Three-component condensation of diethyl isophthaloyldiacetate, aromatic aldehyde, and urea as a new method for the synthesis of 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzenes

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Condensation of diethyl isophthaloyldiacetate, aromatic aldehyde, and urea in the presence of Me_3SiCl proceeds efficiently and faster than in the absence of the latter to form 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene derivatives capable to give inclusion complexes with DMF.

Key words: diethyl isophthaloyldiacetate, the Biginelli reaction, 2-oxo-1,2,3,4-tetrahydropyrimidines, trimethylsilyl chloride, NMR spectra, X-ray analysis.

Special interest to 2-oxo-1,2,3,4-tetrahydropyrimidines (the "Biginelli compounds") is caused in the last years by the finding among their derivatives compounds with important pharmacological properties,[1] including blocators of calcium channels,[2] anti-hypertonic medicins,[3—5] alpha-1a-antagonists, and antagonists of neuropeptide Y (NPY).[7] It was also found that the marine alkaloids containing dihydropyrimidine-5-carboxylate fragment[8,9] are inhibitors of the HIV gp-120-CD4.[10,11]

Nowadays, a plenty of methods for the modification of the Biginelli synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines is developed, among them are methods, which include a classic cyclocondensation of β-ketoester, aldehyde, and urea,[12] methods with the use of microwave and ultrasonic irradiation,[13] with the use of Lewis acids and proton-donor acids such as $ZrCl_4$,[14] $InBr_3$,[15] $Ce(NH_4)_2(NO_3)_6$,[16] $Mn(OAc)_3 \cdot 2H_2O$,[17] $In(OTf)_3$,[18] $InCl_3$,[19] $LaCl_3$,[20] H_2SO_4,[21] AcOH,[22] KSF montmorillonite,[23] polyphosphate esters,[24] BF_3—OEt_2/CuCl/AcOH,[25] HCl (see Refs 26—28), and ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate or 1-*n*-butyl-3-methylimidazolium hexafluorophosphate.[29]

However, the attempts to synthesize various pyrimidine derivatives by this reaction so far were generally limited to the variations in aldehydes or ketones and very rarely in ketoesters, the sources of a two-carbon fragment.[1—29]

As to the use in this reaction of bis-reagents, *viz.*, compounds containing two identical functional groups necessary for the Biginelli reaction, only two papers are published on this subject.[30,31] In one of them, a one-step synthesis of podands with dihydropyrimidine and dihydroazolopyrimidine terminal fragments with the use of 1,7-bis(2-formylphenyl)-1,4,7-trioxaheptane and podands with dihydropyrimidine and dihydropyrimidinethione fragments with the use of 1,5-bis(ureido)-3-oxapentane[30] were presented. In the second work, another one-step synthesis of the rigidly oriented 1,3- and 1,4-bis(pyrimidinyl)benzenes with the use of iso- and terephthalic aldehydes is described.[31]

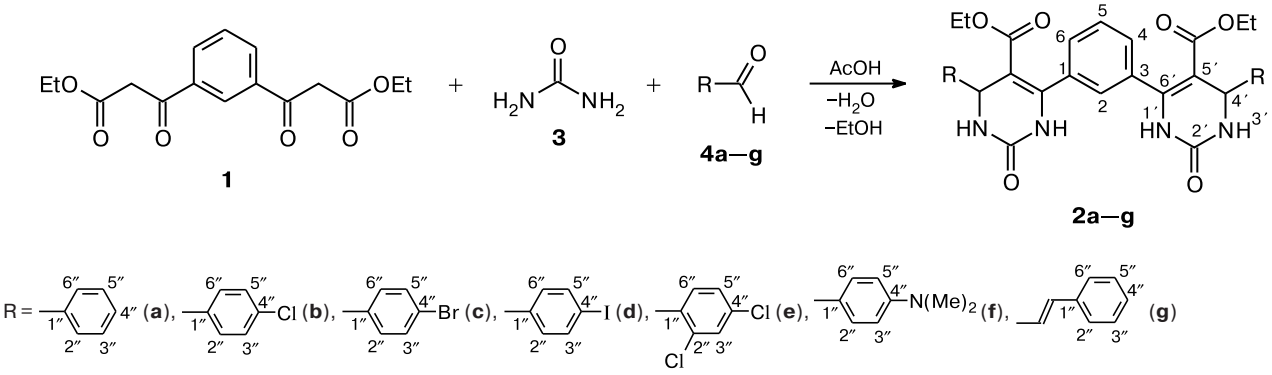
Compounds with two ketoester groups, suppliers of a two-carbon fragment for the construction of pyrimidine ring, so far were not used in the Biginelli reaction. We found that if diethyl isophthaloyldiacetate (**1**) is used in this reaction as the synthetic equivalent of the two-carbon synthons instead of usual ketoester, then the earlier unknown 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene derivatives **2** can be obtained. The keeping of the reaction mixture composed of diester **1**, urea, and the corresponding aldehyde in acetic acid at room temperature for 30 days leads to the final products in low yield (Scheme 1).

An increase in the reaction time and temperature, as well as a change in the concentrations of reagents did not lead to substantial increase in the yields of the target products. When a classic version of the Biginelli reaction (ethanol + catalytic amount of hydrochloric acid, the reaction time of 18—25 h, heating)[26] was used, the yields of the target products were only 3—6%. Attempts to carry out the reaction of diketoester **1** in solution of acetic acid and methanol were not successful at all in the isolation of the desired products, though, earlier

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1233—1239, June, 2008.

1066-5285/08/5706-01257

Scheme 1



we successfully conducted the Biginelli reaction with participation of dichloroacetylaroylmethanes in this solution, which allowed us to reach high yields of perhydropyrimidines.

We found that if the reaction under consideration (see Scheme 1) is carried out in a mixture of DMF and acetonitrile (1 : 2) in the presence of trimethylchlorosilane, the reaction time decreases (to 1 day) and the target 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene derivatives **2a—g** are obtained in higher yields (Scheme 2).

