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New Synthesis of Nitro-Substituted 3,1-Benzoxazines

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Abstract—A new one-step procedure has been proposed for the synthesis of nitro derivatives of 3,1-benzoxazines from substituted *N*-[2-(cyclopent-2-en-1-yl)phenyl]acetamides.

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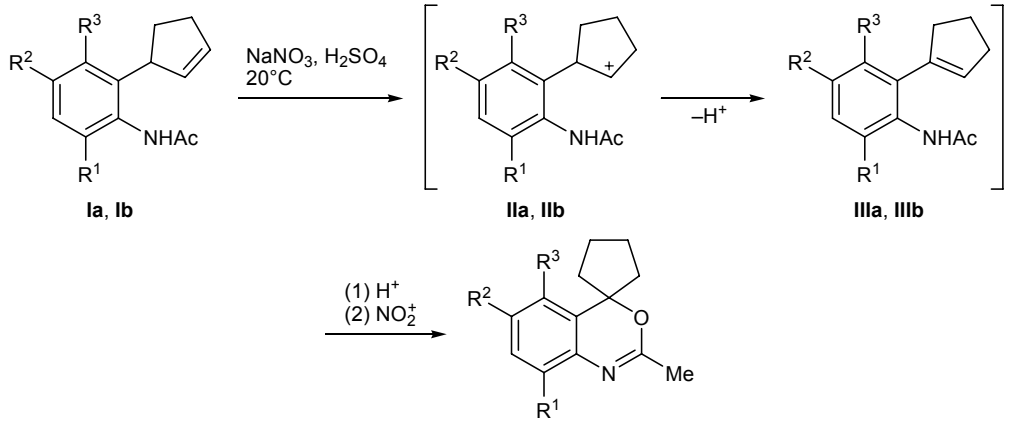
3,1-Benzoxazine derivatives exhibit a high antiviral activity [1] and are used as markers in biochemical studies [2]. Macrocyclic compounds containing 3,1-benzoxazine fragments were isolated from natural sources [3]. Benzoxazines can also be used as intermediate products in the synthesis of some receptor agonists [4]. In view of the above stated, heterocyclic compounds of the 3,1-benzoxazine series attract interest of many researchers [5].

Benzoxazine structures are commonly synthesized from derivatives of aminobenzyl alcohol [6], *o*-vinylanilines [7], or *o*-cyclopropylanilines [8, 9]. We now report on the synthesis of nitro-substituted 3,1-benzoxazines by reaction of acetanilides **Ia** and **Ib** with sulfuric acid in the presence of sodium nitrate (Scheme 1). The reactions were complete almost instantaneously. Presumably, the process includes several protonation–deprotonation steps. Carbocation **II** loses a proton to give compound **III** which is protonated again and undergoes intramolecular cyclization with formation of benzoxazine structure **IV**. The process is accompanied by nitration of the benzene ring to produce 8-nitro derivative **Va** or 6-nitro isomer **Vb**. The presence of an electron-withdrawing nitro group in the aromatic ring reduces the basicity of the endocyclic nitrogen atom in molecules **Va** and **Vb**. Therefore, these compounds can readily be extracted with chloroform from strongly acidic solution. The structure of benzoxazines **Va** and **Vb** was determined on the basis of their elemental compositions and spectral data.

Treatment of acetanilide **Ia** with 98% sulfuric acid at room temperature led to the formation of 3,1-benzoxazine **VI** (Scheme 2). The product turned out to be unstable, and it fairly rapidly decomposed during

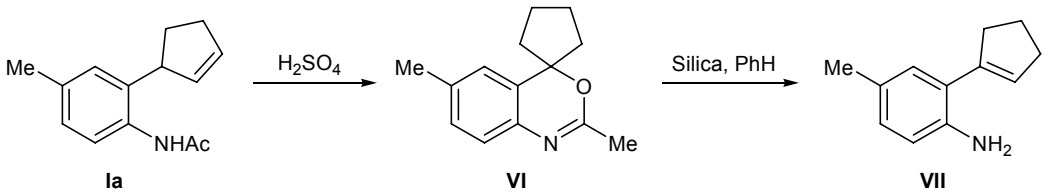
Scheme 1.



