Synthesis of trichloromethylpyrimidines and trichloromethylpyrimido-[4,5-*d*]pyrimidines from alkyl 2-(diaminomethylidene)-3-oxobutyrates and trichloroacetonitrile*

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Heterocyclization of alkyl 2-(diaminomethylidene)-3-oxobutyrates with trichloroacetonitrile yields alkyl 4-amino-6-methyl-2-trichloromethylpyrimidine-5-carboxylates. The latter compounds react with aryl isocyanates to produce the corresponding pyrimidinylureas, which undergo cyclization to 3-aryl-5-methyl-7-trichloromethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-diones under the action of MeONa in MeOH.

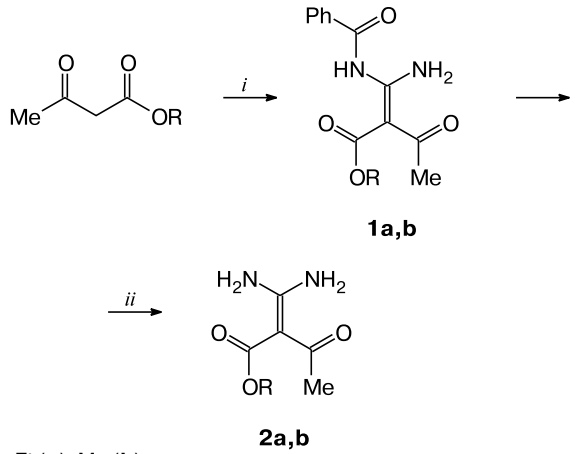
Key words: alkyl 2-(diaminomethylidene)-3-oxobutyrates, trichloroacetonitrile, alkyl 4-amino-6-methyl-2-trichloromethylpyrimidine-5-carboxylates, 7-trichloromethylpyrimido-[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-diones, heterocyclization.

α,α-Dioxoketene aminals are convenient starting reagents for the synthesis of nitrogen-containing heterocycles. In the molecules of these compounds, one can mark out enaminone, enediamine, and β-dicarbonyl fragments, which can take part in different variants of five- and six-membered ring closure.[1—7] In addition, the approach based on the change in the reactivities of ketene aminals upon chelation with boron considerably extends the potential of design of *N*-heterocycles.[8—14]

Apparently, the maximum efficiency in the heterocyclization reactions for electronic and steric reasons is to be expected for ketene aminals containing two unsubstituted NH_2 groups. Earlier it has been found that compounds of this kind can react with aroylketenes to produce 4-pyrimidinone derivatives.[15] Herein, we report on cyclocondensation of alkyl 2-(diaminomethylidene)-3-oxobutyrates with trichloroacetonitrile.

The starting ketene aminals can be obtained directly by the reaction of cyanamide with the corresponding acetoacetates in the presence of catalytic amounts of $Ni(acac)_2$ (see Ref. 16). Instead of cyanamide, in the reactions with keto esters one can use benzoylcyanamide, which is more stable on storage and heating. Although in this case *N*-benzoyl derivatives of aminals are formed, debenzoylation of the latter proceeds smoothly upon treatment with MeONa in MeOH (see Scheme 1).

Scheme 1



R = Et (**a**), Me (**b**)

i. PhCONHCN, cat. $Ni(acac)_2$; *ii*. MeONa, MeOH

Compounds **1a** and **2a** synthesized in this way from ethyl acetoacetate were described earlier.[16] The ^1H NMR spectrum of crystalline *N*-benzoylaminal **1b** obtained similarly shows one set of signals in DMSO-d_6 related apparently to the *Z*-isomer. The rotation barrier around the C=C bond in the analogous push-pull systems is very low,[17] but nevertheless in the spectrum of solution of **1b** in $CDCl_3$ there is a double set of signals (the ratio is ~2 : 1) because the intramolecular hydrogen N—H···O bonds favoring stabilization of isomers are preserved in this solvent.