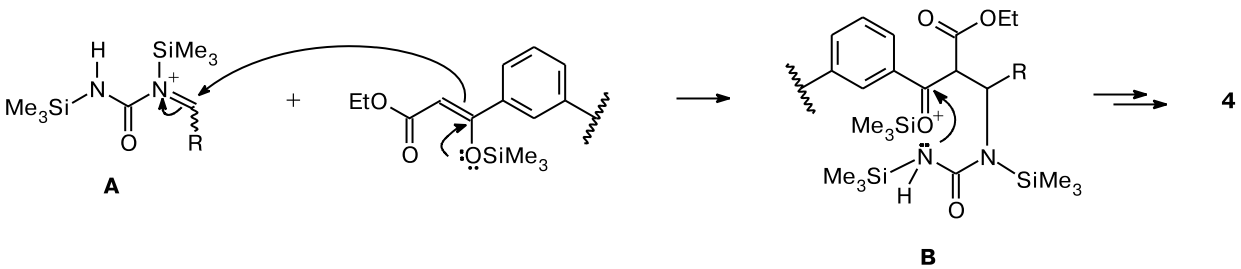
Scheme 2

This result can be explained by the "activation by silicon"[32] of reactions with participation of N-nucleophiles. Nucleophilic addition of the intermediately formed *N*-silylated acyliminium cation **A** (see Refs 33 and 34) to the enol (most likely, predominant) tautomer of β-dicarbonyl compound **1** leads to the intermediate **B**, the cyclization of which with elimination of Me_3SiOH provides the formation of the final product (Scheme 3). This sequence of transformations occurs faster than the reaction in the absence of trimethylchlorosilane. An autocatalysis with HCl, which is eliminated during interaction of Me_3SiCl with the product of this reaction, *i.e.,* water, could have been another cause for the acceleration of the reaction under consideration by trimethylchlorosilane. Though, the carrying out of the process in the flow of dry hydrogen chloride leads to its considerable acceleration neither in MeOH nor in DMF—MeCN, the possibility of catalysis by hydrogen chloride, apparently, can exist since in the course of the reaction, it is formed gradually, which, probably, creates a possibility for the selective course of the process.

It could have been suggested that the order of addition of reagents, as it was observed in Ref. 35, will favor an increase in the yield of final products. However, the condensation of diethyl isophthaloyldiacetate, benzaldehyde, and urea according to the earlier published procedure,[35] when the high yields were obtained by addition of urea into the reaction mixture formed after the keeping of β-dicarbonyl compounds with aldehydes in the system $ClSiMe_3$—DMF for 12 h, did not give the expected result. Variations in the time and temperature of the keeping of diethyl isophthaloyldiacetate and benzaldehyde in the system $ClSiMe_3$—DMF also did not lead to the expected results: the yield of the desired product did not exceed 7%.

The presence of the signals for the protons of the phenyl and phenylene fragments, the singlet signals for

Scheme 3



the four equivalent in pairs NH groups in the regions δ 7.71—7.99 and 8.84—8.96 (the former signals being always broadened), as well as the doublet signals with $^3J_{NH-CH}$ = 3.1—4.3 Hz for the atoms H(4′) in the region δ 4.88—5.78, along with signals for the methyl and methylene protons of the ethoxy groups, is characteristic of the ^{1}H NMR spectra of 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzenes **2a—g**.

The presence of two asymmetric carbon atoms with identical substituents in compounds **2a—g** suggested formation of one racemic form (*S,S*- and *R,R*-enantiomers) and one meso form (*S,R*-form = *R,S*-form). However, as it could be seen from the ^{1}H NMR spectra of crude products and products obtained after recrystallization, no broadening or doubling of the signals is observed in none of the regions in none of the cases, which attests either a selective formation of a single form mentioned above or the formation of both forms, but with identical chemical shifts and spin-spin coupling constants for the protons, which is unlikely.

Another characteristic feature inherent in the ^{1}H NMR spectra of compounds **2a—g** is the presence of three singlet signals at δ 2.75, 2.90, and 7.97, which correspond to the signals for the protons of DMF used as the solvent not only to carry out of the reaction, but also for the recrystallization. As the ^{1}H NMR spectra show, depending on the compound and method of purification, DMF is present in various quantities in the solutions under consideration (from 9.0—12.0 to 2.0—3.0%), which corresponds to complexes composed of the compound under study and DMF in the ratios 1 : 1 and 4 : 1. These data are confirmed by the elemental analysis data for the samples obtained after recrystallization from the corresponding mixtures of solvents and keeping the samples *in vacuo* (1—2 Torr) at ~200 °C for 1 h. The analytically pure samples of compounds **2a—g** are obtained only after thorough removal of DMF *in vacuo* (1—2 Torr) at 250—300 °C for 0.5 h.

Note that 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzenes **2a—g** form inclusion complexes with DMF even if recrystallization of these compounds is carried out with the use of a mixture of solvents (MeOH—DMF, MeCN—DMF, DMF—$CHCl_3$, *etc.*), which is attested by the presence of characteristic singlet signals of DMF in the ^{1}H NMR spectra recorded in DMSO.

The presence of two doublet (δ ~53.5 (J = 145 Hz), ~153.2 (J = 6.6 Hz)) and two singlet (δ ~100.0, ~149.0) signals for two pyrimidine rings and two doublet (δ ~127.0 (J = 157 Hz), ~135.0 (J = 7.5 Hz)), doublet of doublets of doublets (δ ~128.1 (J = 160, 6, 6 Hz)), and doublet of multiplets (δ ~131.5 (J = 160 Hz)) signals for the central benzene ring along with other signals for the carbon atoms of the ester groups and substituents in positions 4′ is characteristic of the ^{13}C NMR spectra of 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene derivatives **2a**,**f**,**g**, that completely agrees with the chemical shift and spin-spin coupling constant ($J_{C,H}$) values for 2-oxo-1,2,3,4-tetrahydropyrimidine[36—41] and 1,3-bis(hetaryl)-benzene derivatives.[42] In addition to the mentioned signals, there are also less intensive singlet signals at δ 31.0, 36.2, and 162.8 in the ^{13}C NMR spectra of compounds **2a**,**f**,**g**, which confirms the formation of inclusion complexes of 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene derivatives with DMF.