Ia, **Ib** **IIa**, **IIb** **IIIa**, **IIIb** **IVa**, **IVb**, **Va**, **Vb**

I–**IV**, $R^1 = R^3 = H$, $R^2 = Me$ (**a**), $R^1 = R^3 = Me$, $R^2 = H$ (**b**); **V**, $R^1 = O_2N$, $R^2 = Me$, $R^3 = H$ (**a**), $R^1 = R^3 = Me$, $R^2 = O_2N$ (**b**).

Scheme 2.



Ia **VI** **VII**

chromatography on silica gel to afford a considerable amount of cyclopentenylaniline **VII** (Scheme 2). The latter was identified by comparison with published data [10].

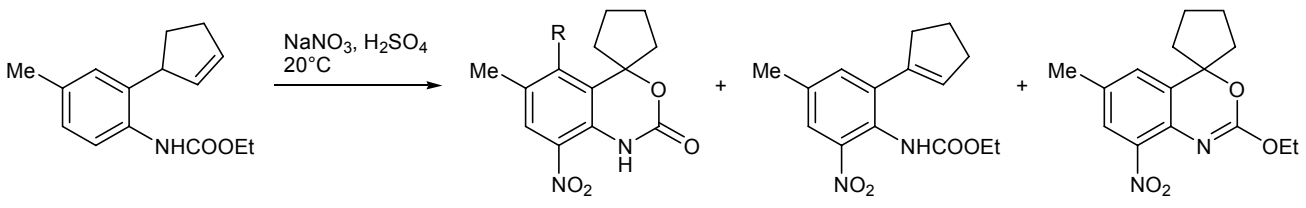
The reaction of carbamate **VIII** with sulfuric acid in the presence of sodium nitrate was not selective. By crystallization from ethanol we isolated 3,1-benzoxazin-2-one **IX**, and chromatographic separation of the mother liquor on silica gel gave (according to the ^{1}H NMR data) a mixture of nitro derivative **X** and 2-ethoxy-3,1-benzoxazine **XI** at a ratio of 1 : 1 in a poor yield (Scheme 3). We failed to improve the yield of **IX** by increasing the time of treatment with sulfuric acid to 1 h and adding afterward $NaNO_3$, followed by prolonged keeping of the reaction mixture in water. However, in this case, after precipitation of compound **IX** from ethanolic solution, crystals of dinitro derivative **XII** separated from the solution in 4–5 days. Increased time of contact of compound **VIII** with sulfuric acid favored complete consumption of carbamate **X**. The ^{1}H NMR spectrum of a mixture of solid components of the mother liquor obtained after crystallization of nitro derivatives **IX** and **XII** lacked signal at δ 6.05 ppm typical of the 2′-H olefinic proton.

Isomer mixture **X**/**XI** displayed in the ^{1}H NMR spectrum two sets of signals. The presence of a characteristic triplet (δ 6.05 ppm, J = 2.0 Hz) from 2′-H at the double bond in the cyclopentene ring and a broadened singlet from the NH proton (δ 8.75 ppm) allowed us to presume that this mixture contains carbamate **X**. Two quartets at δ 4.24 and 4.37 ppm and two triplets typical of methyl protons indicated that both isomers **X** and **XI** contain ethoxy group. Spirocyclopentane and cyclopentene rings gave rise to well distinguishable signals. Multiplet signals at δ 1.83–1.89, 1.95–2.03, and 2.25–2.32 ppm due to methylene protons were assigned to benzoxazine **XI** by comparing with the spectrum of compound **Va**. By analogy with the spectral parameters of compound **VII**, the quintet at δ 2.05 ppm and two signals at δ 2.56–2.64 and 2.66–2.72 ppm (triplets of quartets) were assigned to cyclopentene derivative **X**. Only singlets were observed in the aromatic region. Compound **XII** showed only one one-proton singlet in the aromatic region, indicating the presence of five substituents in the benzene ring.

