Three-component condensation of α-nitroacetophenone, aromatic aldehydes, and methylurea*

*V. F. Sedova, V. P. Krivopalov, and O. P. Shkurko**

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383) 330 9752. E-mail: oshk@nioch.nsc.ru

The three-component condensation of aromatic aldehydes, methylurea, and α-nitroacetophenone affords both *N*(1)- and *N*(3)-methyl-substituted 4,6-diaryl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-ones depending on the structure of aldehyde. Intermediate 4,6-diaryl-4-hydroxy-3-methyl-5-nitrohexahydropyrimidin-2-ones and trisubstituted urea, which is the transformation product of the 4-hydroxy-3-methyl derivative in an acidic medium (retro-Henry reaction), were identified in the reaction mixtures.

Key words: 3,4-dihydropyrimidin-2(1*H*)-ones, hexahydropyrimidin-2-ones, methylurea, aromatic aldehydes, α-nitroacetophenone, Biginelli reaction, retro-Henry reaction.

4-Aryl-3,4-dihydropyrimidinone derivatives have a broad spectrum of biological activities and are considered as promising structures in the design of new drugs.[1] Some of these compounds act as calcium channel blockers, antihypertensive and antibacterial agents, or selective α-adrenoreceptor antagonists.[2—4] *N*-Substituted dihydropyrimidinones, while having an equally broad spectrum of biological activities,[2,3,5] exhibit also properties of neutrophil elastase inhibitors,[6] neuropeptide antagonists,[6c] and cancerostatics.[7]

3,4-Dihydropyrimidin-2-one derivatives can easily be synthesized. One of procedures for their synthesis is based on the three-component condensation of aldehydes, urea, and CH-active compounds (Biginelli reaction).[2,3,8] It was demonstrated[8,9] that the use of alkylureas in the reactions with nitroacetone, acetoacetic ester, and its derivatives results in the regioselective formation of the corresponding *N*(1)-alkyl derivatives of dihydropyrimidinone. The synthesis of only one diaryl-substituted *N*(3)-methyl-3,4-dihydropyrimidin-2-one by the addition of methylurea to the corresponding chalcone was documented.[10] In addition, the formation of a complex mixture of compounds by the three-component condensation of acetylacetone, aldehydes, and alkylureas was reported, although the reaction with urea proceeded in a usual way.[11]

Earlier,[4,12] we have synthesized a series of 4,6-diaryl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-ones exhibiting high antiarrhythmic activity by condensation of α-nitroacetophenone, aromatic aldehydes, and urea. With the aim of extending the range of potential antiarrhythmic agents of this structural type, we studied the behavior of methylurea in the reaction with nitroacetophenone and aromatic aldehydes. We used 3-nitro- (**1**), 4-methoxy- (**2**), and 3-fluorobenzaldehydes (**3**) as aromatic aldehydes. This allowed us to reveal the characteristic features of the individual steps of the three-component condensation and estimate the influence of substituents in the aromatic ring of the aldehyde component on the regioselectivity of the reaction.

Aldehydes **1—3** were found to react with α-nitroacetophenone and methylurea under acid catalysis to form multicomponent mixtures of products (Scheme 1). Only 1-methyl-5-nitro-4-(3-nitrophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4**) was isolated from the mixture obtained in the reaction with aldehyde **1**.

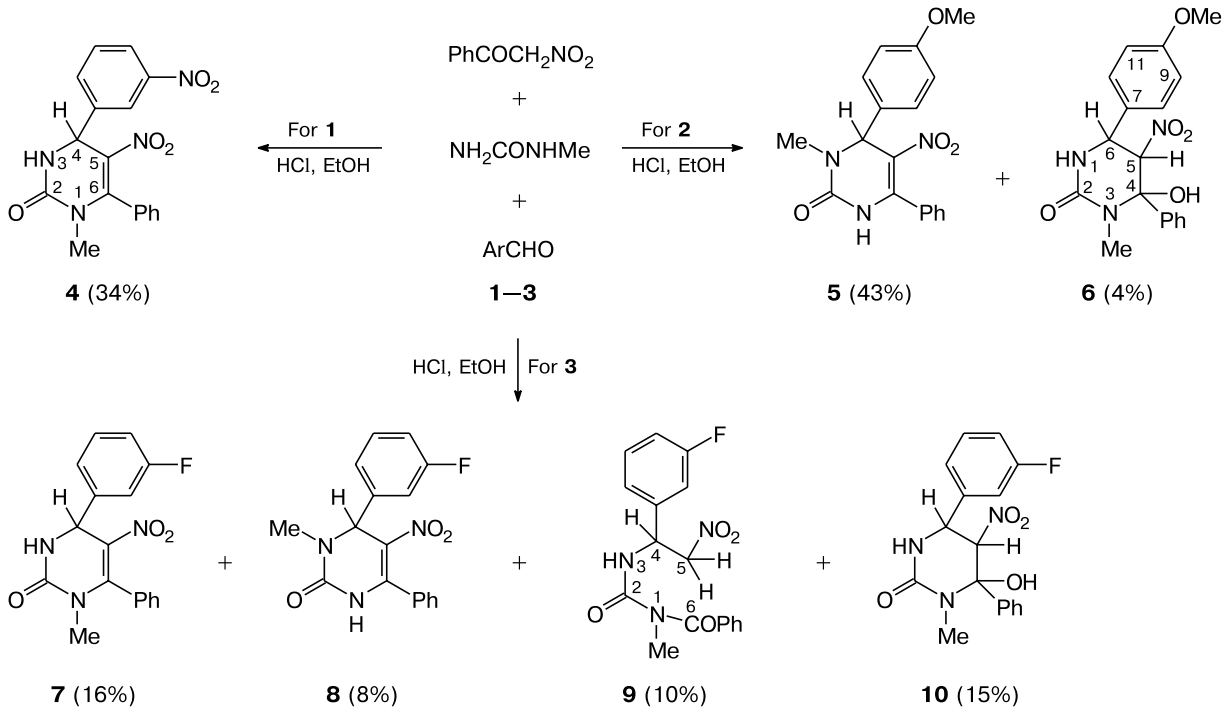
4-(4-Methoxyphenyl)-3-methyl-5-nitro-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**5**) and 4-hydroxy-6-(4-methoxyphenyl)-3-methyl-5-nitro-4-phenylhexahydropyrimidin-2-one (**6**) were isolated from the mixture obtained in the reaction involving aldehyde **2**. The condensation with the involvement of fluorobenzaldehyde **3** afforded a complex mixture of products, from which 1-methyl- and 3-methyldihydropyrimidinones (**7** and **8**, respectively) and N^1-benzoyl-N^3-[1-(3-fluorophenyl)-2-nitroethyl]-N^1-methylurea (**9**) were isolated. In addition, 4-hydroxy-3-methylhexahydropyrimidinone **10** was identified in the mixtures with dihydropyrimidinones **7** and **8**, but we failed to isolate compound **10** in the individual state. The structure of the latter compound was suggested based on the analysis of the ^{1}H and ^{13}C NMR spectra, as well as of the mass spectra of the above-mentioned mixtures taking into account the spectroscopic characteristics of structurally similar analog **6**.