X-ray analysis for one of these compounds, namely, for **2e**, also confirms this.

According to the X-ray data, compound **2e** crystallizes with the molecule of DMF in ratio 1 : 1. The DMF molecule is disordered over two positions with populations of 0.76 and 0.24. In the molecule of compound under study, the methyl group of C(9B) ethoxy fragment is also disordered over two positions with populations of 0.72 and 0.28. Despite of the fact that according to the structural formula, the compound can posses the plane of symmetry or the axis of the second order, the molecule during crystallization loses the symmetry and is located in the crystal in general position (Fig. 1).

The nonequivalence of the structurally identical parts of the molecule is attested by the differences in the torsional angles formed by the pyrimidine rings and the ethoxy group: C(6B)—C(5B)—C(7B)—O(8B) is 170.8(6)° and C(6A)—C(5A)—C(7A)—O(8A) is 158.1(6)°. The positions of the dichloro-substituted benzene rings (C(10A)—C(15A) and C(10B)—C(15B)) relatively to the mean-square planes of the corresponding pyrimidine rings (N(1A)—C(6A) and N(1B)—C(6B)) also somewhat differ: the dihedral angles are equal to 87.3(4) and 83.4(5)°, respectively. The pyrimidine rings themselves (N(1A)—C(6A) and N(1B)—C(6B)) form with the plane of the central benzene ring dihedral angles equal to 70.0(4) and 66.1(5)°, respectively.

In the crystal, the DMF molecule is located in the "chela-like" cavity of the 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene **2e** molecule. And the DMF molecule does not participate in any noticeable intermolecular interactions with the molecule of the compound, in the cavity of which it is located, and it is kept in it, apparently, exclusively by the van der Waals contacts.

At the same time, the DMF molecule located in the cavity participates in the hydrogen bonding with the neighboring molecule of tetrahydropyrimidinylbenzene, which is symmetrically bonded to the molecule, in the cavity of which DMF is located. Parameters of the hydrogen bond N(3A′)—H(3A′)...O(50A) are as follows: d(H(3A′)...O(50A)) is 1.73 Å, the angle N(3A′)—H(3A′)...O(50A) is 166°, (1/2 − x, 1/2 + y, 3/2 − z). Owing to the formation of eight classic hydrogen bonds N—H...O, the H-associates consisting of two DMF molecules and two 1,3-bis(2-oxo-1,2,3,4-tetrahy-

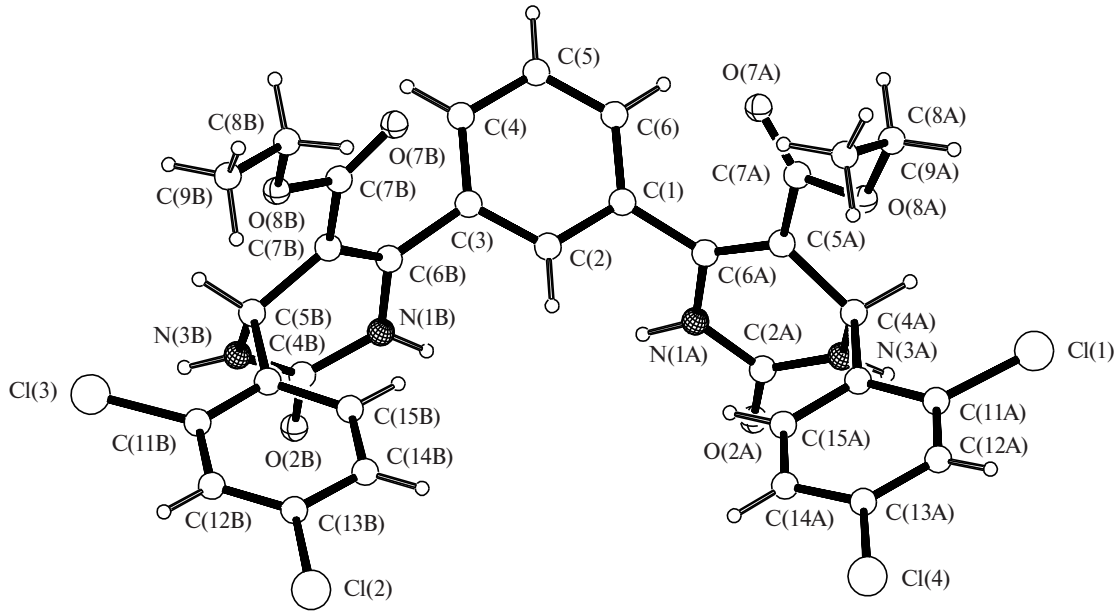


Fig. 1. Geometry of the molecule of compound **2e** in the crystal and the scheme of numeration; the methyl group with greater population is shown, the solvate molecule of DMF is not shown.

dropyrimidin-6-yl)benzene **2e** molecules appear in the crystal (Fig. 2). Parameters of the hydrogen bonds are as follows: for N(1A)—H(1A)...O(1B″), d(H(1A)...O(2B″)) is 1.86 Å, d(N(1A)...O(2B″)) is 2.85 Å, the angle N(1A)—H(1A)...O(2B″) is 176°; for N(1B)—H(1B)...O(2B″), d(H(1B)...O(2B″)) is 2.01 Å, d(N(1B)...O(2B″)) is 2.98 Å, the angle N(1B)—H(1B)...O(2B″) is 165°; for N(3B)—H(3B)...O(2A″), d(H(3B)...O(2A″)) is 1.91 Å, the angle N(3B)—H(3B)...O(2A″) is 166° (operation of symmetry $1/2 - x$, $1/2 - y$, $1 - z$).