The nitration of alkenylanilide **XIII** under analogous conditions afforded benzoxazine **XIV** which was isolated by chromatography in 70% yield (Scheme 4). The mass spectrum of **XIV** (atmospheric pressure chemical ionization) contained the molecular ion peak with m/z 263 $[M + H]^+$ and abundant ion peak with m/z 304 $[M + H + CH_3CN]^+$ due to solvate with acetonitrile. In the negative ion chemical ionization mass spectrum of **XIV** the molecular ion was represented by a peak with m/z 261 $[M - H]^-$.

Thus the reactions of *N*-[2-(cyclopent-2-en-1-yl)-phenyl]- and *N*-{4-methyl-2-[(3*E*)-pent-3-en-2-yl]-phenyl}acetamides with sulfuric acid in the presence of sodium nitrate lead to the formation of 8- or 6-nitro-3,1-benzoxazine derivatives. Under analogous conditions, ethyl [2-(cyclopent-2-en-1-yl)-4-methylphenyl]carbamate is converted into a mixture of 8-nitro-substituted 3,1-benzoxazin-2-one and 2-ethoxy-3,1-benzoxazine. Prolonged contact with excess nitrating mixture favors formation of dinitro-substituted 3,1-benzoxazin-2-one.

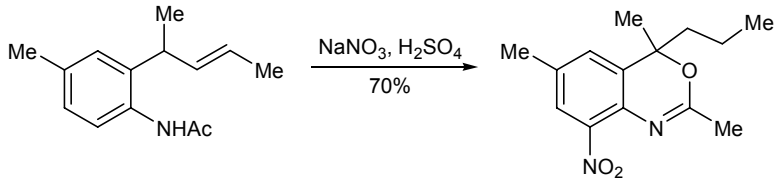
Scheme 3.



VIII **IX**, **XII** **X** 1 : 1 **XI**

IX, R = H; **XII**, R = O_2N.

Scheme 4.



XIII **XIV**

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR Presstige-21 spectrometer with Fourier transform. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance III 500 instrument at 500.13 and 125.73 MHz, respectively, using tetramethylsilane as internal reference. The elemental compositions were determined on a Hewlett Packard M-185B CHN analyzer. The mass spectra of **Va** and **XIV** were recorded on a Shimadzu LCMS-2010EV instrument [atmospheric pressure chemical ionization; eluent methanol–water (50:50) or acetonitrile (100%)]. The mass spectra of **Va**, **Vb**, **IX**, and **XII** were obtained on a ThermoFinnigan MAT 95 XP mass spectrometer with direct sample admission into the ion source under standard conditions. The purity of liquid products was checked by GLC on a Khromos GKh-1000 gas chromatograph (flame ionization detector, carrier gas helium, 1 m×3-mm column packed with 5% of SE-30 on Chromaton N-AW). Qualitative TLC analysis was performed using Sorbfil PTSKh-AF-V-UF plates (*Sorbpolimer* closed corporation, Krasnodar, Russia); spots were detected under UV light (λ 254 nm) or by treatment with iodine vapor.

***N*-[2-(Cyclopent-2-en-1-yl)-3,6-dimethylphenyl]-acetamide (Ib).** Acetic anhydride, 4.2 g (40 mmol), was added to a solution of 3.3 g (17.6 mmol) of 2-(cyclopent-2-en-1-yl)-3,6-dimethylaniline in 20 ml of anhydrous chloroform. The mixture was left to stand for 12 h at room temperature, washed with a saturated solution of $NaHCO_3$ until CO_2 no longer evolved, and extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated on a rotary evaporator, and the residue was purified by column chromatography on silica gel using first benzene and then benzene–ethyl acetate (9:1) as eluent. Yield 2.9 g (72%), R_f 0.14 (C_6H_6–EtOAc, 9:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.67–1.75 m (2H, CH_2), 2.07 s (3H, CH_3), 2.15 s (3H, CH_3), 2.33 s (3H, CH_3), 2.34–2.42 m (2H, CH_2), 2.46–2.60 m (2H, CH_2), 4.26–4.32 m (1H, 1′-H), 5.78–5.81 m (1H, 3′-H), 5.94–5.97 m (1H, 2′-H), 6.99 d (1H, H_{arom}, J = 7.6 Hz), 7.00 s (1H, NH), 7.01 d (1H, H_{arom}, J = 7.6 Hz). Found, %: C 78.48; H 8.26; N 6.04. $C_{15}H_{19}NO$. Calculated, %: C 78.56; H 8.35; N 6.11.