* Dedicated to the memory of Academician N. N. Vorozhtsov on the 100th anniversary of his birth.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1141—1145, June, 2007.

1066-5285/07/5606-1184

Scheme 1



Ar = 3-$O_2NC_6H_4$ (**1**), 4-$MeOC_6H_4$ (**2**), 3-FC_6H_4 (**3**)

The structures of the resulting compounds were established by spectroscopic methods. The UV spectra of compounds **4** and **7** and compounds **5** and **8** show a long-wavelength absorption band at ~348—350 nm characteristic of 5-nitro-3,4-dihydropyrimidin-2-ones,[12] whereas the UV spectra of compounds **6**, **9**, and **10** have only a shoulder at ~269 nm, which is indicative of the presence of the unconjugated aromatic ring in the molecule.

The IR spectra of compounds **4** and **7** show the C=O stretching band at 1700—1710 cm^{-1}. In the IR spectra of compounds **5** and **8**, this band is observed in the range of 1650—1680 cm^{-1}; in the spectra of **6** and **10**, in the range of 1639—1652 cm^{-1}.

The position of the methyl group in compounds **4**, **5**, and **7**—**9** was established based on their ^{1}H NMR spectra. In the spectra of *N*(1)-methyldihydropyrimidinones **4** and **7**, the —N(3)H—C(4)H— fragment is manifested as two doublets of the H(3) and H(4) atoms ($J \approx 3$—5 Hz), whereas only a singlet of the H(4) atom is observed in the spectra of *N*(3)-methyldihydropyrimidinones **5** and **8**.[9b,e,12,13] It is also noteworthy that there is a difference in chemical shifts for the protons of the NH groups in the spectra of isomeric *N*-methyldihydropyrimidinones. The signal for the proton H(1) is observed at $\delta > 10$, whereas the signal for the proton H(3) is observed at higher field (δ 8.6—8.8) (*cf.* lit. data[12]). Compound **9** is characterized by the presence of an ABX system of signals for the H(4), H(5a), and H(5b) atoms in the ^{1}H NMR spectrum. An additional spin-spin coupling constant ($J_{3,4} = 8.1$ Hz) is observed for the signal of the H(4) atom, which confirms the conclusion about the presence of the N(1)—Me and N(3)—H fragments in this structure (*cf.* lit. data[14]).

The ^{1}H NMR spectra of *N*-methyl-substituted hexahydropyrimidinones **6** and **10** show signals for the axial H(5) and H(6) atoms as two doublets ($J = 11$ Hz) at δ 5—6. The absence of additional splitting of the signal for the H(6) atom ($J_{1,6}$) apparently cannot be considered as an indication of the presence of the methyl group at the N(1) atom of the heterocycle, as evidenced from the published data.[15] Hence, we used mass spectrometric data to establish the position of the methyl group in these compounds.

In the ^{13}C NMR spectra, the resonances of the C(2), C(4), C(5), and C(6) atoms are most informative for confirming the structures of the resulting compounds. In the spectra of dihydropyrimidinones **4** and **7** and compounds **5** and **8**, these signals are in the ranges characteristic of *N*-unsubstituted 5-nitrodihydropyrimidinones.[12] The positions of the signals for the C(2) and C(6) atoms in the spectra of hexahydro derivatives **6** and **10** are only slightly different from the positions of the analogous signals in the spectra of dihydro derivatives **4** and **7** and compounds **5** and **8**, whereas the signals for the C(4) and C(5) atoms are shifted upfield (δ 85—95). In the spectrum of trisubstituted urea **9**, the signal for the C(6) atom of the benzoyl group is observed at δ ~172.

