of DMAD the cleavage of the tetrahydropyridine ring was observed with formation of benzylmethyl esters as by-products [4]. Tandem conversions of 1-aryl-substituted tetrahydroisoquinolines begin with a Michael addition leading to the formation of an intermediate zwitterion **A** of the ammonium type, which by cleavage of the C(1)–N^+ bond may be converted into zwitterion **B** with stable benzhydryl cation center. Conversions of zwitterions **A** and **B** determine the formation of the basic products of the tandem reactions.

To elucidate in finer detail the chemistry of the tandem conversions in the reactions with DMAD, methyl propiolate, and acetylacetylene in methanol and acetonitrile we have prepared 6,7-dimethoxy-2,3,3-trimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**) and 6',7'-dimethoxy-1',2'-dimethyl-1',4'-dihydro-2'*H*-spiro-[cyclohexan-1,3'-isoquinoline] (**2**).

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*Devoted to the memory of our teacher – Professor Nikolai Sergeevich Prostakov (1917-2007).

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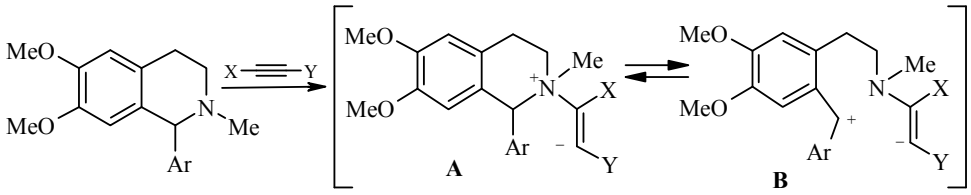
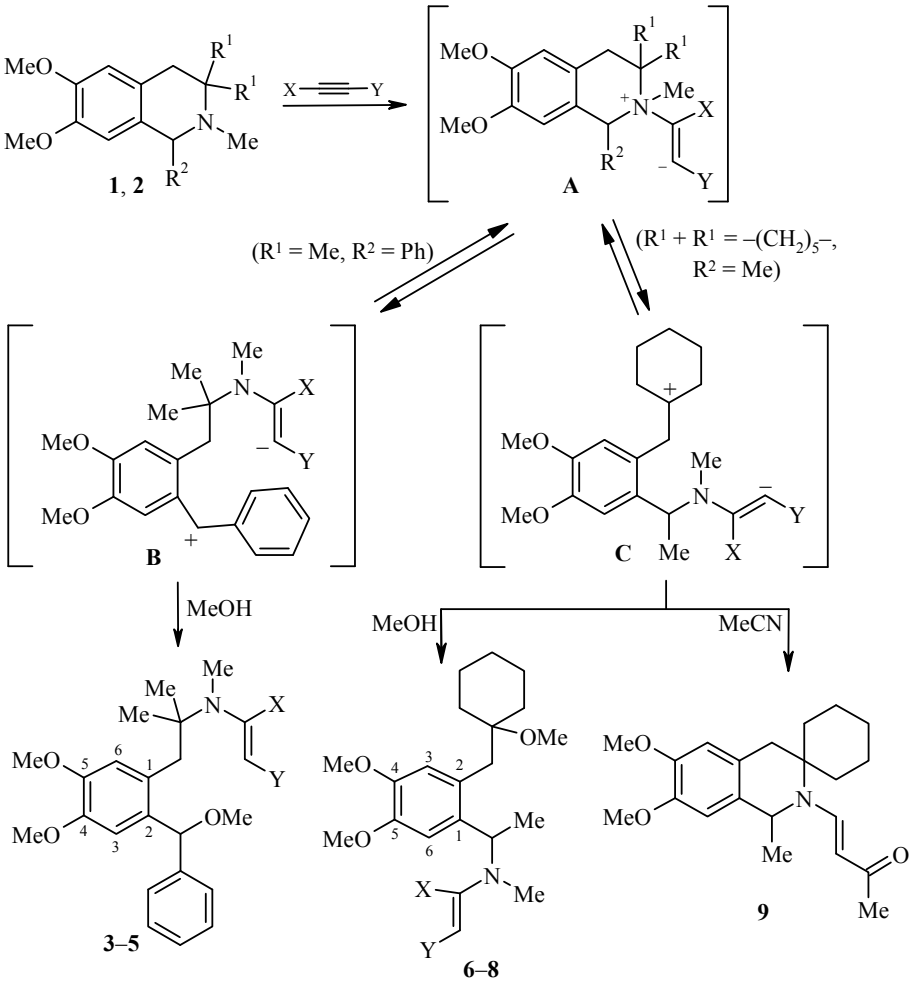


The 3,3-disubstituted tetrahydroisoquinolines **1** and **2** were synthesized by reduction with sodium borohydride of the iodomethylates of the corresponding dihydroisoquinolines, prepared by the Ritter reaction [5].

