ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 1, pp. 102–106. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © I.V. Strashilina, O.A. Mazhukina, O.V. Fedotova, 2018, published in Zhurnal Organicheskoi Khimii, 2018, Vol. 54, No. 1, pp. 103–106.

Variability of the Transformations of 4-Hydroxy-6-methyl-2*H*-pyran-2-one under Modified Biginelli Reaction Conditions

I. V. Strashilina,* O. A. Mazhukina, and O. V. Fedotova

Chernyshevskii Saratov National Research State University, ul. Astrakhanskaya 83, Saratov, 410012 Russia
**e-mail: irinastrashilina@mail.ru*

Received July 5, 2017

Abstract—A modified version of the three-component Biginelli reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with aromatic aldehydes in urea under conventional heating and microwave activation has been studied. Depending on the order of addition of the reactants, substituted (pyrano)chromenones, 10-amino-4a-hydroxy-dihydropyranochromen-2-one, and 3-[amino(phenyl)methyl]-4-hydroxypyran-2-one were obtained.

DOI: 10.1134/S1070428018010098

Natural and synthetic compounds containing a 2*H*-pyran-2-one fragment exhibit a broad spectrum of biological activity, in particular antimicrobial [1], antitumor [2–4], antitubercular [5], and enzyme inhibitory activities [6]. This makes them promising candidates for use in medical practice. Synthesis of hybrid structures containing both 2*H*-pyran-2-one and other pharmacophoric fragments could considerably extend the scope of their application.

In recent years, one-pot multicomponent syntheses involving three and more reactants are increasingly used for the construction of complex heterocyclic systems. An example of such syntheses is the Biginelli reaction. The classical Biginelli reaction is an acid-catalyzed one-pot cyclocondensation of β-keto esters with aldehydes and urea, leading to the formation of substituted 3,4-dihydropyrimidinones [7]. This reaction is a multistep process which can follow several alternative paths [8, 9].

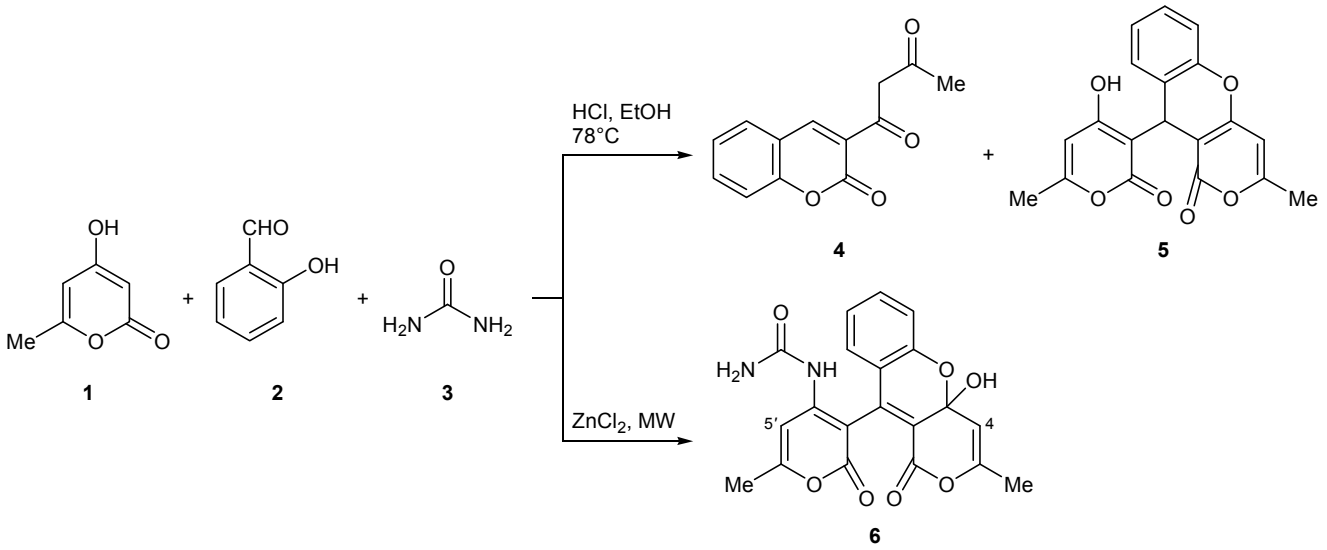
In this work we studied a modified version of the Biginelli reaction of a cyclic β-keto ester, 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), with salicylaldehyde (**2**) and urea (**3**). However, no classical Biginelli reaction products were obtained. Heating of a mixture of equimolar amounts of compounds **1**–**3** in boiling ethanol in the presence of HCl afforded 1-(2-oxo-2*H*-chromen-3-yl)butane-1,3-dione (**4**) and 10-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-methylpyrano[4,3-*b*]chromen-1(10*H*)-one (**5**) which were formed according to the mechanism described in [10] (Scheme 1). In this case, urea was not involved in the condensation, in contrast to the data of [11, 12] where 1-(2-oxo-2*H*-chromen-3-yl)butane-1,3-dione (**4**) was reported to react with ureas, yielding chromenopyrimidine and chromenoquinazoline derivatives. The structure of **4** and **5** was confirmed by ^{1}H and ^{13}C NMR spectra and was consistent with the results given in [10, 12].