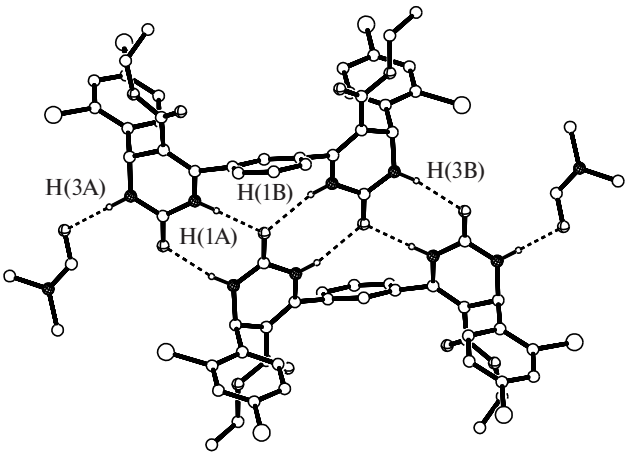


Fig. 2. Fragment formed by two molecules of compound **2e** and two molecules of DMF owing to the hydrogen bond N—H...O (the dotted line). Only hydrogen atoms participating in the hydrogen bonds are shown.

The DMF molecules, located on the ends of the H-associates, enter the cavities of the tetrahydropyrimidinylbenzene molecules from the neighboring symmetrically bonded associates. The compound also form nonclassic hydrogen bonds of the types C—H...O and C—H...Cl, the cumulative influence of which leads to the formation of chains of the molecules along the crystallographic axis 0y. Though the compound forms hydrogen bonds of various types, the density of packing of the molecules in a crystal is not high. The packing coefficient is equal to 64.1%, which is lower than values characteristic of the crystals of organic compounds (65—75%). Apparently, the formation of inclusion compound by the molecules of 1,3-bis[2-oxo-4-(2,4-dichloro)phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-6-yl]benzene and DMF, as well as its stability can be explained in the first place by complementarity of the DMF molecules and the cavity of the "host" molecules.

In conclusion, it can be stated that 1,3-bis(oxotetrahydropyrimidin-6-yl)benzene derivatives **2a—g** obtained by us can be used as the selective receptors for DMF.

Experimental

Melting points were determined on a Boetius apparatus. Mass spectra (electron ionization) were recorded on a ThermoQuest/Finnigan TRACE MS quadrupole mass spectrometer, inlet of the sample was performed through the system of the direct injection with water cooling. IR spectra were recorded on a Vector-22 (Bruker) Fourier spectrometer (Nujol mulls for compounds **2a**,**c**,**e**,**g** and KBr pellets

for compounds **2b**,**d**,**f**) in the range of frequencies 400—3600 cm^{-1}. ^1H NMR spectra for compounds **2a—g** and $^{13}C\{H\}$ NMR spectra for compounds **2a**,**f**,**g** were recorded on a Avance-600 spectrometer (Bruker) (600.00 MHz (^1H) and 150.864 MHz (^{13}C)). Chemical shifts are given in δ scale. A residual signal of the nondeuterated solvents CH_3CN (δ_H 1.96) for compound **1** and DMSO (δ_H 2.52) for compounds **2a—g** were used as the internal standard.

Diethyl isophthaloyldiacetate (1). A mixture of acetoacetic ester (14.6 g, 56.15 mmol), isopropyl ether (40 mL), and water (38 mL) was cooled to 5 °C and a 33% aqueous NaOH (4.8 mL) was added to it. The temperature was kept below 7 °C and pH ~11, isophthaloyl chloride (12.33 g, 60.73 mmol) and 33% aq. NaOH (20 mL) were added simultaneously for 1 h. Then the reaction mixture was kept for 1 h at 40 °C. The organic layer was separated and can be used in the subsequent experiments as the solvent without additional purification, ammonium chloride (6.5 g, 121.60 mmol) was added to the aqueous layer. The mixture was stirred for 18 h followed by the extraction with toluene (3×100 mL). The combined organic layer was dried with $MgSO_4$, the solvent was evaporated *in vacuo*. The product formed was recrystallized from ether. The yield was 8.56 g (46%), yellow crystals, m.p. 43—45 °C. Found (%): C, 62.70; H, 5.93. $C_{16}H_{18}O_6$. Calculated (%): C, 62.74; H, 5.92. IR, ν/cm^{-1}: 1748, 1683, 1629, 1418, 1360, 1347, 1320, 1290, 1261, 1248, 1176, 1146, 1081, 1025, 812, 798, 677, 595. ^1H NMR (CD_3CN), δ: keto form, 1.28 (t, 6 H, 2 $C\underline{H}_3CH_2O$, J = 7.3 Hz); 4.18 (s, 4 H, 2 $C(O)C\underline{H}_2CO_2Et$); 4.25 (q, 4 H, 2 $CH_3C\underline{H}_2O$, J = 7.3 Hz); 7.72 (dd, 1 H, 1 H(5), J = 8.1 Hz, J = 8.1 Hz); 8.28 (d, 2 H, 1 H(4) + 1 H(6), J = 8.1 Hz); 8.55 (s, 1 H, 1 H(2)); enol form, 1.38 (t, 6 H, 2 $C\underline{H}_3CH_2O$, J = 7.3 Hz); 4.36 (q, 4 H, 2 $CH_3C\underline{H}_2O$, J = 7.3 Hz); 5.96 (s, 2 H, 2 $C(OH)=C\underline{H}$); 7.70 (dd, 1 H, 1 H(5), J = 8.1 Hz, J = 8.1 Hz); 8.15 (d, 2 H, 1 H(4) + 1 H(6), J = 8.1 Hz); 8.45 (s, 1 H, 1 H(2)); 12.72 (br.s, 2 H, 2 OH).

Ratio of tautomers, which is calculated from the ^1H NMR spectrum recorded in CD_3CN, is 8 : 1, whereas, in DMSO-d_6 it is 5 : 1 (in both cases, in favor of the keto form).