The tetrahydroisoquinolines **1** and **2** react with alkynes in MeCN at reflux to give multicomponent mixtures, from which no individual reaction products were successfully chromatographically isolated in the pure state (with one exception). In methanol at 20°C, the reaction proceeded more selectively. The basic products isolated from the reaction mixture in 30-62% yields were the methoxybenzhydriles **3-5** and the methoxyethyl-substituted benzenes **6-8**, which were formed as the result of the tetrahydropyridine ring cleavage with participation of methanol; the corresponding benzoazocines were not isolated. We assume that the methyl radical is eliminated from the initial zwitterion as a cation, which then reacts with a molecule of either the alkyne or the solvent.



1 R^1 = Me, R^2 = Ph; **2** $R^1 + R^1 = -(CH_2)_5-$, R^2 = Me;
3, **6** X = H, Y = CO_2Me; **4**, **7** X = H, Y = COMe; **5**, **8** X = Y = CO_2Me

The *N*-butenoyl-substituted isoquinoline **9** (yield 36%) was obtained from reaction of the tetrahydroisoquinoline **2** with acetylacetylene in MeCN.

The interaction of tetrahydroisoquinolines **1** and **2** with alkynes begins with the Michael addition of the nitrogen atom to the triple bond of the alkyne which leads to the zwitterion **A** of the ammonium type. Evidently further cleavage of this zwitterion at the C(1)–N^+ and C(3)–N^+ bonds leads to the formation of stable tertiary and benzhydryl cations **B** and **C**, rearrangement and transformation of which gives rise to the formation of multicomponent mixtures.

1,2,3-Trimethyl- and 1,2,3,5,8-pentamethyltetrahydrobenzothieno[2,3-*c*]pyridines [2] underwent analogous tandem transformations under the influence of alkynes, and the basic reaction products were 2-methoxyethyl-substituted benzothiophenes and the yield of benzothienoazocines did not exceed 6%.

In the mass spectra of all the compounds **5-9**, molecular ion peaks were observed corresponding to the molecular formulas. The ^{1}H NMR spectra were characterized by the presence of singlets in the 2.68-5.52 ppm range of the cyclohexylmethyl and methoxybenzyl substituents. In the spectra of compounds **3**, **4**, **6**, **7** and the tetrahydroisoquinoline **9**, two doublets were observed in the 4.56-5.26 ppm and 7.42-8.01 ppm ranges with coupling constants of 12.4-13.1 Hz which indicate the *trans* configuration of the vinyl unit. A broad singlet of the terminal vinyl proton at 4.18-4.56 ppm was observed in the ^{1}H NMR spectra of compounds **5** and **8** which contain a di(methoxycarbonyl)vinyl fragment.

So it was shown that the basic direction of tandem transformations of tetrahydroisoquinolines with two substituents in positions α and α' to the nitrogen atom under the influence of activated alkynes is cleavage of the tetrahydropyridine fragments with the formation of methoxyalkyl(benzyl)-substituted phenethylamines.

EXPERIMENTAL

IR spectra were recorded with an Infralum FT-801 Fourier spectrometer using KBr pellets. ^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Bruker WP-400 (400 MHz) instrument. Mass spectra (ESI) were obtained with an Agilent 1100 mass spectrometer.

6,7-Dimethoxy-2,3,3-trimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (1) and 6',7'-Dimethoxy-1',2'-dimethyl-1',4'-dihydro-2'*H*-spiro[cyclohexane-1,3'-isoquinoline] (2) (General Method). A solution of 6,7-dimethoxy-3,3-dimethyl-1-phenyl-3,4-dihydroisoquinoline or 6',7'-dimethoxy-1'-methyl-2'*H*-spiro[cyclohexane-1,3'-isoquinoline] (3.7 mmol) with MeI (6.6 mmol) in MeCN (30 ml) was kept for 8 days (monitored by TLC on Sorbfil in EtOAc). The solvent was removed in vacuum. The residue of the quaternary salt was crystallized from an EtOAc–hexane mixture and was reduced without isolation. Sodium borohydride (3.5 mmol) was added portionwise over 1.5 h to a solution of the quaternary salt (3.5 mmol) in MeOH (12 ml) at 20°C. After 12 h (monitored by TLC on Silufol in EtOH) the methanol was evaporated in vacuum. 10% aqueous Na_2CO_3 (20 ml) was added to the residue and extracted with Et_2O (3×40 ml). The organic layer was dried over $MgSO_4$. In the case of isoquinoline **1**, the residue, after evaporation of ether, was recrystallized from ether or an EtOAc–hexane mixture, while in the case of isoquinoline **2**, it was purified on aluminum oxide with a 1:10 EtOAc–hexane mixture.

