Synthesis of 1-arylcytosine-5-carboxylic acid esters

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A reaction of alkyl 2-(diaminomethylidene)-3-oxoalkanoates with arylisocyanates leads to the formation of the corresponding ureas, which upon the action of Na alkoxides cyclize to 1-aryl-6-R-cytosine-5-carboxylates. The latter reacting with arylisocyanates according to the similar scheme give rise to 3,6-diaryl-5-methylpyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-triones.

Key words: 2-(diaminomethylidene)-3-oxobutanoic and 2-(diaminomethylidene)-3-oxo-3-phenylpropanoic acid esters, arylisocyanates, 1-arylcytosine-5-carboxylic acid esters, pyrimido-[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-triones, base-catalyzed intramolecular cyclization.

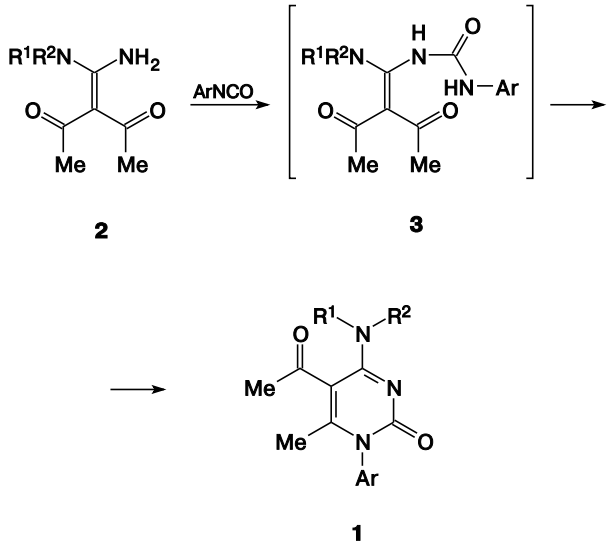
Among cytosine derivatives, which is one of the most important nucleic bases, there are known medicines of antitumor, antiviral, antibacterial, antifungal, and anti-HIV action (see, for example, review[1]). At present, compounds of the cytosine series containing substituents at position 5 of the pyrimidine ring are of particular interest, for example, recently published works on the synthesis of 5-aryloxy-,[2] 5-fluoro-6-fluoromethyl-,[2] 5-aminomethyl-,[3] 5-amino-,[4] and 5-phenylthiocytosines[4] can be mentioned.

Earlier,[5] we have suggested a convenient method for the preparation of 5-acetylcytosines **1** mono- and disubstituted at the exocyclic nitrogen atom from the corresponding diacetyl ketene *N*,*N*-acetals **2** and arylisocyanates (Scheme 1). The heterocyclization was carried out upon reflux of the equimolar mixture of reagents in toluene in the absence of catalysts. It is obvious that ureas **3** are the intermediates in this process, though their formation has not been registered.

In continuation of our works on the synthesis of functionally substituted pyrimidines,[5—10] we studied the action of arylisocyanates on 2-(diaminomethylidene)-3-oxoalkanoic esters, *i.e.*, acyl alkoxycarbonyl ketene aminals unsubstituted at the nitrogen atoms. In the preceding report,[11] it was shown that cyclocondensation of ketene aminals of this type with trichloroacetonitrile results in obtaining 2-trichloromethylpyrimidines with vicinal arrangement of the amino and alkoxycarbonyl groups. Therefore, one could expect that heterocyclization with arylisocyanates would lead (similarly to Scheme 1) to the formation of 1-arylcytosine-5-carboxylic acid esters.

Ethyl cytosine-5-carboxylate unsubstituted at the N(1) atom is usually obtained from urea, cyanoacetic ester, and ethyl orthoformate.[12,13] Thiourea can be used instead of urea, in this case the corresponding 2-thiocytosine

Scheme 1



derivative is isolated, which is further hydrolyzed.[14] Analogous transformations involving *N*-alkylureas lead to 3-alkylcytosine-5-carboxylic acid esters[15,16] and, therefore, such an approach can not be used for the synthesis of 1-substituted cytosines.