The mass spectra of dihydropyrimidinones **4**, **5**, **7**, and **8** contain the following major ions: $[M]^+$, $[M - OH]^+$, $[M - HNO_2 - H]^+$, $[M - C_6H_4R]^+$, $[M - HNO_2 - C_6H_4R]^+$, and $[C_6H_5]^+$ (*cf.* lit. data[12]). The mass spectra of compounds **4**, **5**, **7**, and **8** differ in the intensities of the fragment ions at *m/z* 118 ($[C_6H_5C{=}NCH_3]^+$) and 104 ($[C_6H_5C{=}NH]^+$), which characterize the presence or absence of substituents at the N(1) atom. For *N*(1)-methyl derivatives **4** and **7**, the relative intensities of the line at *m/z* 118 are higher than 39%, whereas the intensities of this line for *N*(3)-methyl derivatives **5** and **8** are <3%. The intensity of the ion at *m/z* 104 in the mass spectra of compounds **5** and **8** is >10%, whereas this ion is not observed for *N*(1)-methyl derivatives **4** and **7**.

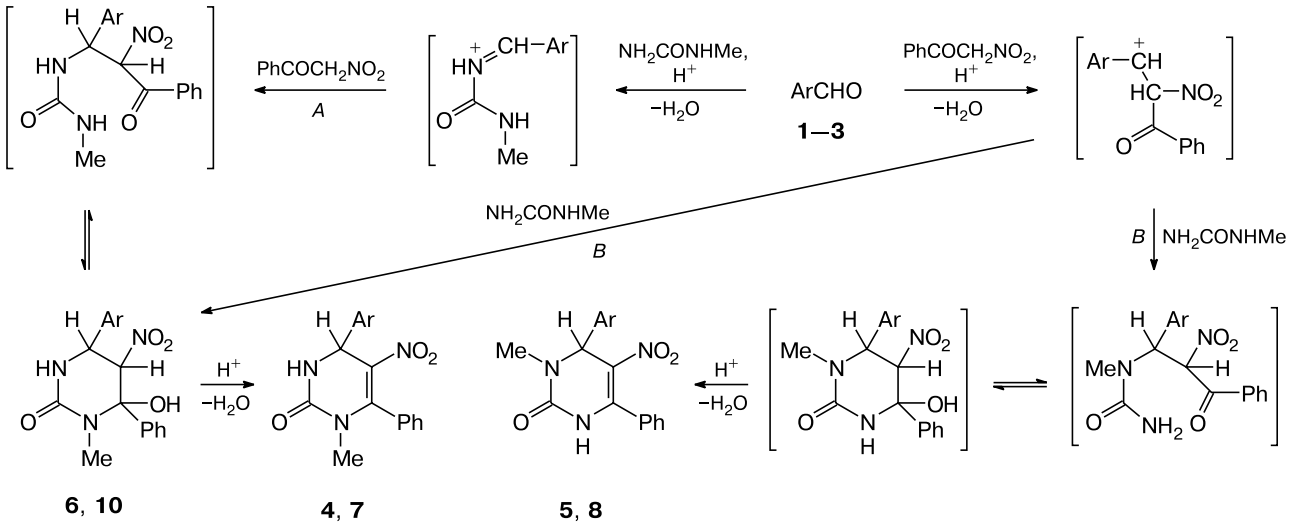
Hexahydropyrimidine derivatives **6** and **10** and substituted urea **9** are characterized by a similar topology and, consequently, their mass-spectrometric behavior is considered jointly. The mass spectra of these compounds are characterized by the presence of the line of $[M]^+$ with very low intensity (<1%). The line with the maximum intensity at *m/z* 105 (100%) belongs to the $[C_6H_5CO]^+$ ion. Based on these facts, we suggested that the electron impact causes the opening of the heterocycle in unstable β-nitro alcohols **6** and **10** accompanied by the C(4)—C(5) bond cleavage and the formation of substituted urea by analogy with the published data.[14] The latter compounds are characterized by the presence of the fragment ions $[M - NO_2]^+$, $[M - HNO_2]^+$, $[M - HNO_2 - C_6H_5CO]^+$, $[M - NO_2 - C_6H_5CONHR]^+$, and $[M - HNO_2 - C_6H_5CONHR]^+$ and ions at *m/z* 105 ($[C_6H_5CO]^+$) and 77 ($[C_6H_5]^+$).[14] All these lines are observed also in the spectrum of compound **9**.

The spectrum of compound **6** shows lines of the fragment ions $[M - NO_2 - C_6H_5CONHCH_3]^+$ at *m/z* 176 (90%) and $[M - HNO_2 - C_6H_5CONHCH_3]^+$ at *m/z* 175 (49%), whereas the ions at *m/z* 190 ($[M - NO_2 - C_6H_5CONH_2]^+$) and 189 ($[M - HNO_2 - C_6H_5CONH_2]^+$) are absent. An analogous pattern is observed in the mass spectrum of compound **10**. Based on these facts, we assigned the structure of *N*(3)-methylhexahydropyrimidin-2-ones to compounds **6** and **10**.