2,6-Dimethyl-8-nitrospiro[3,1-benzoxazine-4,1′-cyclopentane] (Va). Compound **Ia**, 2.6 g (10 mmol), was dissolved in 25 ml of 98% sulfuric acid, and 1.0 g (11.7 mmol) of sodium nitrate was added. When the salt dissolved, the mixture was poured onto 200 g of ice and extracted with chloroform (150 ml). The aqueous phase was neutralized with $NaHCO_3$ and treated with chloroform (50 ml). The organic extracts were combined, washed with a saturated solution of $NaHCO_3$ until CO_2 no longer evolved and with water (50 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using benzene as eluent. Yield 2.15 g (83%), yellow crystals, mp 111–113°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.83–2.00 m (6H, CH_2, 2′-H, 5′-H), 2.10 s (3H, CH_3), 2.21–2.26 m (2H, 2′-H, 5′-H), 2.55 s (3H, CH_3), 6.97 s (1H, H_{arom}), 7.70 s (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.3 and 21.9 (CH_3), 24.0 ($C^{3'}$, $C^{4'}$), 41.3 ($C^{2'}$, $C^{5'}$), 88.3 (C^4), 119.7 and 126.5 (C^5, C^7); 131.0, 134.1, 138.2 (C^{4a}, C^6, C^{8a}); 148.5 (C^8), 161.4 (C^2). Mass spectrum, *m*/*z*: 261 $[M + H]^+$, 260.1165 $[M]^+$. Found, %: C 64.51; H 6.15; N 10.69. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.50; H 6.20; N 10.76. *M* 260.1155.

2,5,8-Trimethyl-6-nitrospiro[3,1-benzoxazine-4,1′-cyclopentane] (Vb) was synthesized in a similar way from 0.458 g (2 mmol) of amide **Ib** and 0.2 g (2.35 mmol) of $NaNO_3$ in 5 ml of 98% H_2SO_4. Yield 0.467 g (85%), R_f 0.8 (C_6H_6–EtOAc, 9:1), mp 99–103°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.84–2.02 m (6H, CH_2, 2′-H, 5′-H), 2.11 s (3H, CH_3), 2.14–2.22 m (2H, 2′-H, 5′-H), 2.31 s (3H, CH_3), 2.36 s (3H, CH_3), 7.55 s (1H, H_{arom}). Mass spectrum: *m*/*z* 274.1321 $[M]^+$. Found, %: C 65.63; H 6.57; N 10.13. $C_{15}H_{18}N_2O_3$. Calculated, %: C 65.68; H 6.61; N 10.21. *M* 274.132.

2,6-Dimethylspiro[3,1-benzoxazine-4,1′-cyclopentane] (VI). Compound **Ia**, 0.43 g (2 mmol), was

added at room temperature to 2 ml of 98% sulfuric acid. After 30 min, the mixture was poured onto 50 g of ice, neutralized with $NaHCO_3$, and extracted with chloroform (100 ml). The extract was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator. Yield of crude product **VI** 0.42 g (98%). Thin-layer chromatography revealed no any impurity. R_f 0.4 (C_6H_6–EtOAc, 9:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.82–1.88 m (2H, 2′-H, 5′-H), 1.94–2.01 m (4H, CH_2), 2.19–2.26 m (2H, 2′-H, 5′-H), 2.11 s (3H, CH_3), 2.34 s (3H, CH_3), 6.89 s (1H, 5-H), 7.02 d (1H, H_{arom}, J = 8.0 Hz), 7.06 d.d (1H, H_{arom}, J = 1.2, 8.0 Hz). Compound **VI** partly decomposed with formation of amine **VII** during chromatographic isolation on silica gel.