Modified versions of the Biginelli reaction with the use of various catalysts and conditions have been proposed. For example, Lewis acids as catalyst and microwave activation made it possible to significantly shorten the reaction time [13, 14].

The reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) with salicylaldehyde and urea in the presence of zinc chloride under microwave irradiation gave 44% of *N*-[3-(4a-hydroxy-3-methyl-1-oxo-1,4a-dihydropyrano[4,3-*b*]chromen-10-yl)-6-methyl-2-oxo-2*H*-pyran-4-yl]urea (**6**) as the only product. Compound **6** is likely to be formed via nucleophilic substitution at the carbonyl group of the oxo tautomer of **5**. The above results suggest initial condensation of **1** with aldehyde and subsequent formation of **5** through hemiketal intermediate.

The ^{1}H NMR spectrum of **6** contained a six-proton singlet at δ 2.08 ppm from the methyl protons, a multiplet at δ 6.61–7.60 ppm due to aromatic protons, and two singlets at δ 5.85 and 8.44 ppm due to vinylic 4-H and 5′-H protons, respectively, of the pyran fragments. The downfield position of the 5′-H signal is deter-

Scheme 1.



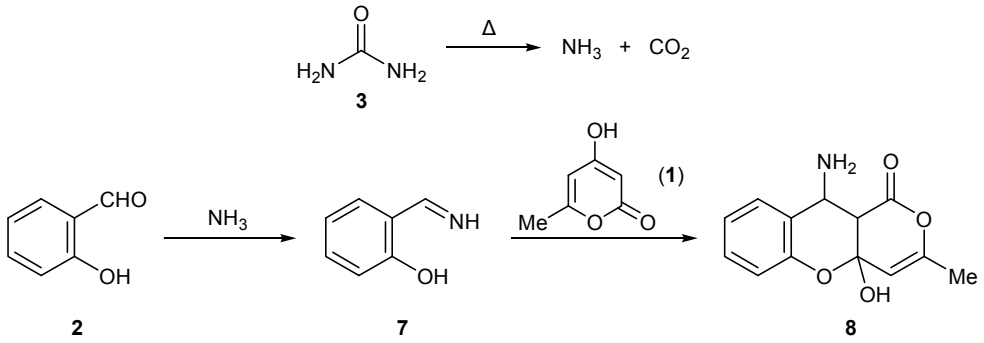
mined by conjugation with the fused system. This is consistent with two-dimensional heteronuclear correlation data (HMQC, HMBC). The HMQC spectrum of **6** showed cross-peaks at δ/δ_C 5.85/99.7 and 8.44/125.0 ppm for vinylic protons of the pyranone fragments. Furthermore, in the HMBC spectrum of **6** we observed a cross-peak δ/δ_C 8.44/151.9 ppm due to correlation between 5′-H and carbonyl carbon atom of the urea fragment. The hemiketal structure of the chromene fragment follows from the cross-peak δ/δ_C 2.21/99.7 ppm in the HMBC spectrum (coupling between the hemiketal hydroxy proton and vinylic carbon atom). Proton of the secondary amino group resonated as a broadened singlet at δ 10.89 ppm, and the primary amino group gave a singlet at δ 11.54 ppm.