We found that reflux of aminals **4a—c** with arylisocyanates in toluene afforded the corresponding ureas **5a—d** precipitating on cooling the reaction mixtures (Scheme 2). No intramolecular cyclization takes place under these conditions. However, upon treatment with sodium alkoxides compounds **5a—d** eliminate water to be transformed to 1-arylcytosine-5-carboxylic acid esters **6a—d**. A solution of MeONa in MeOH is necessary to use

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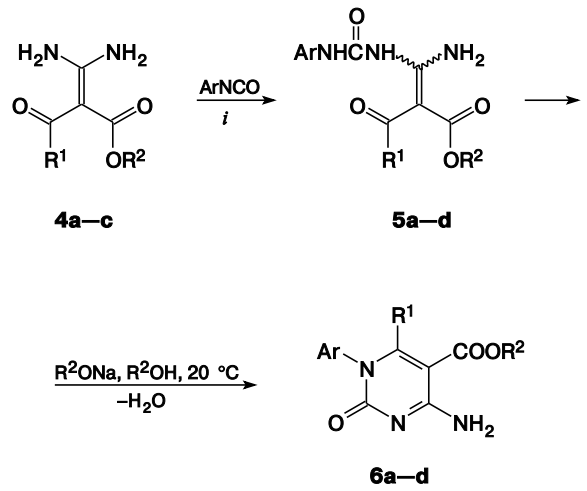
for the synthesis of methyl esters, whereas for obtaining ethyl esters, a solution of EtONa in EtOH. If, for example, urea **5a** is treated with MeONa in MeOH, methyl ester **6b** is smoothly formed instead of ethyl ester **6a** as a result of transesterification.

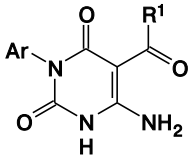
Scheme 2



i. Toluene, Δ

	R^1	R^2	Ar
a	Me	Et	Ph
b	Me	Me	Ph
c	Ph	Et	Ph
d	Me	Et	4-MeC_6H_4

Thus, the acyl groups of compounds **5a—d** participate in the heterocyclization, though, elimination of alcohol from the alkoxycarbonyl fragment can, in principle, lead to the pyrimidine ring closure as well. Thus, for example 6-amino-3-R-uracils were obtained from ethyl 3,3-diaminopropenoate and isocyanates.[17] However, no formation of the corresponding alternative products, *viz.*, uracils of the type **7**, was observed. It should be noted that in the case of the reaction of ketene aminals **4** with trichloroacetonitrile, only the acyl group is involved into the formation of the pyrimidine ring.[11]



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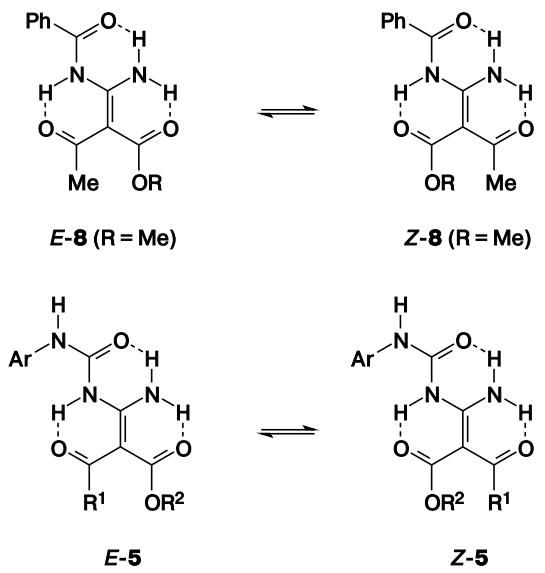
Crystalline adducts **5a—d** are well soluble in DMSO, chloroform, and acetone, but insoluble in hexane. Their mass spectra are characterized by the presence of the molecular ion peaks and the absence of $[M - H_2O]^+$ peaks. Compounds of the type **5** are close in their structures to acetyl alkoxycarbonyl ketene aminal *N*-benzoyl derivatives **8** studied by us earlier.[18] A barrier to rotation around the C=C bond for such push-pull systems is very low and the ^1H NMR spectra of compounds **5** in DMSO-d_6, like in the case of aminals **8**, exhibit one set of signals. However, as it has been shown earlier, ketene aminals **8** form intramolecular hydrogen bonds (IHB) N—H···O in neutral solvents, which promote the rotation to slow down. In fact, their spectra in $CDCl_3$ contain a double set of signals, which indicates the presence of *E*,*Z*-isomers existing in the dynamic equilibrium (Scheme 3).

Scheme 3



Similar picture is observed in the spectra of compounds **5a—d** in $CDCl_3$ (the ratio of isomers ~3.5 : 1). The most low-field of the NH signals belongs to a predominant isomer. Apparently, it should be assigned to the proton involved into the formation of the IHB with participation of the most acidic (carbamide) and most basic (acyl) fragments. Thus, in the spectrum of compound **5a** this signal has chemical shift δ 14.67, whereas chemical shift of the most low-field signal of the minor isomer is equal to δ 12.60 (*cf.* with the corresponding values[11] in the spectrum of compound **8** (R = Me) in $CDCl_3$: for the predominant *E*-isomer, δ 15.70; for the minor *Z*-isomer, δ 13.79). The two-dimensional NMR spectrum $\{^1H—^1H\}$ COSY of urea **5b** in $CDCl_3$ exhibits correlation between the protons of the NH groups with chemical shifts δ 9.66 and 9.89 for the major isomer and with chemical shifts δ 9.58 and 11.77 for the minor isomer, which should be assigned to the protons of the NH_2 group.