According to the classical scheme of the Biginelli reaction (condensation of acetoacetic ester, aromatic aldehyde, and urea) under acid catalysis, it can be hypothesized that aldehydes **1** and **3** react with urea to form the reactive acyliminium cation (Scheme 2). The reaction of the latter with α-nitroacetophenones at the CH-active fragment and the cyclization of the resulting ureido derivatives afford 4-hydroxyhexahydropyrimidin-2-ones, which undergo dehydration to give dihydropyrimidinones **4** and **7**.[2,16] According to the published data,[15,17] the dehydration does not proceed only in the presence of an electron-withdrawing haloalkyl group at position 4 of the heterocycle. The selective formation of *N*(1)-substituted dihydropyrimidinones through the path *A* is attributed to the fact that the reaction of aldehyde with monoalkylureas proceeds only at the unsubstituted NH_2 group of urea[2,8,9].

An alternative pathway of the three-component condensation (see Scheme 2, path *B*) involves the initial reaction of aldehyde with α-nitroacetophenones. As has been shown earlier for other reactions, the resulting carbocation reacts with monoalkylurea both at the alkylamino group[10] and the unsubstituted amino group[9c,17–19] to give the corresponding *N*(1)- (**4** and **7**) or *N*(3)-alkylpyrimidinones (**5** and **8**) or their mixtures. Therefore, depending on the reaction conditions and the structures of the starting reagents, the reaction can follow predomi-

Scheme 2



Ar = 3-$O_2NC_6H_4$ (**1**, **4**), 4-$MeOC_6H_4$ (**2**, **5**), 3-FC_6H_4 (**3**, **7**, **8**)

nantly either the path *A* or path *B*.[20] It cannot be ruled out that the reaction products contain intermediates generated in the transformations involved in both pathways.

The condensation of α-nitroacetophenone, nitrobenzaldehyde **1**, and methylurea follows predominantly the path *A* to give *N*(1)-methylpyrimidinone **4** as the major product. The reaction with methoxybenzaldehyde **2** follows predominantly the path *B* to form *N*(3)-methyl derivative **5**.

The reaction with fluorobenzaldehyde **3** as the aldehyde component takes apparently both paths (*A* and *B*), resulting in the formation of isomeric *N*(1)- and *N*(3)-methyldihydropyrimidinones **7** and **8**, as well as of 4-hydroxy-3-methylhexahydropyrimidin-2-one **10**. Evidently, the heterocycle in compound **10** is partially cleaved under the reaction conditions (retro-Henry reaction) to form *N*(1)-benzoyl-*N*(1)-methylurea **9** (*cf.* lit. data[14]).

To summarize, we found that the three-component acid-catalyzed condensation of α-nitroacetophenone, aromatic aldehydes, and methylurea produces both *N*(1)- (**4** and **7**) and *N*(3)-methyl-substituted dihydropyrimidinones (**5** and **8**). Intermediate 4-hydroxy-3-methylhexahydropyrimidin-2-ones **6** and **10** and trisubstituted urea **9**, which is generated in the retro-Henry reaction of compound **10**, were characterized for the first time.

Experimental

The IR spectra were measured on a Bruker Vector 22 spectrophotometer in KBr pellets. The UV spectra were recorded in solution on a Specord M-40 spectrophotometer. The mass spectra were obtained on a Finnigan MAT 8200 instrument (EI, 70 eV, direct inlet system). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer in DMSO-d_6 using the signals of the solvent as the internal standard (δ_H 2.50 and δ_C 39.50). The purity of the compounds was monitored by TLC on Silufol UV-254 plates using a $CHCl_3$—EtOH mixture (15 : 1) as the eluent.

1-Methyl-5-nitro-4-(3-nitrophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4). A mixture of α-nitroacetophenone (1.5 g, 9 mmol), 3-nitrobenzaldehyde (**1**) (1.1 g, 7 mmol), and methylurea (1.0 g, 13.5 mmol) in ethanol (10 mL) containing concentrated HCl (1 mL) was refluxed for 15 h and kept at ~20 °C for 10 days. The precipitate that formed was filtered off, successively washed with ethanol and a 1 : 1 ethanol—water mixture (2×3 mL), and recrystallized from ethanol. Compound **4** was obtained in a yield of 0.85 g (34%), m.p. 241—243 °C, R_f 0.56. Found (%): C, 57.23; H, 4.18; N, 15.67. $C_{17}H_{14}N_4O_5$. Calculated (%): C, 57.62; H, 3.98; N, 15.81. MS, *m/z* (I_{rel} (%)): 354 $[M]^+$ (16), 337 $[M - OH]^+$ (88), 310 (47), 306 $[M - HNO_2 - H]^+$ (82), 232 $[M - C_6H_4NO_2]^+$ (100), 185 $[M - C_6H_4NO_2 - HNO_2]^+$ (67), 118 $[C_6H_5C{=}NCH_3]^+$ (57), 77 $[C_6H_5]^+$ (45). High-resolution mass spectrum: *m/z* 354.0983 $[M]^+$. $C_{17}H_{14}N_4O_5$. Calculated: M = 354.0964. UV, λ_{max}/nm (logε): 205 (4.14), 249 (3.86), 350 (3.75). IR, ν/cm^{-1}: 3253, 3194 (NH), 2953 (Me), 1707 (C=O), 1525, 1348 (NO_2). ^{1}H NMR, δ: 2.73 (s, 3 H, Me); 5.87 (d, 1 H, H(4), $^3J_{3,4}$ = 4.0 Hz); 7.40—7.62 (m, 5 H, Ph); 7.75 (t, 1 H, H(11), ^3J = 8.0 Hz); 7.96 (d, 1 H, H(10), ^3J = 8.0 Hz); 8.22 (dd, 1 H, H(12), ^3J = 8.0 Hz, ^4J = 2.4 Hz); 8.31 (t, 1 H, H(8), ^4J = 2.0 Hz); 8.78 (d, 1 H, H(3), $^3J_{3,4}$ = 3.6 Hz). ^{13}C NMR, δ: 32.49 (Me); 52.73 (C(4)); 121.51 (C(10)); 123.02 (C(8)); 124.09 (C(5)); 127.01, 127.23, 128.95, 129.04, 130.65, and 132.16 (all C_{Ph}); 129.53 (C(11)); 132.87 (C(12)); 143.72 (C(7)); 148.00 (C(9)); 150.88 (C(6)); 152.00 (C(2)).