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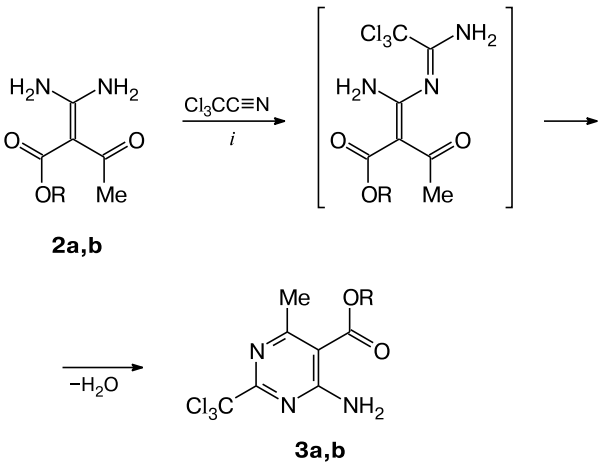
Compounds **2a,b** do not react with nonactivated nitriles (MeCN, PhCN and others). Attempts to carry out cyclocondensation of ketene aminals **2a,b** with trichloroacetonitrile in refluxing THF, benzene, or pyridine were unsuccessful either. Virtually no reaction of ketene aminals in THF and benzene took place, and intense resinification was observed in refluxing pyridine. However, it was possible to obtain alkyl 4-amino-6-methyl-2-trichloromethylpyrimidine-5-carboxylates **3a,b** in 76% and 90% isolated yields, respectively, by heating the reactants in toluene in sealed tubes at 115—125 °C (see Scheme 2).

Scheme 2



R = Et (**a**), Me (**b**)

i. Toluene, 115—125 °C.

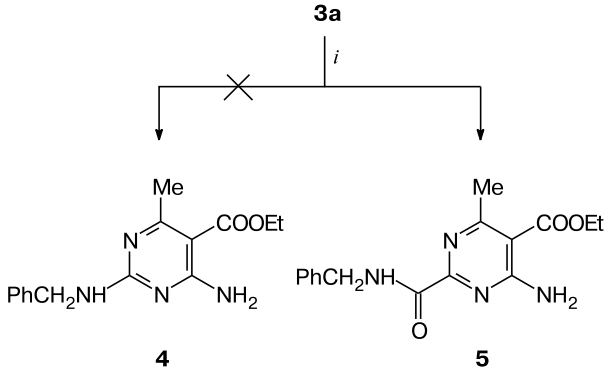
Obviously, enaminones **2a,b** add to the C≡N bond of the nitrile as N-nucleophiles and the adducts obtained afford pyrimidines **3a,b** as a result of intramolecular condensation under the reaction conditions. Expectedly, elimination of water rather than an alcohol occurs, that is, it is the acetyl group, which is more reactive than the alkoxycarbonyl group, that is involved in the cyclization.

Trichloromethylpyrimidines **3a,b** are white crystalline substances well soluble in organic solvents except for petroleum ether. Their structures were confirmed by spectroscopic data. The mass spectra show peaks of the molecular ions. In the ^{1}H NMR spectra, signals for the alkoxycarbonyl groups and a broadened singlet for the NH_2 group (2 H) at δ 7.84—7.90 (in DMSO-d_6) are observed. The ^{13}C NMR spectra of this compounds show the most downfield signal at δ ~170 confirming the absence of the acetyl group. The IR spectra ($CHCl_3$) show absorption bands of the C=O bond of the alkoxycarbonyl fragment (1695 cm^{-1}) and the NH_2 group (3500 and 3372 cm^{-1}).

Among compounds similar in structure to trichloromethylpyrimidines **3a,b**, ethyl 4-amino-6-cyanomethyl-2-trichloromethylpyrimidine-5-carboxylate has been mentioned, which is thought[18] to be obtained upon reaction of trichloroacetonitrile with alkyl 3-amino-2,4-dicyanobut-2-enoate. However, later the reaction product has been identified as a trichloromethylpyridine derivative.[19]

Functionalized pyrimidines **3a,b** attracted our attention as potential starting compounds for the synthesis of new pyrimidine derivatives. Thus examples of the substitution of the CCl_3 group in 4-trichloromethylquinazoline under the action of propylamine or pyrrolidine are known.[20] Analogous transformations of compounds **3a,b** would lead to biologically significant diaminopyrimidine derivatives. However, the reaction of pyrimidine **3a** with benzylamine in a 1 : 1 ratio (reflux in toluene) proceeded in a more complex way and no formation of the corresponding 2-benzylaminopyrimidine **4** was observed (see Scheme 3). According to data from mass spectrometry, ^{1}H NMR and IR spectroscopy, the structure **5** should be assigned to the compound isolated in a low yield following treatment of the reaction mixture with aqueous EtOH. Apparently, the transformation of trichloromethylpyrimidine **3a** into amide **5** is the result of an attack by the amine on the CCl_3 group and the subsequent hydrolysis of the substitution product (cf. Refs 21,22).