In order to exclude initial condensation of salicylaldehyde with 4-hydroxy-6-methyl-2*H*-pyran-2-one, the former was reacted first with urea. Prolonged heating (up to 7 h) promoted thermal decomposition of urea to ammonia which reacted with salicylaldehyde to give 2-iminomethylphenol **7**, and reaction of the latter with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) led to the formation of previously unknown 10-amino-4a-hydroxy-3-methyl-10,10a-dihydropyrano[4,3-*b*]chromen-1(4a*H*)-one (**8**) in 69% yield (Scheme 2).

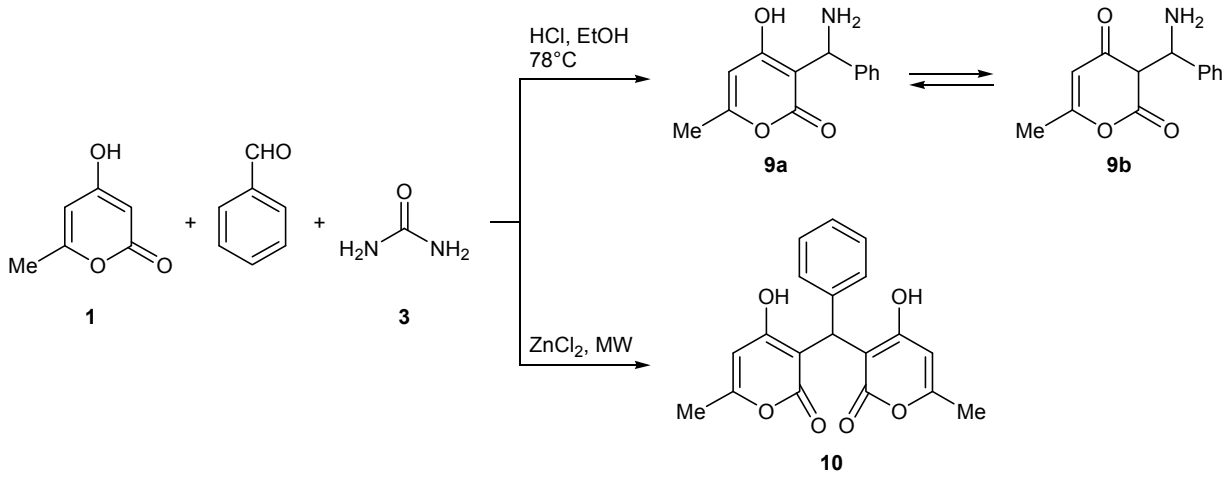
The ^{1}H NMR spectrum of **8** showed a three-proton singlet at δ 2.27 ppm due to methyl group, a multiplet of aromatic protons in the region δ 6.88–7.77 ppm, a singlet at δ 6.13 ppm due to vinylic proton, and two CH doublets at δ 5.12 (J = 8 Hz) and 5.91 ppm (J = 8 Hz). The 4a-OH proton resonated as a singlet at δ 3.71 ppm, and the two-proton singlet at δ 2.11 ppm was assigned to the amino group. In addition, downfield signals of the vinylic proton (δ 8.66 ppm, s), phenolic hydroxy group (δ 8.95 ppm, s) and =NH proton (δ 10.18 ppm, br.s) were observed in the ^{1}H NMR spectrum; these findings, in combination with the intensity of the aromatic multiplet, suggest the presence of an impurity of **7**, which confirms the proposed reaction sequence.

In order to confirm the conclusion on the effect of the *ortho* substituent in the aldehyde component on the

Scheme 2.



Scheme 3.



reaction direction, the condensation was carried out with benzaldehyde instead of salicylaldehyde. As considered above, the thermal reaction involves condensation of benzaldehyde with heterocyclic substrate **1** to form chalcone type intermediate whose reaction with ammonia (generated by decomposition of urea) yields 3-[amino(phenyl)methyl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (**9**) which is difficult to obtain under different conditions (Scheme 3).