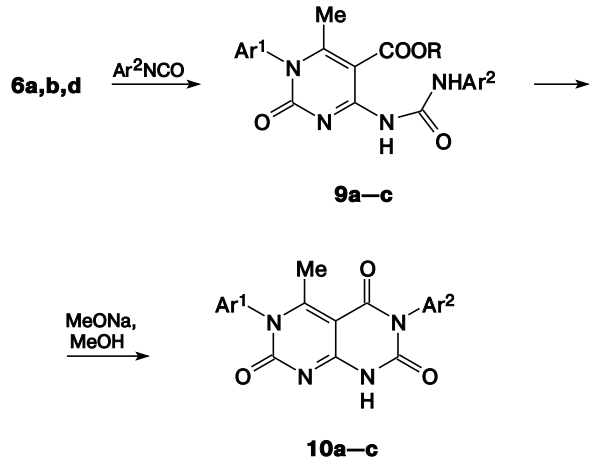
Pyrimidines **6a—d** are colorless crystalline compounds, which are well soluble in DMF, chloroform, and acetone, but insoluble in hexane and benzene. Their mass spectra contain the molecular ion peaks, whereas the IR spectra (KBr) are characterized by the presence of the absorption band for C=O in the region 1670—1675 cm^{-1}. The ^1H NMR spectra exhibit signals for the $COOR^2$ groups, whereas NH_2 protons resonate as two singlets, one of

which is in significantly lower field (see Experimental), that, apparently, is explained by the formation of the N—H···O IHB.

The presence of vicinal amino and alkoxycarbonyl groups at positions 4 and 5 of the pyrimidine ring is favorable for the annulation of the second pyrimidine ring. Earlier, a series of pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives has been obtained by the heterocyclization of the such type pyrimidines with isocyanates.[7,11,19]

We have shown that cytosine-5-carboxylic acid esters can be also used for the synthesis of pyrimidopyrimidines. Reflux of esters **6a,b,d** with arylisocyanates in toluene furnished the corresponding pyrimidin-4-ylureas **9a—c**, which upon the action of MeONa in MeOH were converted to 3,6-diaryl-5-methylpyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-triones **10a—c** (Scheme 4).

Scheme 4



	Ar^1	Ar^2	R
a	Ph	Ph	Me
b	Ph	4-ClC_6H_4	Et
c	4-MeC_6H_4	Ph	Et

Pyrimidinylureas **9a—c** and bicyclic compounds **10a—c** were obtained as white crystalline compounds. Their structures were confirmed by spectral methods (^1H and ^{13}C NMR and IR spectroscopy, mass spectrometry). In particular, the mass spectra of pyrimidopyrimidine derivatives **10** are characterized by the presence of intensive peaks of molecular ions. In the ^1H NMR spectra (DMSO-d_6) of these compounds, in contrast to ureas **9a—c**, there are no signals for the protons of the COOR groups and one broad singlet for the NH at δ 12.10—12.13 is observed.

Pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-triones are poorly studied. Separate representatives of this type of compounds have been synthesized earlier from uracil derivatives.[20—22]

Experimental

^1H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), ^{13}C and two-dimensional NMR spectra {^1H—^1H} COSY, {^1H—^{13}C} HSQC, and HMBC were recorded on a Bruker Avance 600 spectrometer (600 MHz (^1H) and 150 MHz (^{13}C), respectively). Residual signals of the deuterated solvents (7.27 for $CDCl_3$ and 2.50 for DMSO-d_6 in the ^1H NMR spectra and 39.50 for DMSO-d_6 in the ^{13}C NMR spectrum) were used as a reference. IR spectra were recorded on a Specord-M82 spectrometer, mass spectra, on a Kratos MS-30 instrument (EI, 70 eV, temperature of the ionization chamber was 250 °C, direct injection of compounds). Ketene aminals **4a—c** were synthesized according to the known procedures.[11,23] Arylisocyanates were purchased from Lancaster, anhydrous toluene was obtained by distillation over Na, commercial anhydrous ethanol and methanol were used after fractional distillation.

2-[Amino(*N*′-arylureido)methylidene]-3-oxobutanoic and 2-[amino(*N*′-phenylureido)methylidene]-3-oxo-3-phenylpropanoic acid esters (5a—d). A mixture of the corresponding ketene aminal **4a—c** (8.0 mmol) and phenyl- or 4-tolylisocyanate (12 mmol) in anhydrous toluene (6 mL) was refluxed for 6 h, cooled to 20 °C, a precipitate formed was filtered off (for **5c**, toluene was evaporated *in vacuo*, the residue was recrystallized from the benzene—hexane solvent mixture), washed with toluene, recrystallized from the corresponding solvent to obtain colorless crystalline compounds **5a—d**.