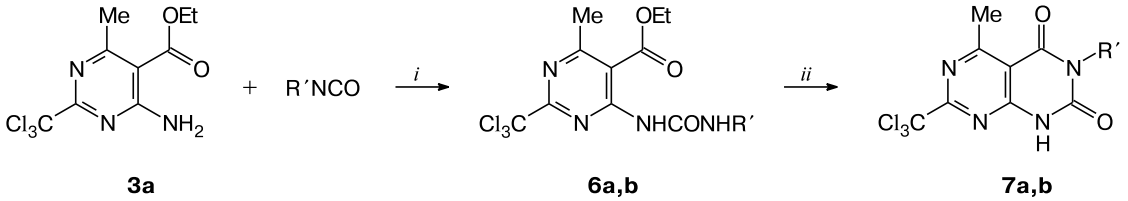
Scheme 3



i. $PhCH_2NH_2$, toluene, Δ.

The presence of vicinal NH_2 и COOR groups is favorable for the second nitrogen-containing ring annulation. Previously[23], we have reported that the reaction of alkyl 4-amino-2-acetylaminopyrimidine-5-carboxylates with phenyl isocyanate yielded pyrimido[4,5-*d*]pyrimidine derivatives *via* the corresponding ureas. Trichloromethylpyrimidine **3a** also reacts with aryl isocyanate in refluxing toluene. However, the reaction rate is comparatively low and the excess of isocyanate is required. Thus, ureas **6a,b** were obtained in 63-85% isolated yields, that is, the presence of the electron-withdrawing CCl_3 group in aminopyrimidines **3a,b** does not prevent the latter from addition

Scheme 4



3a **6a,b** **7a,b**

R′ = Ph (**a**), 4-MeC_6H_4 (**b**)

i. Toluene, Δ; *ii*. MeONa, MeOH, 20 °C.

to aryl isocyanates (see Scheme 4). White or yellowish compounds **6a,b** are well soluble in chloroform, acetone, but poorly soluble in toluene, MeOH, and DMSO. Their structures were confirmed by the data from IR, ^{1}H NMR, and ^{13}C NMR, and mass spectra. Ureas **6a,b** in turn easily undergo cyclization into pyrimido[4,5-*d*]pyrimidine-2,4-diones **7a,b**, in 79—90% isolated yields under the action of MeONa in MeOH at 20 °C.

White crystalline compounds **7a,b** synthesized are well soluble in chloroform, acetone, and DMSO. Their structures were confirmed by spectroscopic data. Thus the mass spectra show intense peaks of molecular ions. Signals for the ethoxycarbonyl group are absent from the ^{1}H and ^{13}C NMR spectra. There is a signal for only one NH group at δ 8.80—8.90 (^{1}H NMR, $CDCl_3$). The IR spectra ($CHCl_3$) show absorption bands of two carbonyl groups (744 and 1692—1712 cm^{-1}).

Thus, with the use of esters **2** as reagents of heterocyclic synthesis it is possible to obtain fused pyrimidines containing trichloromethyl group rather than only trichloromethylpyrimidines.

There are patent data dealing with the application of a number of 2-trichloromethylpyrimidines as fungicides.[24—26] Pyrimido[4,5-*d*]pyrimidines also represent the class of heterocyclic compounds that are promising in biological aspects. In particular, pyrimido[4,5-*d*]pyrimidine-2,4-dione derivatives possess antiallergic[27] and antihypertensive activities.[28]

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer, IR spectra were recorded on a Specord-M82 instrument, mass spectra (EI, 70 eV, temperature of ionization chamber is 250 °C) were obtained on a Kratos MS-30 mass spectrometer using a direct inlet system. Ketene aminal **2a** was synthesized using the known method.[16] Anhydrous toluene obtained by distillation over metallic sodium, trichloroacetonitrile and aryl isocyanates (Lancaster) were used in the syntheses. Column chromatography was carried out using Silica gel 60 (0.063—0.200 mm) (Merck).