Ethyl [2-(cyclopent-2-en-1-yl)-4-methylphenyl]-carbamate (VIII). A solution of 2 g of ethyl chloroformate in 5 ml of methylene chloride was added dropwise under stirring to a solution of 1.73 g (10 mmol) of 4-methyl-2-(cyclopent-2-en-1-yl)-aniline in 10 ml of anhydrous methylene chloride, and 2 g of K_2CO_3 was then added at room temperature. When the reaction was complete, the mixture was treated with 10 ml of water, stirred for 20 min, and extracted with 50 ml of methylene chloride. The organic phase was separated, washed with water, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel. Yield 2.32 g (95%); the product was a gradually crystallizing material, mp 74–76°C, R_f 0.8 (C_6H_6–EtOAc, 9:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.81 t (3H, CH_3, J = 7.0 Hz), 1.56–1.75 m (1H, 5′-H), 2.26 s (3H, CH_3), 2.49–2.60 m (3H, 5′-H, 4′-H), 3.95 m (1H, 1′-H), 4.20 q (2H, CH_2, J = 7.0 Hz), 5.72–5.74 m (1H, 2′-H), 6.01–6.04 m (1H, 3′-H), 6.53 br.s (1H, H_{arom}), 6.94 s (1H, 3-H), 7.02 d (1H, H_{arom}, J = 7.9 Hz), 7.62 br.s (1H, NH). Found, %: C 73.36; H 7.16; N 5.68. $C_{15}H_{19}NO_2$. Calculated, %: C 73.44; H 7.21; N 5.71.

6-Methyl-8-nitrospiro[3,1-benzoxazine-4,1′-cyclopentane]-2(1*H*)-one (IX) was synthesized as described above for compound **Va** from 0.49 g (2 mmol) of amide **VIII** and 0.2 g (2.35 mmol) of $NaNO_3$ in 5 ml of 98% H_2SO_4. The residue obtained after treatment of the reactions mixture and removal of the solvent was crystallized from ethanol, and the yellow crystals were filtered off. Yield 0.1 g (19%), mp 247–248°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.87–2.14 m (6H, CH_2, 2′-H, 5′-H), 2.35–2.40 m (2H, 2′-H, 5′-H), 2.56 s (3H, CH_3), 7.10 s (1H, H_{arom}), 7.50 s (1H, H_{arom}), 9.35 s (1H, NH). Mass spectrum: m/z 262.0939 $[M]^+$. Found, %: C 59.49; H 5.33; N 10.61. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.38; N 10.68. M 262.0948.

The mother liquor was evaporated, and the residue was subjected to column chromatography on silica gel using benzene as eluent to isolate 0.09 g (18%) of a mixture containing (according to the spectral data) carbamate **X** and ethoxybenzoxazine **XI** at a ratio of ~1:1.

6-Methyl-5,8-dinitrospiro[3,1-benzoxazine-4,1′-cyclopentane]-2(1*H*)-one (XII). A solution of 0.49 g (2 mmol) of compound **VIII** in 5 ml of 98% sulfuric acid was stirred for 1 h, 0.22 g (2.58 mmol) of sodium nitrate was added, and the mixture was stirred for 2 h and poured onto ice. The mixture was then treated as described above for compound **Va**. Crystals of **IX** separated from the alcoholic solution, 0.1 g, were filtered off. After 5 days, crystals of dinitro derivative **XII** separated from the mother liquor. Yield 0.126 g (20%), mp 203–205°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.90–2.17 m (6H, CH_2, 2′-H, 5′-H), 2.38 s (3H, CH_3), 2.40–2.41 m (2H, 2′-H, 5′-H), 7.40 s (1H, H_{arom}), 9.20 s (1H, NH). Mass spectrum: m/z: 307.0782 $[M]^+$. Found, %: C 59.49; H 5.33; N 10.61. $C_{13}H_{13}N_3O_6$. Calculated, %: C 50.82; H 4.26; N 13.68. M 307.0799.