1,3-Bis(5-ethoxycarbonyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-6-yl)benzene (2a). ***A.*** A mixture of ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), benzaldehyde (**4a**) (0.34 g, 3.26 mmol), and acetic acid (30 mL) was stirred for 1 h until complete dissolution and kept for 30 days at ~20 °C. The solvent was evaporated *in vacuo*, methanol was added to the crystal-like mixture, the crystals formed were filtered off, dried in air, and recrystallized from ethyl acetate—DMF (5 : 1). The yield was 0.43 g (47.0%), white crystals, m.p. 298—299 °C. Found (%): C, 67.80; H, 5.35; N, 9.92. $C_{32}H_{30}N_4O_6$. Calculated (%): C, 67.83; H, 5.34; N, 9.89. MS, m/z (I_{rel} (%)): 566 $[M]^+$ (3), 520 (37), 494 (26), 474 (28), 448 (32), 447 (100), 443 (63), 404 (40), 354 (27), 224 (22), 210 (28), 206 (18), 194 (38), 178 (20), 132 (51), 131 (45), 104 (24), 103 (33), 77 (18). IR, ν/cm^{-1}: 3338, 3224, 3105, 1704, 1667, 1343, 1302, 1270, 1251, 1204, 1095, 827, 812, 781, 753, 709, 699, 654, 472. ^1H NMR (DMSO-d_6), δ: 0.89 (t, 6 H, 2 $C\underline{H}_3CH_2O$, J = 7.0 Hz); 3.82—3.88 (m, 4 H, 2 $CH_3C\underline{H}_2O$); 5.31 (d, 2 H, 2 H(4′), J = 3.4 Hz); 7.31 (dd, 2 H, 2 H(4″), J = 7.0 Hz, J = 7.0 Hz); 7.37 (dd, 1 H, 1 H(5), J = 7.7 Hz, J = 7.7 Hz); 7.38—7.46 (m, 11 H, 1 H(2) + 1 H(4) + 1 H(6) + 2 H(2″) + 2 H(3″) + 2 H(5″) + 2 H(6″)); 7.95 (br.s, 2 H, 2 N(3′)H); 8.92 (s, 2 H, 2 N(1′)H). ^{13}C NMR (DMSO-d_6), δ: 14.30 (q, 2 C, 2 $\underline{C}H_3CH_2O$, J = 126.8 Hz); 53.22 (d, 2 C, 2 C(4′), J = 146.6 Hz); 60.12 (tq, 2 C, 2 $CH_3\underline{C}H_2O$, J = 147.5 Hz, J = 4.2 Hz); 101.28 (br.s, 2 C, 2 C(5′)); 127.12 (dm, 4 C, 2 C(3″) + 2 C(5″), J = 158.9 Hz); 127.49 (d, 1 C, 1 C(2), J = 162.8 Hz); 128.08 (ddd, 1 C, 1 C(5), J = 160.4 Hz, J = 6.1 Hz, J = 6.0 Hz); 128.17 (ddd, 2 C, 2 C(4″), J = 161.6 Hz, J = 7.8 Hz, J = 7.8 Hz); 129.25 (dd, 4 C, 2 C(2″) + 2 C(6″), J = 160.0 Hz, J = 7.2 Hz); 131.36 (dm, 2 C, 1 C(4) + 1 C(6), J = 156.8 Hz); 134.78 (d, 2 C, 1 C(1) + 1 C(3), J = 7.8 Hz); 144.94 (br.s, 2 C, 2 C(1″)); 148.27 (br.s, 2 C, 2 C(6′)); 153.02 (d, 2 C, 2 C(2′), J = 6.6 Hz); 165.79 (s, 2 C, 2 $\underline{C}O_2CH_2CH_3$).

B. Trimethylsilyl chloride (0.71 g, 6.53 mmol) was added dropwise to a mixture of ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.39 g, 6.53 mmol), benzaldehyde (**4a**) (0.34 g, 3.26 mmol), MeCN (6 mL), and DMF (3 mL). The reaction mixture was heated for 25 h at 80 °C. The solvent was evaporated *in vacuo*, ether and methanol (4 : 1) were added to the crystal-like mixture, the crystals formed were filtered off and dried in air. The yield was 0.52 g (56.0%), white crystals, m.p. 298—299 °C.

C. Dry gaseous hydrogen chloride (obtained according to the procedure described earlier[43] from NaCl (0.95 g, 16.30 mmol) and 98% H_2SO_4 (1.48 mL, 27.71 mmol)) was passed through a stirred solution of ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and benzaldehyde (**4a**) (0.34 g, 3.26 mmol) in methanol (30 mL) at ~15 °C for 1 h. The reaction mixture was refluxed for 10 h. The solvent was evaporated *in vacuo*, ether was added to the crystal-like mixture, the crystals formed were filtered off and dried in air. The yield was 0.05 g (5.4%), white crystals, m.p. 298—299 °C.

D. Dry gaseous hydrogen chloride (obtained according to the procedure described earlier[43] from NaCl (0.95 g, 16.30 mmol) and 98% H_2SO_4 (1.48 mL, 27.71 mmol)) was passed through a stirred solution of ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and benzaldehyde (**4a**) (0.34 g, 3.26 mmol) in DMF—acetonitrile (6 + 12 mL) at 23 °C for 1 h. The reaction mixture was heated for 15 h at 75 °C. The solvent was evaporated *in vacuo*, ether and methanol (5 : 2) were added to the crystal-like mixture, the crystals formed were filtered off and dried in air. The yield was 0.04 g (4.3%), white crystals, m.p. 298—299 °C.

Spectral characteristics of compounds obtained by the methods *A*—*D* are identical.