Methyl 2-(diaminomethylidene)-3-oxobutyrate (2b). Methyl 2-[amino(benzoylamino)methylidene]-3-oxobutyrate **1b** was obtained from methyl acetoacetate and benzoylcyanamide according to a previously reported method[29] in a yield of 67%, m.p. 117—118 °C (EtOH). Found (%): C, 59.67; H, 5.49; N, 10.48. $C_{13}H_{14}N_2O_4$. Calculated (%): C, 59.53; H, 5.38; N, 10.68. MS (EI), *m/z*: 262 $[M]^+$. ^{1}H NMR ($CDCl_3$, *E*/*Z*-isomers in a ~2 : 1 ratio), δ: 2.49/2.46 (s, 3 H, Me); 3.81/3.84 (s, 3 H, OMe); 7.60 (m, 3 H, Ph); 8.05 (m, 2 H, Ph); 10.0/11.8 (br.s, 2 H, NH_2); 15.70/13.79 (s, 1 H, NH). ^{1}H NMR (DMSO-d_6), δ: 2.35 (s, 3 H, Me); 3.75 (s, 3 H, OMe); 7.62 (t, 2 H, *m*-Ph, *J* = 8.0 Hz); 7.72 (t, 1 H, *p*-Ph, *J* = 8.0 Hz); 7.94 (d, 2 H, *o*-Ph, *J* = 8.0 Hz); 9.72 (br.s, 1 H, NH); 10.20, 14.95 (both br.s, 2 H, NH_2). Ester **2b** was obtained by treatment of compound **1b** with MeONa in MeOH according to the known method[16] in a yield of 95%, m.p. 120—121 °C (benzene). Found (%): C, 45.54; H, 6.33; N, 17.52. $C_6H_{10}N_2O_3$. Calculated (%): C, 45.56; H, 6.37; N, 17.72. MS (EI), *m/z*: 158 $[M]^+$. IR, ($CHCl_3$), ν/cm^{-1}: 3480, 3400—2800 (NH); 1656 (CO); 1602. ^{1}H NMR (DMSO-d_6), δ: 2.20 (s, 3 H, Me); 3.61 (s, 3 H, OMe); 6.85 (br.s, 2 H, 2 NH); 9.30 (br.s, 2 H, 2NH).

Ethyl 4-amino-6-methyl-2-trichloromethylpyrimidine-5-carboxylate (3a). A mixture of ketene aminal **2a** (0.344 g, 2 mmol) and CCl_3CN (0.40 mL, 4 mmol) in dry toluene (8 mL) was heated for 16 h in a sealed tube at 115—125 °C. The solvent was evaporated *in vacuo*, the residue was chromatographed on a column with SiO_2 (eluent — benzene). Compound **3a** was obtained in a yield of 0.45 (76%), m.p. 113—114 °C (hexane). Found (%): C, 36.30; H, 3.53; Cl, 35.68; N, 14.03. $C_9H_{10}Cl_3N_3O_2$. Calculated (%): C, 36.20; H, 3.38; Cl, 35.62; N, 14.08. MS (EI) (hereinafter peaks of ions only for ^{35}Cl isotope are given), *m/z* (I_{rel} (%)): 297 $[M]^+$ (14), 262 $[M - Cl]^+$ (65), 252 $[M - OEt]^+$ (20), 36 (100). IR, ($CHCl_3$), ν/cm^{-1}: 3500, 3372 (NH_2); 1692 (CO); 1600, 1544. ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, $\underline{Me}CH_2$, *J* = 7.0 Hz); 2.50 (s, 3 H, Me); 4.32 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.90 (br.s, 2 H, NH_2). ^{13}C NMR ($CDCl_3$), δ: 14.27 ($\underline{Me}CH_2$); 26.50 (Me); 61.87 (CH_2); 96.53 (CCl_3); 104.26 (C(5)); 164.00, 164.77 (C(2), C(4)); 166.95 ($\underline{C}O_2Et$); 170.72 (C(6)).

Methyl 4-amino-6-methyl-2-tricloromethylpyrimidine-5-carboxylate (3b) was prepared analogously to compound **3a** from ketene aminal **2b** and CCl_3CN. The yield was 91%, m.p. 114—115 °C (hexane). Found (%): C, 33.95; H, 2.97; Cl, 37.57; N, 14.80. $C_8H_8Cl_3N_3O_2$. Calculated (%): C, 33.77; H, 2.83; Cl, 37.38; N, 14.78. MS (EI), *m/z* (I_{rel} (%)): 283 $[M]^+$ (33), 252 $[M - OMe]^+$ (37), 251 $[M - MeOH]^+$ (48), 248 $[M - Cl]^+$ (100), 217 $[M - Cl - OMe]^+$ (66). IR, ($CHCl_3$), ν/cm^{-1}: 3500, 3370 (NH_2); 1695 (CO); 1602, 1545. ^{1}H NMR ($CDCl_3$), δ: 2.74 (s, 3 H, Me); 3.98 (s, 3 H, OMe); signals for

the protons of NH_2 group were not recorded in $CDCl_3$ (as in the case of **3a**). ^{1}H NMR (DMSO-d_6), δ: 2.50 (s, 3 H, Me); 3.88 (s, 3 H, OMe); 7.84 (br.s, 2 H, NH_2).