6,7-Dimethoxy-2,3,3-trimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (1). Yield 86%. R_f 0.6 (Sorbfil, EtOAc). White needle crystals; mp 89°C (Et_2O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, s, 3-α-CH_3); 1.25 (3H, s, 3-β-CH_3); 2.02 (3H, s, NCH_3); 2.48 (1H, d, *J* = 14.9) and 2.96 (1H, d, *J* = 14.9, 4-CH_2); 3.43 (3H, s, 6-OCH_3); 3.70 (3H, s, 7-OCH_3); 4.24 (1H, s, H-1); 6.12 (1H, s, H-5); 6.63 (1H, s, H-8); 7.22-7.33 (5H, m, H Ph). Mass spectrum, *m/z*: 312 $[M+H]^+$. Found, %: C 77.17; H 8.11; N 4.51. $C_{20}H_{25}NO_2$. Calculated, %: C 77.14; H 8.09; N 4.50.

6',7'-Dimethoxy-1',2'-dimethyl-1',4'-dihydro-2'*H*-spiro[cyclohexane-1,3'-isoquonline] (2). Yield 80%. R_f 0.2 (Silufol, EtOAc). Orange oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, d, *J* = 6.4, 1-CH_3); 1.20-1.70 (10H, m, H cyclohexyl); 2.20 (3H, s, NCH_3); 2.56-2.66 (2H, m, 4-CH_3); 3.82 (3H, s, 6-OCH_3); 3.84

(3H, s, 7-OCH_3); 3.91 (1H, q, J = 6.4, H-1); 6.53 (1H, s, H-5); 6.62 (1H, s, H-8). Mass spectrum, *m/z*: 290 $[M+H]^+$. Found, %: C 74.51; H 9.49; N 4.65. $C_{18}H_{27}NO_2$. Calculated, %: C 74.70; H 9.40; N 4.84.

Interaction of Compounds 1 and 2 with Activated Alkynes (General Method). An activated alkyne (1.2 mmol) was added to a solution of tetrahydroisoquinoline **1** or **2** (1.0 mmol) in MeOH (10 ml) and kept at room temperature for 7-12 days. The reaction was monitored by TLC on Sorbfil plates in 1:1 EtOAc–hexane. At the end of the reaction, the solvent was evaporated and the residue was purified on silica gel. Compounds **3-8** were isolated by chromatography on silica gel (150 Å) with 1:10 to 1:5 EtOAc–hexane as eluent.

Compound **9** was obtained by boiling the starting isoquinoline **2** (250 mg, 0.86 mmol) in anhydrous MeCN (10 ml) with acetylacetylene (68 mg, 1.00 mmol) for 2 days. At the end of the reaction, the solvent was evaporated and the residue was purified on silica gel (60 Å) with $CHCl_3$ as eluent.

Methyl (2*E*)-3-[(2-{4,5-dimethoxy-2-[methoxy(phenyl)methyl]phenyl}-1,1-dimethylethyl)(methyl)-amino]acrylate (3). Yield 62%. R_f 0.7 (Sorbfil, EtOAc). White crystals; mp 123-124°C. IR spectrum, ν, cm^{-1}: 1722 (CO_2Me). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, s) and 1.36 (3H, s, $CH_2C(C\underline{H}_3)_2$); 2.11 (2H, s, $C\underline{H}_2CMe_2$); 2.83 (3H, s, NCH_3); 3.46 (3H, s, CH(Ph)$OC\underline{H}_3$); 3.71 (3H, $CO_2C\underline{H}_3$); 3.84 (3H, s, 5-OCH_3); 3.91 (3H, s, 4-OCH_3); 4.67 (1H, d, J = 12.7, CH=C<u>H</u>–CO_2Me); 5.46 (1H, d, C<u>H</u>(Ph)OMe); 6.41 (1H, s, H-6); 7.04 (1H, s, H-3); 7.31-7.40 (5H, m, H Ph); 7.78 (1H, d, J = 12.7, C<u>H</u>= CH–CO_2Me). Mass spectrum, *m/z*: 428 $[M+H]^+$. Found, %: C 70.00; H 7.80; N 3.10. $C_{25}H_{33}NO_5$. Calculated, %: C 70.23; H 7.78; N 3.28.