Ethyl 2-[amino(*N*′-phenylureido)methylidene]-3-oxobutanoate (5a). The yield was 69%, m.p. 160—162 °C (from benzene). Found (%): C, 58.03; H, 6.11; N, 14.38. $C_{14}H_{17}N_3O_4$. Calculated (%): C, 57.72; H, 5.88; N, 14.42. MS, *m*/*z* (I_{rel} (%)): 291 $[M]^+$ (36), 246 $[M - EtO]^+$ (13), 213 $[M - Ph - H]^+$ (63), 199 $[M - PhNH]^+$ (35), 172 $[M - PhNCO]^+$ (20), 152 $[M - PhNH_2 - EtOH]^+$ (63), 119 $[PhNCO]^+$ (71), 93 $[PhNH_2]^+$ (100). IR ($CHCl_3$), ν/cm^{-1}: 3420, 3365, 3250—2820 (NH, CH), 1710 (CO), 1660 (CO), 1620. ^1H NMR (DMSO-d_6), δ: 1.29 (t, 3 H, MeCH_2, *J* = 7.0 Hz); 2.35 (s, 3 H, Me); 4.20 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.05 (t, 1 H, *p*-Ph, *J* = 7.8 Hz); 7.31 (t, 2 H, *m*-Ph, *J* = 7.8 Hz); 7.51 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 9.54 (br.s, 1 H, NH); 10.30 (br.s, 2 H, 2 NH); 13.11 (br.s, 1 H, NH). ^1H NMR ($CDCl_3$), δ, *E*-isomer: 1.34 (t, 3 H, MeCH_2, *J* = 7.0 Hz); 2.41 (s, 3 H, Me); 4.26 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.15 (t, 1 H, *p*-Ph, *J* = 7.8 Hz); 7.41 (m, 4 H, Ph); 7.88 (br.s, 1 H, NHPh); 9.61, 9.87 (both br.s, 2 H, NH_2); 14.67 (br.s, 1 H, NH). The spectrum also exhibits signals for the minor *Z*-isomer (19%): 11.71 (br.s, 1 H, NH from NH_2); 12.60 (br.s, 1 H, NH), the rest of signals overlap with the signals for the major isomer.

Methyl 2-[amino(*N*′-phenylureido)methylidene]-3-oxobutanoate (5b). The yield was 90%, m.p. 170—172 °C (from benzene—ethanol). Found (%): C, 56.13; H, 5.38; N, 15.04. $C_{13}H_{15}N_3O_4$. Calculated (%): C, 56.31; H, 5.45; N, 15.15. MS, *m*/*z* (I_{rel} (%)): 277 $[M]^+$ (54), 245 $[M - MeOH]^+$ (10), 185 $[M - PhNH]^+$ (35), 158 $[M - PhNCO]^+$ (38), 152 $[M - PhNH_2 - MeOH]^+$ (71), 143 $[M - PhNCO - Me]^+$ (56), 119 $[PhNCO]^+$ (86), 93 $[PhNH_2]^+$ (100). IR (KBr), ν/cm^{-1}: 3340, 3250, 3200 (NH, CH), 1710 (CO), 1660 (CO), 1620, 1600, 1540. ^1H NMR ($CDCl_3$), δ, *E*-isomer: 2.38 (s, 3 H, Me); 3.78 (s, 3 H, OMe); 7.12 (t, 1 H, *p*-Ph, *J* = 7.8 Hz); 7.38 (m, 4 H, *m*-Ph, *o*-Ph); 8.02 (br.s, 1 H, NHPh); 9.66, 9.82 (both br.s, 2 H, NH_2); 14.61 (br.s, 1 H, NH). The spectrum also exhibits signals for the minor

Z-isomer (21%): 9.58, 11.71 (both br.s, 2 H, NH_2); 12.48 (br.s, 1 H, NH), the rest of signals overlap with the signals for the major isomer.