4-(4-Methoxyphenyl)-3-methyl-5-nitro-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (5) and **4-hydroxy-6-(4-methoxyphenyl)-3-methyl-5-nitro-4-phenylhexahydropyrimidin-2(1*H*)-one (6).** A mixture of α-nitroacetophenone (1.8 g, 11 mmol), 4-methoxybenzaldehyde (**2**) (1.2 g, 9 mmol), and methylurea (1.3 g, 18 mmol) in ethanol (15 mL) containing concentrated HCl (1.5 mL) was refluxed for 16 h and kept at ~4 °C for 15 days. The precipitate that formed was filtered off, successively washed with ethanol, a saturated $NaHCO_3$ solution, water, and ethanol, and dried. Compound **5** was obtained in a yield of 1.3 g (43%), m.p. 249—251 °C (from an ethanol—dioxane mixture), R_f 0.75. Found (%): C, 63.30; H, 5.26; N, 12.28. $C_{18}H_{17}N_3O_4$. Calculated (%): C, 63.71; H, 5.05; N, 12.38. MS, *m/z* (I_{rel} (%)): 339 $[M]^+$ (14), 322 $[M - OH]^+$ (81), 293 $[M - NO_2]^+$ (85), 291 $[M - HNO_2 - H]^+$ (100), 232 $[M - C_6H_4OMe]^+$ (74), 185 $[M - C_6H_4OMe - HNO_2]^+$ (64), 118 (3), 104 $[C_6H_5C{=}NH]^+$ (20), 77 $[C_6H_5]^+$ (22). High-resolution mass spectrum, found: *m/z* 339.1126 $[M]^+$. $C_{18}H_{17}N_3O_4$. Calculated: M = 339.1290. UV, λ_{max}/nm (logε): 203 (4.50), 231 (4.28), 350 (3.89). IR, ν/cm^{-1}: 3367, 3196 (NH), 2997, 2931 (Me), 1677 (C=O), 1492, 1328 (NO_2), 1257. ^{1}H NMR, δ: 2.79 (s, 3 H, NMe); 3.77 (s, 3 H, OMe); 5.65 (s, 1 H, H(4)); 6.99 (d, 2 H, H(9), H(11), ^3J = 8.0 Hz); 7.35—7.65 (m, 7 H, H(8), H(12), Ph); 10.22 (s, 1 H, H(1)). ^{13}C NMR, δ: 32.32 (NMe); 55.03 (OMe); 60.15 (C(4)); 114.23 (C(9), C(11)); 122.52 (C(5)); 127.58, 128.24, 129.68, and 131.32 (all C_{Ph}); 128.24 (C(8), C(12)); 132.17 (C(7)); 148.22 (C(6)); 150.01 (C(2)); 159.28 (C(10)).

After separation of compound **5**, the mother liquor was kept at ~20 °C for 10 days. The white precipitate that formed was filtered off, washed with ethanol, and dried on a filter. Hexahydropyrimidinone **6** was obtained in a yield of 0.13 g (4%), m.p. 155—157 °C (from ethanol). Found (%): C, 60.35; H, 5.69; N, 11.49. $C_{18}H_{19}N_3O_5$. Calculated (%): C, 60.49; H, 5.36; N, 11.76. MS, *m/z* (I_{rel} (%)): 357 $[M]^+$ (0.5), 311 $[M - NO_2]^+$ (12), 310 $[M - HNO_2]^+$ (32), 205 $[M - HNO_2 - COC_6H_5]^+$ (33), 176 $[M - NO_2 - C_6H_5CONHMe]^+$ (90), 175 $[M - HNO_2 - C_6H_5CONHMe]^+$ (49), 161 (35), 134 (40), 105 $[COC_6H_5]^+$ (100), 77 $[C_6H_5]^+$ (85). High-resolution mass spectrum, found: *m/z* 357.1297 $[M]^+$. $C_{18}H_{19}N_3O_5$. Calculated: M = 357.1325. UV, λ_{max}/nm (logε): 204 (4.43), 225 (4.31), 269 (3.81). IR, ν/cm^{-1}: 3325, 3271, 3182 (OH, NH), 2936, 2840 (Me), 1639 (C=O), 1559, 1372, 1329 (NO_2). ^{1}H NMR, δ: 2.48 (s, 3 H, NMe); 3.74 (s, 3 H, OMe); 5.17 (d, 1 H, H(5), $^3J_{5,6}$ = 11.0 Hz); 5.33 (d, 1 H, H(6), $^3J_{5,6}$ = 11.0 Hz); 6.92 (d, 2 H, H(9), H(11), ^3J = 8.8 Hz); 7.19 (br.s, 2 H, NH, OH); 7.33—7.50 (m, 5 H, Ph); 7.57 (d, 2 H, H(8), H(12), ^3J = 8.8 Hz). ^{13}C NMR, δ: 29.75 (NMe); 52.85 (C(6)); 54.98 (OMe); 85.39 (C(5)); 93.59 (C(4)); 113.69 (C(9), C(11)); 126.51, 128.11, 128.23, 128.63, 129.41 (C(8), C(12), C_{Ph}); 139.07 (C(7)); 154.71 (C(2)); 159.42 (C(10)).