2,4,6-Trimethyl-8-nitro-4-propyl-4*H*-3,1-benzoxazine (XIV) was synthesized as described above for compound **Va** from 0.434 g (2 mmol) of amide **XIII** and 0.2 g (2.35 mmol) of $NaNO_3$ in 5 ml of 98% H_2SO_4. The product was isolated by column chromatography on silica gel using benzene as eluent. Yield 0.367 g (70%), yellow viscous material, R_f 0.8 (C_6H_6–EtOAc, 9:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 t (3H, CH_3, J = 7.0 Hz), 1.18–1.42 m (2H, CH_2), 1.61 s (3H, CH_3), 1.78–2.03 m (2H, CH_2), 2.12 s (3H, CH_3), 2.57 s (3H, CH_3), 6.92 s (1H, H_{arom}), 7.70 s (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.0, 20.3, 21.7, 27.9 (CH_3); 16.8, 44.1 (CH_2); 80.8 (C^4); 118.8, 127.3 (C^5, C^7); 131.0, 134.1, 137.6 (C^{4a}, C^6, C^{8a}); 148.5 (C^8), 161.7 (C^2). Mass spectrum, m/z: 263 $[M + H]^+$, 304 $[M + H + CH_3CN]^+$. Found, %: C 64.05; H 6.86; N 10.62. $C_{14}H_{18}N_2O_3$. Calculated, %: C 64.10; H 6.92; N 10.68. M 262.3044.

REFERENCES

1. Pierce, M.E., Parsons, R.L., Jr., Radesca, L.A., Lo, Y.S., Silverman, St., Moore, J.R., Islam, Q., Choudhury, A., Fortunak, J.M.D., Nguyen, D., Luo, C., Morgan, S.G., Davis, W.P., Confalone, P.N., Chen, C., Tillyer, R.D., Frey, L., Tan, L., Xu, F., Zhao, D., Thompson, A.S.,

Corley, E.G., Grabowski, E.J.J., Reamer, R., and Reider, P.J., *J. Org. Chem*., 1998, vol. 63, p. 8536.

2. Azim, E., Dupuy, J.M., Lepage, F., Veyre, A., and Madelmont, J.C., *J. Label. Compds. Radiopharm*., 1997, vol. 39, p. 907.
3. Gala, F., D'Auria, M.V., De Marino, S., Sepe, V., Zollo, F., Smith, C.D., Keller, S.N., and Zampella, A., *Tetrahedron*, 2009, vol. 65, p. 51.
4. Zhang, P., Terefenko, E.A., Feusone, A., Zhang, Z., Zhu, Y., Cohen, J., Winneker, R., Wrobel, J., and Yardley, J., *Bioorg. Med. Chem. Lett*., 2002, vol. 12, p. 787.
5. Gromachevskaya, E.V., Kvitkovskii, F.V., Kosulina, T.P., and Kul'nevich, V.G., *Khim. Geterotsikl. Soedin*., 2003, p. 163.
6. Gromachevskaya, E.V., Kosulina, T.P., and Kul'nevich, V.G., *Khim. Geterotsikl. Soedin*., 1993, p. 537.
7. Gataullin, R.R., Afon'kin, I.S., Fatykhov, A.A., Spirikhin, L.V., and Abdrakhmanov, I.B., *Russ. J. Org. Chem*., 2001, vol. 37, p. 834.
8. Mochalov, S.S., Gazzaeva, R.A., Fedotov, A.N., Shabarov, Yu.S., and Zefirov, N.S., *Khim. Geterotsikl. Soedin*., 2003, p. 922.
9. Trofimova, E.V., Archegov, B.P., Fedotov, A.N., Gazaeva, R.A., Mochalov, S.S., and Zefirov, N.S., *Khim. Geterotsikl. Soedin*., 2009, p. 1368.
10. Gataullin, R.R., Nasyrov, M.F., Abdrakhmanov, I.B., and Tolstikov, G.A., *Russ. J. Org. Chem*., 2002, vol. 38, p. 1525.