Microwave-assisted reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with benzaldehyde and urea in the presence of zinc chloride afforded 3,3′-(phenylmethylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (**10**) (Scheme 3). Urea does not participate in the formation of **10**. The product structure was determined on the basis of the ^{1}H and ^{13}C NMR data, which were in agreement with those given in [15].

The ^{1}H NMR spectrum of substituted 2*H*-pyran-2-one **9** contained a singlet at δ 1.27 ppm from two protons of the amino group, a signal of the methyl group at δ 2.20 ppm, a multiplet of aromatic protons in the region δ 6.79–8.07 ppm, and a singlet of the vinylic proton at δ 6.08 ppm. Also, a broadened singlet was observed at δ 10.95 ppm, which was assigned to enolic OH proton involved in intramolecular hydrogen bond with the amino group. Simultaneously, two CH doublets at δ 4.10 and 5.80 ppm with similar coupling constants (J = 8 Hz) were present. These findings suggest that compound **9** in solution exists as a mixture of enol and ketone tautomers **9a** and **9b**.

Thus, the reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with aromatic aldehydes and urea preferentially involves the condensation of the methylene and carbonyl components, and only the condensation products are capable of reacting with urea. However, the path through the formation of aldehyde imine and its subsequent reaction with 1,3-diketone is also possible, which demonstrates diversity of the examined multicomponent transformation.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 20–25°C on a Varian 400 spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. The reactions were carried out in an Anton Paar Monowave 300 microwave reactor (constant temperature mode). The reaction temperature was controlled with a fiber-optic temperature sensor (850 W). The elemental analyses were obtained on a Vario Micro Cube analyzer. The progress of reactions was monitored, and the products were identified and checked for purity, by TLC, ^{1}H and ^{13}C NMR, and HMQC and HMBC methods. Silufol UV-254 plates were used for TLC (eluent hexane–ethyl acetate–chloroform, 3:1:1); spots were visualized by treatment with iodine vapor and under ultraviolet light.

1-(2-Oxo-2*H*-chromen-3-yl)butane-1,3-dione (4) and 10-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-methyl-1*H*,10*H*-pyrano[4,3-*b*]chromen-1-one (5). A mixture of 0.5 g (3.9 mmol) of 4-hydroxy-6-methylpyran-2-one (**1**), 0.41 mL (0.48 g, 3.9 mmol) of 2-hydroxybenzaldehyde (**2**), 0.24 g (3.9 mmol) of urea (**3**), 15 mL of ethanol, and several drops of concentrated aqueous HCl was refluxed for 24 h. The colorless crystals of **5** were filtered off, washed with hot ethanol, and dried. Yield 0.26 g (4%), mp 248–250°C [10]. ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, CH_3),

2.29 s (3H, CH_3), 5.08 s (1H, CH), 5.92 s (1H, =CH), 6.18 s (1H, =CH), 6.96–7.26 m (4H, H_{arom}), 9.99 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.6 ($C^{13'}$), 19.8 (C^{13}), 39.3 (C^{10}), 100.8 (C^4), 102.1 ($C^{5'}$), 107.9, 108.1, 115.9, 116.3, 119.4, 127.8 (C_{arom}), 122.3 ($C^{3'}$), 123.1 (C^{10a}), 129.7 (C^{4a}), 130.0 ($C^{4'}$), 145.3 ($C^{6'}$), 145.6 (C^3), 161.6 (C^1), 164.8 ($C^{2'}$). Found, %: C 67.21; H 4.48. $C_{19}H_{14}O_6$. Calculated, %: C 67.45; H 4.17.

The filtrate was cooled, and the yellow–orange crystals of **4** were filtered off, washed with ethanol, and dried. Yield 1.45 g (62%), mp 151–152°C [12]. ^1H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 6.85 s (1H, =CH), 7.35–7.96 m (4H, H_{arom}), 8.76 s (1H, =CH), 15.96 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 27.5 ($C^{4'}$), 101.6 (C^3), 116.6, 118.5, 120.6, 124.9, 129.5, 134.0 (C_{arom}), 116.9 (C^4), 125.3 ($C^{2'}$), 154.4 ($C^{3'}$), 158.0 (C^2), 171.9 ($C^{1'}$). Found, %: C 68.13; H 4.55. $C_{13}H_{10}O_4$. Calculated, %: C 67.82; H 4.38.