Ethyl 2-[amino(*N*′-phenylureido)methylidene]-3-oxo-3-phenylpropanoate (5c). The yield was 81%, m.p. 163—165 °C (from benzene—hexane). Found (%): C, 64.58; H, 5.11; N, 11.84. $C_{19}H_{19}N_3O_4$. Calculated (%): C, 64.58; H, 5.42; N, 11.89. MS, *m/z* (I_{rel} (%)): 353 $[M]^+$ (5), 261 $[M - PhNH]^+$ (4), 234 $[M - PhNCO]^+$ (7), 105 $[PhCO]^+$ (100), 93 $[PhNH_2]^+$ (78). IR ($CHCl_3$), ν/cm^{-1}: 3415, 3380, 3320—2840 (NH, CH), 1715 (CO), 1660 (CO), 1630. ^{1}H NMR (DMSO-d_6), δ: 0.54 (t, 3 H, Me, *J* = 7.0 Hz); 3.71 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.09 (t, 1 H, *p*-Ph, *J* = 7.8 Hz); 7.31—7.43 (m, 7 H, 2 Ph); 7.51 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 9.52 (br.s, 1 H, NH); 9.82 (br.s, 1 H, NH); 10.48 (br.s, 1 H, NH); 12.29 (br.s, 1 H, NH). ^{1}H NMR ($CDCl_3$), δ, *E*-isomer: 0.64 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 3.80 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.05—7.45 (m, 10 H, 2 Ph); 8.10 (br.s, 1 H, NHPh); 9.48, 9.58 (both br.s, 2 H, NH_2); 13.68 (br.s, 1 H, NH). The spectrum also exhibits signals for the minor *Z*-isomer (23.5%): 10.80 (br.s, 1 H, NH from NH_2); 12.02 (br.s, 1 H, NH), the rest of signals overlap with the signals for the major isomer.

Ethyl 2-[amino(*N*′-4-tolylureido)methylidene]-3-oxobutanoate (5d). The yield was 79%, m.p. 165—167 °C (from benzene). Found (%): C, 59.00; H, 6.42; N, 13.47. $C_{15}H_{19}N_3O_4$. Calculated (%): C, 59.01; H, 6.27; N, 13.76. MS, *m/z* (I_{rel} (%)): 305 $[M]^+$ (7), 172 $[M - MeC_6H_4NCO]^+$ (17), 157 $[M - MeC_6H_4NCO - Me]^+$ (29), 133 $[MeC_6H_4NCO]^+$ (85), 107 $[MeC_6H_4NH_2]^+$ (100). IR (KBr), ν/cm^{-1}: 3312, 3192, 2984 (NH, CH), 1704 (CO), 1656 (CO), 1612, 1544, 1512. ^{1}H NMR (DMSO-d_6), δ: 1.26 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 2.26 (s, 3 H, Me); 2.35 (s, 3 H, Me); 4.19 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.11 (d, 2 H, *m*-C_6H_4, *J* = 7.8 Hz)*; 7.39 (d, 2 H, *o*-C_6H_4, *J* = 7.8 Hz); 9.58 (br.s, 1 H, NH); 10.26 (br.s, 1 H, NH); 10.31, 13.10 (both br.s, 2 H, NH_2). ^{1}H NMR ($CDCl_3$), δ, *E*-isomer: 1.34 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 2.33 (s, 3 H, Me); 2.42 (s, 3 H, Me); 4.25 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.15 (d, 2 H, *m*-C_6H_4, *J* = 7.8 Hz); 7.29 (d, 2 H, *o*-C_6H_4, *J* = 7.8 Hz); 7.94 (br.s, 1 H, NHC_6H_4); 9.64, 9.86 (both br.s, 2 H, NH_2); 14.56 (br.s, 1 H, NH). The spectrum also exhibits signals for the minor *Z*-isomer (22%): 9.60, 11.69 (both br.s, 2 H, NH_2), 12.50 (br.s, 1 H, NH), the rest of signals overlap with the signals for the major isomer.

4-Amino-1-aryl-6-methyl(phenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylic esters (6a—d). A mixture of urea **5a—d** (2 mmol) and solution of the corresponding R^2ONa (1 mmol) in anhydrous R^2OH (10 mL) was stirred for 15—30 min at 20 °C until a precipitate was completely dissolved (for the synthesis of pyrimidine **6b** from urea **5a**, 2 mmol of MeONa in anhydrous MeOH (10 mL) was used and the reaction time was increased to 1 h for accomplishing transesterification of the ester group). The solvent was evaporated dry *in vacuo* at 20 °C, the residue was washed with water, dried, and washed with diethyl ether (10 mL) to obtain white crystalline compounds **6a—d**.