(3*E*)-4-[(2-{4,5-Dimethoxy-2-[methoxy(phenyl)methyl]phenyl}-1,1-dimethylethyl)(methyl)amino]-but-3-en-2-one (4). Yield 60%. R_f 0.8 (Sorbfil, EtOAc). Yellow crystals; mp 111-113°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, s) and 1.27 (3H, s, $CH_2C(C\underline{H}_3)_2$); 1.90 (3H, s, CH=CH–$COC\underline{H}_3$); 2.50 (2H, s, $C\underline{H}_2CMe_2$); 2.83 (3H, s, NCH_3); 3.30 (3H, s, CH(Ph)$OC\underline{H}_3$); 3.63 (3H, s, 5-OCH_3); 3.71 (3H, s, 4-OCH_3); 5.07 (1H, d, J = 12.5, CH=C<u>H</u>–COMe); 5.52 (1H, s, C<u>H</u>(Ph)OMe); 6.28 (1H, s, H-6); 6.98 (1H, s, H-3); 7.20-7.65 (5H, m, H Ph); 7.42 (1H, d, J = 12.5, C<u>H</u>=CH–COMe). Mass spectrum, *m/z*: 412 $[M+H]^+$. Found, %: C 72.63; H 8.05; N 3.42. $C_{25}H_{33}NO_4$. Calculated, %: C 72.96; H 8.08; N 3.40.

Dimethyl (2*E*)-2-[(2-{4,5-Dimethoxy-2-[methoxy(phenyl)methyl]phenyl}-1,1-dimethylethyl)(methyl) amino]but-2-enedioate (5). Yield 40%. R_f 0.4 (Sorbfil, EtOAc). Yellow oil. IR spectrum, ν, cm^{-1}: 1737, 1655 (CO_2Me). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, s) and 1.23 (3H, s, $CH_2C(C\underline{H}_3)_2$); 2.03 (3H, s, NCH_3); 2.37 (1H, d, J = 14.9) and 3.02 (1H, d, J = 14.9, $C\underline{H}_2CMe_2$); 3.49 (3H, s, CH(Ph)$OC\underline{H}_3$); 3.66 (3H, s, $CO_2C\underline{H}_3$); 3.75 (3H, s, $CO_2C\underline{H}_3$); 3.81 (3H, s, 5-OCH_3); 3.87 (3H, s, 4-OCH_3); 4.18 (1H, br. s, =C<u>H</u>–CO_2Me); 5.49 (1H, s, C<u>H</u>(Ph)OMe); 6.05 (1H, s, H-6); 7.45 (1H, s, H-3); 7.14-7.24 (5H, m, H Ph). Mass spectrum, *m/z*: 486 $[M+H]^+$. Found, %: C 66.45; H 7.05; N 2.85. $C_{27}H_{35}NO_7$. Calculated, %: C 66.79; H 7.27; N 2.88.

Methyl (2*E*)-3-[(1-{4,5-Dimethoxy-2-[(1-methoxycyclohexyl)methyl]phenyl}ethyl)(methyl)amino]-acrylate (6). Yield 42%. R_f 0.7 (Sorbfil, EtOAc). Orange oil. IR spectrum, ν, cm^{-1}: 1722 (CO_2Me). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, d, J = 6.8, $CHC\underline{H}_3$); 1.36-1.70 (10H, m, H cyclohexyl); 2.69 (3H, s, NCH_3); 3.15 (2H, s, $C\underline{H}_2Ar$); 3.62 (3H, s, OCH_3); 3.79 (3H, s, $CO_2C\underline{H}_3$); 3.80 (3H, s, 5-OCH_3); 3.81 (3H, s, 4-OCH_3); 4.40-4.60 (1H, m, C<u>H</u>Me); 4.56 (1H, d, J = 13.1, CH=C<u>H</u>–CO_2Me); 6.56 (1H, s, H-6); 6.58 (1H, s, H-3); 7.89 (1H, d, J = 13.1, C<u>H</u>=CH–CO_2Me). Mass spectrum, *m/z*: 406 $[M+H]^+$. Found, %: C 68.00; H 8.41; N 3.56. $C_{23}H_{35}NO_5$. Calculated, %: C 68.12; H 8.70; N 3.45.