1,3-Bis[4-(4-chlorophenyl)-5-ethoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl]benzene (2b) was obtained similarly from ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and 4-chlorobenzaldehyde (**4b**) (0.46 g, 3.26 mmol). The yield was 0.59 g (56.8%, method *A*), 0.68 g (66.0%, method *B*), m.p. 304—306 °C (ethyl acetate—DMF, 5 : 1). Found (%): C, 60.42; H, 4.49; Cl, 11.13; N, 8.82. $C_{32}H_{28}Cl_2N_4O_6$. Calculated (%): C, 60.48; H, 4.44; Cl, 11.16; N, 8.82. MS, m/z (I_{rel} (%)): 636 $[M\ (^{35}Cl^{37}Cl)]^+$ (2), 635 (1), 634 $[M\ (^{35}Cl)_2]^+$ (2), 588 (22), 542 (24), 518 (21), 517 (69), 516 (38), 515 (100), 477 (51), 472 (38), 388 (34), 308 (19), 292 (22), 266 (25), 245 (43), 244 (64), 224 (59), 168 (37), 44 (80). IR, ν/cm^{-1}: 3228, 3103, 1704, 1681, 1645, 1490, 1412, 1338, 1293, 1262, 1243, 1198, 1092, 1014, 839, 798, 772, 702, 649, 465. ^1H NMR (DMSO-d_6), δ: 0.88 (t, 6 H, 2 $C\underline{H}_3CH_2O$, J = 7.0 Hz); 3.84 (q, 4 H, 2 $CH_3C\underline{H}_2O$, J = 7.0 Hz); 5.31 (d, 2 H, 2 H(4′), J = 3.1 Hz); 7.37 (dd, 1 H, 1 H(5), J = 7.7 Hz, J = 7.7 Hz); 7.43—7.47 (m, 11 H, 1 H(2) + 1 H(4) + 1 H(6) + 2 *p*-$ClC_6\underline{H}_4$); 7.98 (br.s, 2 H, 2 N(3′)H); 8.95 (br.s, 2 H, 2 N(1′)H).

1,3-Bis[4-(4-bromophenyl)-5-ethoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl]benzene (2c) was obtained similarly from ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and 4-bromobenzaldehyde (**4c**) (0.60 g, 3.26 mmol). The yield was 0.53 g (45.0%, method *A*), 0.63 g (53.0%, method *B*), white crystals, m.p. 286—288 °C (ethyl acetate—DMF, 5 : 1). Found (%): C, 53.00; H, 3.93; Br, 22.10; N, 7.70. $C_{32}H_{28}Br_2N_4O_6$. Calculat-

53.06; H, 3.90; Br, 22.06; N, 7.73. MS, *m/z* (I_{rel} (%)): 726 [M ($^{81}Br)_2$]$^+$ (0.2), 724 [M ($^{79}Br^{81}Br$)]$^+$ (0.3), 722 [M ($^{79}Br)_2$]$^+$ (0.3), 604 (17), 212 (12), 117 (51), 103 (21), 59 (100). IR, ν/cm^{-1}: 3335, 3226, 3104, 1703, 1703, 1486, 1411, 1342, 1294, 1265, 1249, 1204, 1096, 1010, 801, 707, 655, 473. ^{1}H NMR (DMSO-d_6), δ: 0.89 (t, 6 H, 2 C$\underline{H}_3$CH$_2$O, *J* = 7.0 Hz); 3.83—3.88 (m, 4 H, 2 CH$_3$C$\underline{H}_2$O); 5.29 (d, 2 H, 2 H(4′), *J* = 3.7 Hz); 7.37—7.61 (m, 12 H, 1 H(2) + 1 H(4) + 1 H(5) + 1 H(6) + 2 *p*-BrC$_6\underline{H}_4$); 7.99 (br.s, 2 H, 2 N(3′)H); 8.96 (s, 2 H, 2 N(1′)H).

1,3-Bis[5-ethoxycarbonyl-4-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl]benzene (2d) was obtained similarly from ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and 4-iodobenzaldehyde (**4d**) (0.76 g, 3.26 mmol). The yield was 0.61 g (45.7%, method *A*), 0.70 g (52.0%, method *B*), white crystals, m.p. 294—296 °C (ethyl acetate—DMF, 5 : 1). Found (%): C, 46.91; H, 3.46; I, 31.08; N, 6.82. $C_{32}H_{28}I_2N_4O_6$. Calculated (%): C, 46.96; H, 3.45; I, 31.01; N, 6.85. MS, *m/z* (I_{rel} (%)): 818 [M]$^+$ (2), 775 (40), 774 (60), 729 (42), 728 (46), 727 (16), 726 (27), 357 (17), 272 (18), 258 (44), 257 (45), 230 (42), 224 (22), 183 (18), 155 (100), 130 (47), 103 (25), 102 (28), 29 (45). IR, ν/cm^{-1}: 3336, 3223, 3105, 1702, 1668, 1600, 1444, 1341, 1247, 1202, 1095, 1005, 805, 762, 705, 653, 471. ^{1}H NMR (DMSO-d_6), δ: 0.89 (t, 6 H, 2 C$\underline{H}_3$CH$_2$O, *J* = 7.0 Hz); 3.81—3.89 (m, 4 H, 2 CH$_3$C$\underline{H}_2$O); 5.26 (d, 2 H, 2 H(4′), *J* = 3.4 Hz); 7.23 (d, 4 H, 2 H(3″) + 2 H(5″), *J* = 8.4 Hz); 7.36 (dd, 1 H, 1 H(5), *J* = 7.6 Hz, *J* = 7.6 Hz); 7.42—7.45 (m, 3 H, 1 H(2) + 1 H(4) + 1 H(6)); 7.77 (d, 4 H, 2 H(2″) + 2 H(6″), *J* = 8.4 Hz); 7.98 (br.s, 2 H, 2 N(3′)H); 8.95 (br.s, 2 H, 2 N(1′)H).