Condensation of α-nitroacetophenone with 3-fluorobenzaldehyde (3) and methylurea. A mixture of α-nitroacetophenone (1.5 g, 9 mmol), aldehyde **3** (0.9 g, 7 mmol), and methylurea (1.0 g, 13.5 mmol) in ethanol (10 mL) containing concentrated HCl (1.0 mL) was refluxed for 11 h and kept at ~4 °C for 7 days. The precipitate that formed (1.25 g) was filtered off and successively washed with ethanol, a saturated $NaHCO_3$ solution, water, and ethanol. ***N*^{1}-Benzoyl-*N*^{3}-[1-(3-fluorophenyl)-2-nitroethyl]-*N*^{1}-methylurea (9)** was obtained in a yield of 0.25 g (10%). An analytically pure sample was obtained after threefold recrystallization from ethanol, m.p. 169—171 °C, R_f ~0.9. Found (%): C, 59.34; H, 4.83; F, 5.63; N, 11.97. $C_{17}H_{16}FN_3O_4$. Calculated (%): C, 59.12; H, 4.67; F, 5.50; N, 12.17. MS, m/z (I_{rel} (%)): 345 $[M]^+$ (0.7), 299 $[M - NO_2]^+$ (31), 298 $[M - HNO_2]^+$ (43), 193 $[M - HNO_2 - COC_6H_5]^+$ (32), 164 $[M - NO_2 - C_6H_5CONHCH_3]^+$ (12), 163 $[M - HNO_2 - C_6H_5CONHCH_3]^+$ (9), 105 $[COC_6H_5]^+$ (100), 77 $[C_6H_5]^+$ (35). High-resolution mass spectrum, found: m/z 345.1115 $[M]^+$. $C_{17}H_{16}FN_3O_4$. Calculated: M = 345.1125. UV, λ_{max}/nm (logε): 203 (4.45), 269 (3.44). IR, ν/cm^{-1}: 3270, 3184 (NH), 2912 (Me), 1640 (C=O), 1557, 1402, 1370 (NO_2). ^{1}H NMR, δ: 3.11 (s, 3 H, Me); 5.01 (dd, 1 H, H_A(5), $^2J_{A,B}$ = 13.8 Hz, $^3J_{4,5}$ = 5.7 Hz); 5.05 (dd, 1 H, H_B(5), $^2J_{A,B}$ = 13.8 Hz, $^3J_{4,5}$ = 7.9 Hz); 5.56 (dt, 1 H, H(4), $^3J_{3,4}$ = 8.1 Hz, $^3J_{4,5A}$ = 7.9 Hz, $^3J_{4,5B}$ = 5.7 Hz); 7.10—7.55 (m, 9 H, Ar); 9.33 (d, 1 H, H(3), $^3J_{3,4}$ = 8.1 Hz). ^{13}C NMR, δ: 34.10 (Me); 51.66 (C(4)); 77.73 (C(5)); 113.67 (d, C(10), $J_{C,F}$ = 22.3 Hz); 114.75 (d, C(8), $J_{C,F}$ = 20.9 Hz); 122.88 (C(12)); 126.93, 128.10, 130.63, and 135.72 (all C_{Ph}); 130.50 (d, C(11), $J_{C,F}$ = 8.2 Hz); 140.11 (d, C(7), $J_{C,F}$ = 7.1 Hz); 154.99 (C(2)); 162.05 (d, C(9), $^1J_{C,F}$ = 242 Hz); 172.38 (C(6)).