(3*E*)-4-[(1-{4,5-Dimethoxy-2-[(1-methoxycyclohexyl)methyl]phenyl}ethyl(methyl)amino]but-3-en-2-one (7). Yield 40%. R_f 0.5 (Sorbfil, EtOAc). Orange oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, d, J = 6.2, $CHC\underline{H}_3$); 1.35-1.75 (10H, m, H cyclohexyl); 2.00 (3H, s, CH=CH–$COC\underline{H}_3$); 2.65 (3H, s, NCH_3); 2.80 (2H, s, $C\underline{H}_2Ar$); 3.17 (3H, s, OCH_3); 3.72 (3H, s, 5-OCH_3); 3.79 (3H, s, 4-OCH_3); 4.23 (1H, m, C<u>H</u>Me); 5.11 (1H, d, J = 12.5, CH=C<u>H</u>–COMe); 6.25 (1H, s, H-6); 6.86 (1H, s, H-3); 7.62 (1H, d, J = 12.5, C<u>H</u>=CH–COMe). Mass spectrum, *m/z*: 390 $[M+H]^+$. Found, %: C 70.74; H 9.15; N 3.69. $C_{23}H_{35}NO_4$. Calculated, %: C 70.92; H 9.06; N 3.60.

Dimethyl (2*E*)-2-[(1-{4,5-Dimethoxy-2-[1-methoxycyclohexyl)methyl]phenyl}ethyl(methyl)amino]-but-2-enedioate (8). Yield 30%. R_f 0.4 (Sorbfil, EtOAc). Orange oil. IR spectrum, ν, cm^{-1}: 1737, 1655 (CO_2Me). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (3H, d, J = 6.2, $CHC\underline{H}_3$); 1.45-1.85 (10H, m, H cyclohexyl); 2.60

(3H, s, NCH_3); 2.68 (2H, s, CH_2Ar); 3.20 (3H, s, OCH_3); 3.56 (3H, s, 2-CO_2CH_3); 3.75 (3H, s, 5-OCH_3); 3.79 (3H, s, 3-CO_2CH_3); 3.82 (3H, s, 4-OCH_3); 4.26 (1H, d, J = 6.2, C<u>H</u>Me); 4.56 (1H, br. s, =C<u>H</u>–CO_2Me); 6.25 (1H, s, H-6); 6.86 (1H, s, H-3). Mass spectrum, *m/z*: 464 $[M+H]^+$. Found, %: C 64.79; H 8.03; N 3.02. $C_{25}H_{37}NO_7$. Calculated, %: C 64.77; H 8.05; N 3.02.

(3*E*)-4-(6',7'-Dimethoxy-1'-methyl-1',4'-dihydro-2'*H*-spiro[cyclohexane-1,3'-isoquinolin]-2'-yl)but-3-en-2-one (9). Yield 36%. R_f 0.6 (Sorbfil, EtOAc). Yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25-1.70 (10H, m, H cyclohexyl); 1.45 (3H, d, J = 6.9, 1-CH_3); 2.10 (3H, s, $COCH_3$); 2.74 (1H, d, J = 15.1) and 3.08 (1H, d, J = 15.1, 4-CH_2); 3.84 (3H, s, 6-OCH_3); 3.85 (3H, s, 7-OCH_3); 4.59 (1H, q, J = 6.9, H-1); 5.26 (1H, d, J = 12.4, CH=C<u>H</u>–COMe); 6.64 (1H, s, H-8); 6.65 (1H, s, H-5); 8.01 (1H, d, J = 12.4, C<u>H</u>=CH–COMe). Mass spectrum, *m/z*: 344 $[M+H]^+$. Found, %: C 73.45; H. 8.49; N 4.07. $C_{21}H_{29}NO_3$. Calculated, %: C 73.44; H 8.51; N 4.08.

REFERENCES

1. L. G. Voskressensky, L. N. Kulikova, T. N. Borisova, and A. V. Varlamov, *Adv. Heterocycl. Chem.,* **96**, 81 (2008).
2. L. G. Voskressensky, T. N. Borisova, A. V. Listratova, E. A. Sorokina, S. V. Tolkunov, and A. V. Varlamov, *Izv. Akad Nauk, Ser. Khim.,* 1003 (2007).
3. L. G. Voskressensky, T. N. Borisova, T. A. Vorob'eva, A. I. Chernyshev, and A. V. Varlamov, *Izv. Akad Nauk, Ser. Khim.,* 2513 (2005).
4. L. G. Voskressensky, A. V. Listratova, T. N. Borisova, G. G. Alexandrov, and A. V. Varlamov. *Eur. J. Org. Chem.,* 6106 (2007).
5. V. A. Glushkov, Yu. S. Rozhkova, M. I. Vakhrin, and Yu. V. Shklyaev, *Khim. Geterotsikl. Soed.,* 1198 (2005). [*Chem. Heterocycl. Compd.,* **41**, 1022 (2005)].