1,3-Bis[4-(2,4-dichlorophenyl)-5-ethoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl]benzene (2e) was obtained similarly from ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and 2,4-dichlorobenzaldehyde (**4e**) (0.57 g, 3.26 mmol). The yield was 0.47 g (41.3%, method *A*), 0.57 g (49.6%, method *B*), white crystals, m.p. 301—303 °C (acetonitrile—DMF, 8 : 1). Found (%): C, 54.08; H, 4.28; Cl, 20.24; N, 8.00. $C_{32}H_{26}Cl_4N_4O_6$. Calculated (%): C, 54.56; H, 3.72; Cl, 20.13; N, 7.95. MS, *m/z* (I_{rel} (%)): 704 [M (($^{35}Cl)_3{}^{37}Cl$)]$^+$ (0.5), 702 [M (2 ($^{35}Cl)_2$)]$^+$ (0.4), 658 (15), 587 (21), 585 (43), 583 (30), 513 (18), 511 (25), 386 (24), 301 (20), 293 (28), 292 (17), 291 (18), 279 (36), 242 (40), 228 (41), 223 (33), 202 (15), 200 51), 36 (18), 32 (22), 28 (100). IR, ν/cm^{-1}: 3231, 3089, 1716, 1646, 1586, 1443, 1369, 1338, 1289, 1257, 1206, 1098, 1043, 800, 748, 702, 659, 474. ^{1}H NMR (DMSO-d_6), δ: 0.86 (t, 6 H, 2 C$\underline{H}_3$CH$_2$O, *J* = 7.0 Hz); 3.80 (q, 4 H, 2 CH$_3$C$\underline{H}_2$O, *J* = 7.0 Hz); 5.78 (d, 2 H, 2 H(4′), *J* = 3.0 Hz); 7.40 (dd, 1 H, 1 H(5), *J* = 7.5 Hz, *J* = 7.5 Hz); 7.48—7.65 (m, 9 H, 1 H(2) + 1 H(4) + 1 H(6) + 2 *p*-Cl$_2$C$_6\underline{H}_3$); 7.95 (br.s, 2 H, 2 N(3′)H); 8.96 (br.s, 2 H, 2 N(1′)H).

1,3-Bis[5-ethoxycarbonyl-4-(4-dimethylaminophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl]benzene (2f) was obtained similarly from ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and 4-dimethylaminobenzaldehyde (**4f**) (0.49 g, 3.26 mmol). The yield was 0.56 g (53.0%, method *A*), 0.64 g (59.5%, method *B*), white crystals, m.p. 282—284 °C (ethyl acetate—DMF, 5 : 1). Found (%): C, 66.20; H, 6.21; N, 12.85. $C_{36}H_{40}N_6O_6$. Calculated (%): C, 66.24; H, 6.18; N, 12.87. MS, *m/z* (I_{rel} (%)): 653 (5), 652 [M]$^+$ (11), 532 (26), 531 (84), 458 (18), 274 (21), 230 (22), 175 (43), 174 (31), 145 (30), 128 (38), 120 (54), 104 (100), 91 (48), 78 (38), 77 (53). IR, ν/cm^{-1}: 3232, 1700, 1617, 1525, 1445, 1343, 1278, 1244, 1199, 1167, 1093, 1012, 798, 782, 704, 651, 465. ^{1}H NMR (DMSO-d_6), δ: 0.90 (t, 6 H, 2 C$\underline{H}_3$CH$_2$O, *J* = 7.0 Hz); 2.89 (s, 12 H, 2 N(CH$_3$)$_2$); 3.81—3.88 (m, 4 H, 2 CH$_3$C$\underline{H}_2$O); 5.19 (d, 2 H, 2 H(4′), *J* = 3.1 Hz); 6.74 (d, 4 H, 2 H(3″) + 2 H(5″), *J* = 8.5 Hz); 7.22 (d, 4 H, 2 H(2″) + 2 H(6″), *J* = 8.5 Hz); 7.36 (dd, 1 H, 1 H(5), *J* = 7.6 Hz, *J* = 7.6 Hz); 7.40—7.42 (m, 3 H, 1 H(2) + 1 H(4) + 1 H(6)); 7.81 (br.s, 2 H, 2 N(3′)H); 8.84 (br.s, 2 H, 2 N(1′)H). ^{13}C NMR (DMSO-d_6), δ: 14.48 (q, 2 C, 2 $\underline{C}$H$_3$CH$_2$O, *J* = 127.4 Hz); 41.11 (br.s, 4 C, 2 N(CH$_3$)$_2$); 54.67 (d, 2 C, 2 C(4′), *J* = 143.6 Hz); 60.16 (tq, 2 C, 2 CH$_3\underline{C}$H$_2$O, *J* = 147.2 Hz, *J* = 4.2 Hz); 101.14 (br.s, 2 C, 2 C(5′)); 113.34 (dm, 4 C, 2 C(3″) + 2 C(5″), *J* = 156.8 Hz); 127.54 (d, 1 C, 1 C(2), *J* = 163.4 Hz); 127.93 (dm, 4 C, 2 C(2″) + 2 C(6″), *J* = 155.6 Hz); 128.12 (ddd, 1 C, 1 C(5), *J* = 160.4 Hz, *J* = 6.1 Hz, *J* = 6.0 Hz); 131.51 (dm, 2 C, 1 C(4) + 1 C(6), *J* = 164.0 Hz); 132.90 (br.s, 2 C, 2 C(4″)); 134.97 (d, 2 C, 1 C(1) + 1 C(3), *J* = 7.2 Hz); 147.83 (br.s, 2 C, 2 C(1″)); 150.68 (br.s, 2 C, 2 C(6′)); 153.28 (d, 2 C, 2 C(2′), *J* = 6.6 Hz); 165.99 (s, 2 C, 2 $\underline{C}$O$_2$CH$_2$CH$_3$).