***N*-[3-(4a-Hydroxy-3-methyl-1-oxo-1*H*,4a*H*-pyrano[4,3-*b*]chromen-10-yl)-6-methyl-2-oxo-2*H*-pyran-4-yl]urea (6).** A porcelain dish was charged with 0.5 g (3.9 mmol) of compound **1**, 0.41 mL (0.48 g, 3.9 mmol) of 2-hydroxybenzaldehyde (**2**), 0.24 g (3.9 mmol) of urea (**3**), and several drops of a 10% solution of zinc chloride in ethanol. The mixture was subjected to microwave irradiation over a period of 3 h. When the reaction was complete, the yellow crystals of **6** were washed with water and dried. Yield 0.22 g (44%), mp 180–182°C. ^1H NMR spectrum, δ, ppm: 2.08 s (6H, CH_3), 2.10 s (1H, OH), 5.85 s (1H, =CH), 6.61–7.60 m (4H, H_{arom}), 8.44 s (1H, =CH), 10.89 s (1H, NH), 11.54 s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 19.5 (C^{13}), 19.8 ($C^{13'}$), 88.6 (C^{4a}), 99.7 (C^4), 123.4 ($C^{3'}$), 125.0 ($C^{5'}$), 125.1, 126.3, 128.4, 129.5, 130.3, 136.2 (C_{arom}), 128.6 (C^{10a}), 131.2 (C^{10}), 141.7 ($C^{4'}$), 143.8 (C^3), 143.7 ($C^{6'}$), 163.7 ($C^{1'}$), 165.2 ($C^{2'}$), 167.1 (C^{14}). Found, %: C 61.03; H 4.13; N 6.68. $C_{20}H_{16}N_2O_7$. Calculated, %: C 60.61; H 4.07; N 7.07.

10-Amino-4a-hydroxy-3-methyl-10,10a-dihydropyrano[4,3-*b*]chromen-1(4a*H*)-one (8). A mixture of 0.94 mL (1.10 g, 9 mmol) of 2-hydroxybenzaldehyde (**2**), 0.54 g (9 mmol) of urea (**3**), and several drops of concentrated aqueous HCl in ethanol was refluxed until the initial aldehyde disappeared. Compound **1**, 1 g (9 mmol), was added, and the mixture was refluxed for 20 h at 75°C. When the reaction was complete, the mixture was evaporated in air, and the orange crystals of **8** were washed with water and dried. Yield 1.42 g (69%), mp 158–159°C. ^1H NMR spectrum, δ, ppm: 6.13 s (1H, =CH), 2.11 s (2H, NH_2), 2.27 s (3H, CH_3), 3.71 s (1H, OH), 5.12 d (1H, CH, J = 8 Hz), 5.91 d (1H, CH, J = 8 Hz), 6.88–7.77 m (8H, H_{arom}), 8.66 s (1H, =CH), 8.95 s (1H, OH), 10.18 br.s (1H, =NH). Found, %: C 64.08; H 4.92; N 5.37. $C_{13}H_{13}NO_4$. Calculated, %: C 63.67; H 4.52; N 5.71.

3-[Amino(phenyl)methyl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (9) was synthesized as described above for compound **4** from 0.5 g (4.5 mmol) of **1**, 0.6 mL (0.48 g, 4.5 mmol) of benzaldehyde, and 0.27 g (4.5 mmol) of urea (**3**) in the presence of concentrated aqueous HCl; reaction time 32 h. Yield 0.87 g (84%), red crystals, mp 156–158°C. ^1H NMR spectrum, δ, ppm: 1.27 s (2H, NH_2), 2.20 s (3H, CH_3), 4.10 d (1H, CH, J = 8 Hz), 5.80 d (1H, CH, J = 8 Hz), 6.08 s (1H, =CH), 6.79–8.07 m (5H, H_{arom}), 10.95 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.7 (C^{14}), 34.7 (C^7), 103.2 (C^5), 104.6 (C^3), 126.4, 126.6, 126.7, 128.3, 128.5, 130.1 (C_{arom}), 135.4 (C^6), 161.1 (C^4), 168.8 (C^2). Found, %: C 67.89; H 5.84; N 5.98. $C_{13}H_{13}NO_3$. Calculated, %: C 67.52; H 5.67; N 6.06.