The combined mother liquors were concentrated *in vacuo* to dryness. Compounds **7** and **8** were isolated as analytically pure samples by fractional crystallization of the residue (1.15 g) from ethanol. Compound **10**, which is better soluble in ethanol, was concentrated in tail fractions. According to the ^{1}H NMR spectroscopic data, the total yield of **6-(3-fluorophenyl)-4-hydroxy-3-methyl-5-nitro-4-phenylhexahydropyrimidin-2-one (10)** was 15%. The spectroscopic characteristics of this compound were obtained by analyzing the spectra of a mixture of compounds **7** and **10** (3 : 1). MS, m/z (I_{rel} (%)): 299 $[M - NO_2]^+$ (10), 298 $[M - HNO_2]^+$ (13), 193 $[M - HNO_2 - COC_6H_5]^+$ (9), 164 $[M - NO_2 - C_6H_5CONHCH_3]^+$ (4), 163 $[M - HNO_2 - C_6H_5CONHCH_3]^+$ (3), 105 $[COC_6H_5]^+$ (100), 77 $[C_6H_5]^+$. IR, ν/cm^{-1}: 3371, 3240, 3187 (OH, NH), 1652 (C=O), 1557, 1376, 1326 (NO_2). ^{1}H NMR, δ: 2.48 (s, 3 H, Me); 5.27 (d, 1 H, H(5), $^3J_{5,6}$ = 11.0 Hz); 5.49 (d, 1 H, H(6), $^3J_{5,6}$ = 11.0 Hz); 7.10—7.65 (m, 11 H, Ar, NH, OH). ^{13}C NMR, δ: 29.82 (Me); 53.12 (C(6)); 85.51 (C(5)); 92.88 (C(4)); 115.07 (d, C(10), $J_{C,F}$ = 22.5 Hz); 115.57 (d, C(8), $J_{C,F}$ = 19.5 Hz); 124.74 (C(12)); 126.77, 128.14, 128.31, and 138.94 (all C_{Ph}); 130.21 (d, C(11), $J_{C,F}$ = 8.2 Hz); 139.70 (d, C(7), $J_{C,F}$ = 7.1 Hz); 154.61 (C(2)); 162.02 (d, C(9), $^1J_{C,F}$ = 242 Hz).

4-(3-Fluorophenyl)-1-methyl-5-nitro-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (7). The yield was 0.37 g (16%), m.p. 185—188 °C (from ethanol), R_f 0.65. Found (%): C, 62.26; H, 4.31; F, 5.72; N, 12.86. $C_{17}H_{14}FN_3O_3$. Calculated (%): C, 62.38; H, 4.31; F, 5.81; N, 12.84. MS, m/z (I_{rel} (%)): 327 $[M]^+$ (18), 310 $[M - OH]^+$ (75), 279 $[M - HNO_2 - H]^+$ (100), 232 $[M - C_6H_4F]^+$ (97), 185 $[M - C_6H_4F - HNO_2]^+$ (69), 118 $[C_6H_5C=NCH_3]^+$ (39), 77 $[C_6H_5]^+$ (48). High-resolution mass spectrum, found: m/z 327.1018 $[M]^+$. $C_{17}H_{14}FN_3O_3$. Calculated: M = 327.1019. UV, λ_{max}/nm (logε): 348 (3.68). IR, ν/cm^{-1}: 3371 (NH), 2954 (Me), 1706 (C=O), 1335 (NO_2). ^{1}H NMR, δ: 2.73 (s, 3 H, Me); 5.71 (d, 1 H, H(4), $^3J_{3,4}$ = 4.0 Hz); 7.10—7.62 (m, 9 H, Ar); 8.65 (d, 1 H, H(3), $^3J_{3,4}$ = 4.0 Hz). ^{13}C NMR, δ: 32.32 (Me); 52.87 (C(4)); 113.36 (d, C(10), $J_{C,F}$ = 21.8 Hz); 114.86 (d, C(8), $J_{C,F}$ = 20.9 Hz); 122.21 (d, C(12), $J_{C,F}$ = 2.7 Hz); 124.54 (C(5)); 126.87, 127.35, 129.36, and 132.24 (all C_{Ph}); 130.84 (d, C(11), $J_{C,F}$ = 8.2 Hz); 144.37 (d, C(7), $J_{C,F}$ = 6.2 Hz); 150.95 (C(6)); 151.37 (C(2)); 162.23 (d, C(9), $^1J_{C,F}$ = 243 Hz).

4-(3-Fluorophenyl)-3-methyl-5-nitro-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (8). The yield was 0.19 g (8%), m.p. 223—225 °C (from ethanol), R_f 0.74. Found (%): C, 62.46; H, 4.29; F, 5.74; N, 12.59. $C_{17}H_{14}FN_3O_3$. Calculated (%): C, 62.38; H, 4.31; F, 5.81; N, 12.84. MS, m/z (I_{rel} (%)): 327 $[M]^+$ (10), 310 $[M - OH]^+$ (34), 279 $[M - HNO_2 - H]^+$ (26), 232 $[M - C_6H_4F]^+$ (100), 185 $[M - C_6H_4F - HNO_2]^+$ (39), 104 $[C_6H_5C=NH]^+$ (11), 77 $[C_6H_5]^+$ (17). High-resolution mass spectrum, found: m/z 327.1021 $[M]^+$. $C_{17}H_{14}FN_3O_3$. Calculated: M = 327.1019. IR, ν/cm^{-1}: 3194 (NH), 2924, 2810 (Me), 1652 (C=O), 1499, 1326 (NO_2). ^{1}H NMR, δ: 2.79 (s, 3 H, Me); 5.74 (s, 1 H, H(4)); 7.10—7.60 (m, 9 H, Ar); 10.28 (s, 1 H, H(1)). ^{13}C NMR, δ: 32.58 (Me); 60.21 (C(4)); 114.08 (d, C(10), $J_{C,F}$ = 21.6 Hz); 115.38 (d, C(8), $J_{C,F}$ = 20.8 Hz); 121.83 (C(5)); 122.90 (C(12)); 127.68, 128.32, 129.89, and 131.95 (all C_{Ph}); 131.12 (d, C(11), $J_{C,F}$ = 8.1 Hz); 142.16 (d, C(7), $J_{C,F}$ = 6.2 Hz); 149.01 (C(6)); 149.95 (C(2)); 162.20 (d, C(9), $^1J_{C,F}$ = 243 Hz).