1,3-Bis[5-ethoxycarbonyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidin-6-yl]benzene (2g) was obtained similarly from ester **1** (0.50 g, 1.63 mmol), urea (**3**) (0.29 g, 4.89 mmol), and cinnamaldehyde **4g** (0.43 g, 3.26 mmol). The yield was 0.49 g (49.0%, method *A*), 0.60 g (58.7%, method *B*), white crystals, m.p. 275—278 °C (ethyl acetate—DMF, 5 : 1). Found (%): C, 69.82; H, 5.57; N, 9.00. $C_{36}H_{34}N_4O_6$. Calculated (%): C, 69.89; H, 5.54; N, 9.06. MS, *m/z* (I_{rel} (%)): 619 (3), 618 [M]$^+$ (7), 500 (29), 499 (50), 456 (16), 452 (26), 395 (24), 394 (42), 302 (25), 258 (21), 228 (29), 207 (32), 198 (24), 197 (25), 158 (49), 131 (21), 130 (80), 115 (100), 91 (92), 77 (20), 44 (20), 28 (25). IR, ν/cm^{-1}: 3229, 3099, 1727, 1680, 1645, 1491, 1338, 1292, 1248, 1199, 1096, 963, 781, 750, 692, 651. ^{1}H NMR (DMSO-d_6), δ: 0.98 (t, 6 H, 2 C$\underline{H}_3$CH$_2$O, *J* = 7.0 Hz); 3.93—3.95 (m, 4 H, 2 CH$_3$C$\underline{H}_2$O); 4.88 (dd, 2 H, 2 H(4′), *J* = 6.0 Hz, *J* = 4.3 Hz); 6.38 (dd, 2 H, 2 C$\underline{H}$=CH—Ph, *J* = 15.8 Hz, *J* = 6.0 Hz); 6.52 (d, 2 H, 2 CH=C$\underline{H}$—Ph, *J* = 15.8 Hz); 7.27 (dd, 2 H, 2 H(4″), *J* = 7.3 Hz, *J* = 7.3 Hz); 7.34 (dd, 1 H, 1 H(5), *J* = 7.2 Hz, *J* = 7.2 Hz); 7.35 (dd, 4 H, 2 H(3″) + 4 H(5″), *J* = 7.6 Hz, *J* = 7.3 Hz); 7.39 (dd, 1 H, 1 H(2), *J* = 1.2 Hz, *J* = 1.2 Hz); 7.44 (dd, 2 H, 1 H(4) +1 H(6), *J* = 7.2 Hz, *J* = 1.2 Hz); 7.47 (d, 4 H, 2 H(2″) + 2 H(6″), *J* = 7.6 Hz); 7.71 (br.s, 2 H, 2 N(3′)H); 8.86 (br.s, 2 H, 2 N(1′)H). ^{13}C NMR (DMSO-d_6), δ: 14.36 (q, 2 C, 2 $\underline{C}$H$_3$CH$_2$O, *J* = 126.8 Hz); 53.14 (d, 2 C, 2 C(4′), *J* = 144.8 Hz); 60.04 (tq, 2 C, 2 CH$_3\underline{C}$H$_2$O, *J* = 147.2 Hz, *J* = 4.2 Hz); 99.83 (br.s, 2 C, 2 C(5′)); 127.10 (dm, 4 C, 2 C(3″) + 2 C(5″), *J* = 158.6 Hz); 127.28 (d, 1 C, 1 C(2), *J* = 163.4 Hz); 128.09 (ddd, 1 C, 1 C(5), *J* = 159.2 Hz, *J* = 6.6 Hz, *J* = 6.6 Hz); 128.28 (ddd, 2 C, 2 C(4″), *J* = 161.6 Hz, *J* = 8.4 Hz, *J* = 8.4 Hz); 129.29 (dd, 4 C, 2 C(2″) + 2 C(6″), *J* = 161.6 Hz, *J* = 7.5 Hz); 129.40 (d.br.d, 2 C, 2 $\underline{C}$H=CH—Ph, *J* = 150.8 Hz, *J* ≈ 4.0 Hz); 130.41 (dd, 2 C, 2 CH=$\underline{C}$H—Ph, *J* = 153.2 Hz, 4.8 Hz); 131.46 (dm, 2 C, 1 C(4) + 1 C(6), *J* = 162.8 Hz); 134.01 (d, 2 C, 1 C(1) + 1 C(3), *J* = 7.8 Hz); 137.09 (br.s, 2 C, 2 C(1″)); 148.29 (br.s, 2 C, 2 C(6′)); 153.36 (d, 2 C, 2 C(2′), *J* = 7.2 Hz); 165.56 (s, 2 C, 2 $\underline{C}$O$_2$CH$_2$CH$_3$).

X-ray analysis of compound 2e. Crystals $C_{32}H_{26}Cl_4N_4O_6 \cdot C_3H_7NO$, suitable for the X-ray study were obtained from DMF—MeCN.

The experiment was carried out at 20 °C on a Enraf—Nonius CAD-4 automatic diffractometer with the use of monochromatic Cu-Kα-radiation (λ = 1.54184 Å). The unit parameters: *a* = 31.673(3) Å, *b* = 14.190(1) Å, *c* = 21.224(2) Å, β = 127.28(7)°, *V* = 7590(11) Å^3, *Z* = 8, M = 777.46, d_{calc} = 1.36 g cm^{-3}, μ(Cu) = 32.80 cm^{-1}, space group *C*2/*c*. Intensities of 8371 reflections were measured (ω-scanning, 2θ < 57.4°), 1868 reflections from them were with $I > 2\sigma$. The structure was decoded by the direct

method by the SIR program[44] and refined first in isotropic, then in anisotropic approximation with the use of the SHELXL[45] and WinGX[46] programs. Coordinates of hydrogen atoms of the NH group were revealed from the differential series of electron density, coordinates of the rest of hydrogen atoms were calculated on the basis of stereochemical criteria and refined by the riding model. The final values of divergence factors are as follows: $R = 0.0597$, $R_w = 0.1316$ on 1868 independent reflections with $F^2 \geq 2\sigma$.

Preliminary data processing was carried out with the use of the MolEN program.[47] Analysis of the molecular and crystal structures and intermolecular interactions was performed with the use of the PLATON program.[48] Coordinates of atoms and their temperature parameters for compound **2e** were deposited with the Cambridge Structural Database (CCDC 639961).

This work was financially supported by the Russian Foundation for Basic Research (Project Nos 07-03-00613-a and 05-03-33008).

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Received June 14, 2007;
in revised form January 11, 2008