3,3′-(Phenylmethylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (10) was synthesized as described above for compound **6** from 0.5 g (3.9 mmol) of **1**, 0.46 mL (0.48 g, 3.9 mmol) of benzaldehyde, and 0.24 g (3.9 mmol) of urea in the presence of 10% ethanolic $ZnCl_2$ under microwave irradiation over a period of 2 h. The colorless crystals were washed with ethanol and dried. Yield 0.61 g (65%), mp 214–215°C [15]. ^1H NMR spectrum, δ, ppm: 2.29 s (6H, CH_3), 5.76 s (1H, CH), 6.06 s (2H, =CH), 6.97–7.50 m (5H, H_{arom}), 10.73 s (2H, OH), 10.93 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 17.9 (C^{15}), 18.3 (C^{25}), 34.0 (C^7), 102.4, 103.1 (C^5, $C^{5'}$), 110.2, 110.4 (C^3, $C^{3'}$), 127.4, 127.8, 128.0, 128.2, 128.6, 139.4 (C_{arom}), 143.8, 144.2 (C^6, $C^{6'}$), 160.3, 160.4 (C^2, $C^{2'}$), 166.0, 166.2 (C^4, $C^{4'}$). Found, %: C 67.33; H 4.58. $C_{19}H_{16}O_6$. Calculated, %: C 67.05; H 4.84.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 16-03-00730).

REFERENCES

1. Evidente, A., Zonno, M.C., Andolfi, A., Troise, C., Cimmino, A., and Vurro, M., *J. Antibiot*., 2012, vol. 65, no. 4, p. 203.
2. Marrison, L.R., Dickinson, J.M., and Fairlamb, I.J.S., *Bioorg. Med. Chem. Lett*., 2002, vol. 12, no. 24, p. 3509.
3. Narasimhulu, M., Arepalli, S.K., Janapala, V.R., and Yenamandra, V., *Tetrahedron Lett*., 2009, vol. 65, no. 15, p. 2989.

4. Dong, Y., Nakagawa-Goto, K., Lai, C.-Y., Morris-Natschke, S.L., Bastow, K.F., and Lee, K.-H., *ChemInform*, 2011, vol. 42, no. 34, p. 2341.
5. Prado, S., Ledeit, H., Michel, S., Koch, M., Darbord, J.C., Cole, S.T., Tillequin, F., and Brodin, P., *Bioorg. Med. Chem*., 2006, vol. 14, p. 5423.
6. Praveen Rao, P.N., Amini, M., Li, H., Habeeb, A.G., and Knaus, E.E., *J. Med. Chem*., 2003, vol. 46, no. 23, p. 4872.
7. Kappe, C.O., *QSAR Comb. Sci*., 2003, vol. 22, no. 6, p. 630.
8. Sweet, F.S. and Fissekis, J.D., *J. Am. Chem. Soc*., 1973, vol. 95, p. 8741.
9. Kappe, C.O., *J. Org. Chem*., 1997, vol. 62, p. 7201.
10. De March, P., Moreno-Mañas, M., Pleixats, R., and Roca, I.L., *J. Heterocycl. Chem*., 1984, vol. 21, no. 5, p. 1371.
11. Mazhukina, O.A., Platonova, A.G., Fedotova, O.V., and Reshetov, P.V., *Chem. Heterocycl. Compd*., 2012, vol. 48, no. 8, p. 1278.
12. Strashilina, I.V., Mazhukina, O.A., Fedotova, O.V., and Al' Mansuri, S.M.R., *Izv. Saratov. Univ., Nov. Ser. Khim. Biol. Ekol*., 2014, vol. 14, no. 3, p. 30.
13. Vdovina, S.V. and Mamedov, V.A., *Russ Chem. Rev*., 2008, vol. 77, p. 1017.
14. Kappe, C.O., Kumar, D., and Varma, R.S., *Synthesis*, 1999, vol. 10, p. 1799.
15. De March, P., Moreno-Mañas, M., Pi, R., and Trius, A., *J. Heterocycl. Chem*., 1982, vol. 19, no. 2, p. 335.