Ethyl 4-amino-6-methyl-2-oxo-1-phenyl-1,2-dihydropyrimidine-5-carboxylate (6a). The yield was 65%, m.p. 196—198 °C (from ethanol). Found (%): C, 61.49; H, 5.64; N, 15.14. $C_{14}H_{15}N_3O_3$. Calculated (%): C, 61.53; H, 5.53; N, 15.38. MS, *m/z* (I_{rel} (%)): 273 $[M]^+$ (56), 245 $[M - CO]^+$ (13), 227 $[M - EtOH]^+$ (21), 119 $[PhNCO]^+$ (37), 118 $[PhNCO - H]^+$ (46), 101 (100), 93 $[PhNH_2]^+$ (88). IR (KBr), ν/cm^{-1}: 3400, 3130, 3075 (NH, CH), 1672 (CO), 1620, 1594, 1560. ^{1}H NMR ($CDCl_3$), δ: 1.35 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 2.25 (s, 3 H, Me); 4.33 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.05, 7.80 (both br.s, 2 H, NH_2); 7.20 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 7.50 (m, 3 H, *m*-Ph, *p*-Ph).

Methyl 4-amino-6-methyl-2-oxo-1-phenyl-1,2-dihydropyrimidine-5-carboxylate (6b). The yields from ureas **5a** and **5b** were 61 and 70%, respectively, m.p. 247—249 °C (from methanol). Found (%): C, 60.09; H, 5.08; N, 16.00. $C_{13}H_{13}N_3O_3$. Calculated (%): C, 60.23; H, 5.05; N, 16.21. MS, *m/z* (I_{rel} (%)): 259 $[M]^+$ (100), 244 $[M - Me]^+$ (22), 231 $[M - CO]^+$ (22), 226 $[M - MeOH - H]^+$ (89), 199 $[M - CO_2 - Me - H]^+$ (78). IR (KBr), ν/cm^{-1}: 3400, 3072 (NH, CH), 1672 (CO), 1592, 1560, 1492. ^{1}H NMR ($CDCl_3$), δ: 2.27 (s, 3 H, Me); 3.87 (s, 3 H, OMe); 6.93, 7.78 (both br.s, 2 H, NH_2); 7.19 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 7.50 (m, 3 H, *m*-Ph, *p*-Ph).

Ethyl 4-amino-2-oxo-1,6-diphenyl-1,2-dihydropyrimidine-5-carboxylate (6c). The yield was 65%, m.p. 268—270 °C (from ethanol). Found (%): C, 67.83; H, 5.17; N, 12.71. $C_{19}H_{17}N_3O_3$. Calculated (%): C, 68.05; H, 5.11; N, 12.53. IR ($CHCl_3$), ν/cm^{-1}: 3500, 3280 (NH, CH), 1675 (CO), 1615. ^{1}H NMR ($CDCl_3$), δ: 0.60 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 3.80 (q, 2 H, CH_2, *J* = 7.0 Hz); 6.56, 7.95 (both br.s, 2 H, NH_2); 6.97—7.22 (m, 10 H, 2 Ph).

Ethyl 4-amino-6-methyl-2-oxo-1-(4-tolyl)-1,2-dihydropyrimidine-5-carboxylate (6d). The yield was 58%, m.p. 217—219 °C (from ethanol). Found (%): C, 62.78; H, 5.72; N, 14.77. $C_{15}H_{17}N_3O_3$. Calculated (%): C, 62.71; H, 5.96; N, 14.62. MS, *m/z* (I_{rel} (%)): 287 $[M]^+$ (58), 240 $[M - C_2H_5OH - H]^+$ (26), 213 $[M - CO_2 - C_2H_5 - H]^+$ (20), 91 $[MeC_6H_4]^+$ (100). IR (KBr), ν/cm^{-1}: 3400, 3080 (NH, CH), 1668 (CO), 1568, 1496. ^{1}H NMR ($CDCl_3$), δ: 1.35 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 2.26 (s, 3 H, Me); 2.40 (s, 3 H, Me); 4.35 (q, 2 H, CH_2, *J* = 7.0 Hz); 6.69, 7.80 (both br.s, 2 H, NH_2); 7.07 (d, 2 H, *o*-C_6H_4, *J* = 7.8 Hz); 7.31 (d, 2 H, *m*-C_6H_4, *J* = 7.8 Hz).

Methyl 6-methyl-2-oxo-1-phenyl-4-(*N*′-phenylureido)-1,2-dihydropyrimidine-5-carboxylate (9a). A mixture of pyrimidine **6b** (0.23 g, 0.9 mmol) and phenylisocyanate (0.14 mL, 1.3 mmol) in anhydrous toluene (3 mL) was refluxed for 6 h, cooled to 20 °C, a precipitate formed was filtered off, washed with toluene and light petroleum to obtain white crystals of compound **9a** (0.27 g, 79%), m.p. 250—252 °C (from benzene—methanol). Found (%): C, 63.66; H, 4.91; N, 15.02. $C_{20}H_{18}N_4O_4$. Calculated (%): C, 63.49; H, 4.79; N, 14.81. MS, *m/z* (I_{rel} (%)): 378 $[M]^+$ (1), 259 $[M - PhNCO]^+$ (55), 144 (28), 119 $[PhNCO]^+$ (100). IR (KBr), ν/cm^{-1}: 3424, 3184 (NH, CH), 1696 (CO), 1672 (CO), 1584, 1524. ^{1}H NMR ($CDCl_3$), δ: 2.33 (s, 3 H, Me); 3.97 (s, 3 H, OMe); 7.11 (t, 1 H, *p*-PhNH, *J* = 7.8 Hz); 7.22 (d, 2 H, *o*-PhN, *J* = 7.8 Hz); 7.33 (t, 2 H, *m*-PhNH, *J* = 7.8 Hz); 7.60 (m, 5 H, 2 Ph); 10.09 (br.s, 1 H, NH); 11.99 (br.s, 1 H, NH).