References

1. D. A. Horton, G. T. Bourn, and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
2. C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879.
3. C. O. Kappe, *Eur. J. Med. Chem.*, 2000, **35**, 1043.
4. A. O. Bryzgalov, M. P. Dolgikh, I. V. Sorokina, T. G. Tolstikova, V. F. Sedova, and O. P. Shkurko, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1418.
5. PCT Int. Appl. 2006 097617; PCT Int. Appl. 2005 009392; *Chem. Abstrs*, 2005, **142**, 198087; PCT Int. Appl. 98 51311; *Chem. Abstrs*, 1999, **130**, 25077.
6. (a) PCT Int. Appl. 2005 82863; *Chem. Abstrs*, 2005, **143**, 286440; (b) PCT Int. Appl. 2005 82864; *Chem. Abstrs*, 2005, **143**, 286441; (c) PCT Int. Appl. 98 33791; *Chem. Abstrs*, 1998, **129**, 148989.
7. PCT Int. Appl. 00 06565; *Chem. Abstrs*, 2000, **132**, 137405.
8. C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937; A. Stadler and C. O. Kappe, *J. Comb. Chem.*, 2001, **3**, 624.
9. (a) K. Singh, D. Arora, and S. Singh, *Tetrahedron Lett.*, 2006, **47**, 4205; (b) H. Salehi and Q.-X. Guo, *Synth. Commun.*, 2004, **34**, 171; (c) M. J. Lusch and J. A. Tallarico, *Org. Lett.*, 2004, **6**, 3237; (d) A. Dondoni and A. Massi, *Molecular Diversity*, 2003, **6**, 261; (e) S. A. Kravchenko, V. V. Pirozhenko, S. I. Vdovenko, A. E. Sorochinskii, and G. Ya. Remennikov, *Khim. Geterotsikl. Soedin.*, 2003, 216 [*Chem. Heterocycl. Compd.*, 2003, **39**, 188 (Engl. Transl.)]; (f) F. S. Falsone and C. O. Kappe, *ARKIVOC*, 2001, 122; (g) H. Namazi, Y. R. Mirzaei, and H. Azamat, *J. Heterocycl. Chem.*, 2001, **38**, 1051.
10. A. R. Marzinzik and E. R. Felder, *J. Org. Chem.*, 1998, **63**, 723.

11. E. S. Putilova, G. V. Kryshtal´, G. M. Zhdankina, N. A. Troitskii, and S. G. Zlotin, *Zh. Org. Khim.*, 2005, **41**, 524 [*Russ. J. Org. Chem.*, 2005, **41**, 512 (Engl. Transl.)].
12. V. F. Sedova, T. V. Voevoda, T. G. Tolstikova, and O. P. Shkurko, *Khim.-farm. Zh.*, 2002, **36**, No. 6, 4 [*Pharm. Chem. J.*, 2002, **36**, 284 (Engl. Transl.)].
13. C. O. Kappe and P. Roscher, *J. Heterocycl. Chem.*, 1989, **26**, 55.
14. V. F. Sedova, V. P. Krivopalov, and O. P. Shkurko, *Zh. Org. Khim.*, 2007, **43**, 87 [*Russ. J. Org. Chem.*, 2007, **43**, 90 (Engl. Transl.)].
15. E. S. Putilova, N. A. Troitskii, S. G. Zlotin, O. G. Khudina, Ya. V. Burgart, V. I. Saloutin, and O. N. Chupakhin, *Zh. Org. Khim.*, 2006, **42**, 1407 [*Russ. J. Org. Chem.*, 2006, **42**, 1392 (Engl. Transl.)]; V. A. Mamedov, L. V. Mustakimova, I. T. Gubaidullin, S. V. Vdovina, I. A. Litvinov, and V. S. Reznik, *Khim. Geterotsikl. Soedin.*, 2006, 1414 [*Chem. Heterocycl. Compd.*, 2006, **42**, 1229 (Engl. Transl.)].
16. C. O. Kappe, *J. Org. Chem.*, 1997, **62**, 7201.
17. M. V. Pryadeina, Ya. V. Burgart, M. I. Kodess, V. I. Saloutin, and O. N. Chupakhin, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1210 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1261].
18. G. Ya. Remennikov, I. V. Boldyrev, N. A. Kapran, and L. K. Kurilenko, *Khim. Geterotsikl. Soedin.*, 1993, 388 [*Chem. Heterocycl. Compd.*, 1993, **29**, 325 (Engl. Transl.)].
19. F. Sweet and J. D. Fissekis, *J. Am. Chem. Soc.*, 1973, **95**, 8741.
20. Z. D. Aron and L. E. Overman, *Chem. Commun.*, 2004, 253.

Received February 13, 2007;
in revised form June 18, 2007