Ethyl 4-[*N*′-(4-chlorophenyl)ureido]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyrimidine-5-carboxylate (9b). A mixture of pyrimidine **6a** (0.1 g, 0.4 mmol) and 4-chlorophenylisocyanate (0.1 g, 0.6 mmol) in anhydrous toluene (3 mL) was refluxed for 10 h. The solvent was evaporated *in vacuo*, the residue was recrystallized from the benzene—hexane solvent mixture to obtain white crystals of compound **9b** (0.14 g, 87%), m.p. 186—188 °C. Found (%): C, 59.35; H, 4.68; N, 12.76; Cl, 8.47. $C_{21}H_{19}ClN_4O_4$. Calculated (%): C, 59.09; H, 4.49;

* Here and in the ^{1}H NMR spectra that follow, positions of the protons in the disubstituted benzene ring is given with respect to the carbon atom bound to the nitrogen atom.

N, 13.13; Cl, 8.31. MS, *m/z* (I_{rel} (%)): 273 $[M - ClC_6H_4NCO]^+$ (9), 152 $[ClC_6H_4NCO - H]^+$ (100). IR ($CHCl_3$), ν/cm^{-1}: 3380, 3180 (NH, CH), 1704 (CO), 1680 (CO), 1604, 1592, 1524. ^{1}H NMR ($CDCl_3$), δ: 1.40 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 2.31 (s, 3 H, Me); 4.42 (q, 2 H, CH$_2$, *J* = 7.0 Hz); 7.22 (m, 4 H, *o*-Ph, *m*-C_6H_4); 7.58 (m, 5 H, *m*-Ph, *p*-Ph, *o*-C_6H_4); 10.19 (br.s, 1 H, NH); 12.08 (br.s, 1 H, NH).

Ethyl 6-methyl-2-oxo-1-(4-tolyl)-4-(*N*´-phenylureido)-1,2-dihydropyrimidine-5-carboxylate (9c) was synthesized similarly to urea **9a** from pyrimidine **6d** and PhNCO. The yield was 76%, m.p. 178—180 °C. Found (%): C, 65.18; H, 5.39; N, 13.49. $C_{22}H_{22}N_4O_4$. Calculated (%): C, 65.01; H, 5.46; N, 13.78. MS, *m/z* (I_{rel} (%)): 406 $[M]^+$ (2), 287 $[M - PhNCO]^+$ (88), 286 $[M - PhNCO - H]^+$ (100), 258 $[M - MeC_6H_4NCO - Me]^+$ (32), 240 (73), 213 $[M - MeC_6H_4NCO - Me - OEt]^+$ (75), 119 $[PhNCO]^+$ (69). IR (KBr), ν/cm^{-1}: 3408—3000 (NH, CH), 1710 (CO), 1680 (CO), 1596, 1532. ^{1}H NMR ($CDCl_3$), δ: 1.40 (t, 3 H, MeCH$_2$, *J* = 7.0 Hz); 2.35 (s, 3 H, Me); 2.43 (s, 3 H, Me); 4.42 (q, 2 H, CH$_2$, *J* = 7.0 Hz); 7.08 (d, 2 H, *o*-C_6H_4, *J* = 7.8 Hz); 7.19 (t, 1 H, *p*-Ph, *J* = 7.8 Hz); 7.31 (m, 4 H, *m*-Ph, *m*-C_6H_4); 7.61 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 10.12 (br.s, 1 H, NH); 11.97 (br.s, 1 H, NH).

5-Methyl-3,6-diphenylpyrimido[4,5-*d*]pyrimidine-2,4,7-(1*H*,3*H*,6*H*)-trione (10a). A mixture of urea **9a** (0.1 g, 0.3 mmol) and MeONa (0.3 mmol) in MeOH (5 mL) was stirred for 10 min at 20 °C until urea was completely dissolved. The reaction mixture was acidified with AcOH to pH 6, the solvent was evaporated dry *in vacuo*, the residue was washed with water, dried, and washed with diethyl ether to obtain bicycle **10a** (0.065 g, 72%), m.p. > 300 °C. Found (%): C, 65.48; H, 3.88; N, 16.03. $C_{19}H_{14}N_4O_3$. Calculated (%): C, 65.89; H, 4.07; N, 16.18. MS, *m/z* (I_{rel} (%)): 346 $[M]^+$ (100), 318 $[M - CO]^+$ (41), 226 $[M - PhNCO - H]^+$ (22), 212 $[M - PhNCO - Me]^+$ (17), 199 $[M - PhNCO - CO]^+$ (33), 77 $[Ph]^+$ (46). IR (KBr), ν/cm^{-1}: 3496, 3176, 3056 (NH, CH), 1736 (CO), 1708 (CO), 1668, 1612, 1536. ^{1}H NMR (DMSO-d_6), δ: 2.46 (s, 3 H, Me); 7.28 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 7.38 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 7.49 (m, 3 H, Ph); 7.59 (m, 3 H, Ph); 12.12 (br.s, 1 H, NH).

3-(4-Chlorophenyl)-5-methyl-6-phenylpyrimido[4,5-*d*]-pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (10b) was synthesized similarly to compound **10a** from urea **9b**. The yield was 51%, m.p. > 300 °C (from benzene—methanol). Found (%): C, 59.53; H, 3.60; Cl, 9.51; N, 14.44. $C_{19}H_{13}ClN_4O_3$. Calculated (%): C, 59.93; H, 3.44; Cl, 9.31; N, 14.71. MS, *m/z* (I_{rel} (%)): 380 $[M]^+$ (100), 352 $[M - CO]^+$ (57), 199 $[M - ClC_6H_4NCO - CO]^+$ (43), 118 $[PhNCO - H]^+$ (58), 76 $[C_6H_4]^+$ (95). IR (KBr), ν/cm^{-1}: 3430, 3064, 2924 (NH, CH), 1740 (CO), 1688 (CO), 1612, 1592, 1540. ^{1}H NMR (DMSO-d_6), δ: 2.45 (s, 3 H, Me); 7.34 (d, 2 H, *o*-C_6H_4, *J* = 8.4 Hz); 7.36 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 7.52 (t, 1 H, *p*-Ph, *J* = 7.8 Hz); 7.55 (d, 2 H, *m*-C_6H_4, *J* = 8.4 Hz); 7.58 (t, 2 H, *m*-Ph, *J* = 7.8 Hz); 12.13 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 19.56 (Me); 95.35 (C(4a)); 127.72 (*o*-Ph); 128.87 (*m*-C_6H_4); 129.10 (*p*-Ph); 129.69 (*m*-Ph); 131.02 (*o*-C_6H_4); 132.89 (*p*-C_6H_4); 134.08 (*ipso*-C_6H_4); 137.52 (*ipso*-Ph); 149.80, 159.54, 160.74 (C(2), C(4), C(7), C(8a)); 167.39 (C(5)). Assignment of signals in the ^{1}H and ^{13}C NMR spectra was performed based on the two-dimensional spectra {^{1}H—^{1}H} COSY, {^{1}H—^{13}C} HSQC, and HMBC.

5-Methyl-3-phenyl-6-(4-tolyl)-pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (10c) was synthesized similarly to compound **10a** from urea **9c**. The yield was 55%, m.p. 283—285 °C. Found (%): C, 66.48; H, 4.25; N, 15.15. $C_{20}H_{16}N_4O_3$. Calculated (%): C, 66.66; H, 4.48; N, 15.55. MS, *m/z* (I_{rel} (%)): 360 $[M]^+$ (100), 332 $[M - CO]^+$ (69), 240 $[M - PhNCO - H]^+$ (51), 226 $[M - MeC_6H_4NCO - H]^+$ (53), 213 $[M - PhNCO - CO]^+$ (89), 132 $[MeC_6H_4NCO - H]^+$ (86), 91 $[MeC_6H_4]^+$ (93). IR (KBr), ν/cm^{-1}: 3440, 3176 (NH, CH), 1740 (CO), 1684 (CO), 1616, 1536, 1508. ^{1}H NMR (DMSO-d_6), δ: 2.38 (s, 3 H, Me); 2.46 (s, 3 H, Me); 7.22 (d, 2 H, *o*-Ph, *J* = 7.8 Hz); 7.29 (d, 2 H, *o*-C_6H_4, *J* = 7.8 Hz); 7.38 (d, 2 H, *m*-C_6H_4, *J* = 7.8 Hz); 7.48 (m, 3 H, Ph); 12.10 (br.s, 1 H, NH).

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