Ethyl 4-amino-2-(*N*-benzylcarbamoyl)-6-methylpyrimidine-5-carboxylate (5). A mixture of pyrimidine **3a** (0.1 g, 0.34 mmol) and benzylamine (0.04 mL, 0.4 mmol) in toluene (5 mL) was refluxed for 6 h. The precipitate that formed was identified by ^{1}H NMR spectrum as benzylamine hydrochloride, m.p. 261—263 °C, and was filtered off. The filtrate was concentrated *in vacuo*, the residue was recrystallized from EtOH. White crystalline compound **5** well soluble in chloroform and acetone was obtained in a yield of 0.02 g (19%), m.p. 213—215 °C. Found (%): C, 61.11; H, 5.88; N, 17.39. $C_{16}H_{18}N_4O_3$. Calculated (%): C, 61.14; H, 5.77; N, 17.82. MS (EI), *m/z* (I_{rel} (%)): 314 $[M]^+$ (42), 286 $[M - CO]^+$ (13), 269 $[M - OEt]^+$ (15), 181 $[M - PhCH_2NCO]^+$ (86), 107 $[PhCH_2NH_2]^+$ (63), 106 $[PhCH_2NH]^+$ (100), 91 $[PhCH_2]^+$ (52). IR, (KBr), ν/cm^{-1}: 3424 (NH); 3368 (NH); 3240, 3192, 1700 (CO); 1680 (CO); 1612, 1516. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, $\underline{Me}CH_2$, *J* = 7.1 Hz); 2.68 (s, 3 H, Me); 4.40 (q, 2 H, $\underline{CH_2}Me$, *J* = 7.1 Hz); 4.66 (d, 2 H, $\underline{CH_2}Ph$, *J* = 5.5 Hz); 7.38 (m, 5 H, Ph); 8.35 (br.s, 1 H, NH).

Ethyl 4-(*N*-arylureido)-6-methyl-2-trichloromethylpyrimidine-5-carboxylates (6a,b). A mixture of pyrimidine **3a** (0.3 g, 1 mmol) and phenyl isocyanate (0.4 mL, 3.7 mmol) or *p*-tolyl isocyanates (0.4 mL, 3.2 mmol) in dry toluene (2 mL) was refluxed for 7 h, then it was cooled to 20 °C, the precipitate that formed was filtered off and washed with petroleum ether. Thus, compounds **6a,b** were obtained.

Ethyl 6-methyl-4-(*N*-phenylureido)-2-trichloromethylpyrimidine-5-carboxylate (6a), yield 0.36 g (85%), m.p. 204—206 °C. Found (%): C, 46.24; H, 3.64; Cl, 25.31; N, 13.41. $C_{16}H_{15}Cl_3N_4O_3$. Calculated (%): C, 46.01; H, 3.62; Cl, 25.46; N, 13.41. MS (EI), *m/z* (I_{rel} (%)): 416 $[M]^+$ (9), 297 $[M - PhNCO]^+$ (13), 262 $[M - PhNCO - Cl]^+$ (30), 225 $[M - PhNCO - C_2H_4 - CO_2]^+$ (29), 217 $[M - PhNCO - Cl - OEt]^+$ (43), 119 $[PhNCO]^+$ (100), 91 $[PhN]^+$ (94). IR, ($CHCl_3$), ν/cm^{-1}: 3248 (NH); 1692 (CO); 1588, 1536. IR, (KBr), ν/cm^{-1}: 3224 (NH); 1712 (CO); 1676 (CO); 1604, 1556, 1536. ^{1}H NMR ($CDCl_3$), δ: 1.50 (t, 3 H, $\underline{Me}CH_2$, *J* = 7.0 Hz); 2.88 (s, 3 H, Me), 4.55 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.15 (t, 1 H, *p*-Ph, *J* = 8.0 Hz); 7.38 (t, 2 H, *m*-Ph, *J* = 8.0 Hz); 7.62 (d, 2 H, *o*-Ph, *J* = 8.0 Hz); 10.19 (br.s, 1 H, NH); 11.29 (br.s, 1 H, $\underline{NH}Ph$). ^{13}C NMR ($CDCl_3$), δ: 14.10 ($\underline{Me}CH_2$); 26.73 (Me); 62.99 (CH_2); 95.80 (CCl_3); 107.03 (C(5)); 120.19 (*o*-Ph); 124.17 (*p*-Ph); 129.05 (*m*-Ph); 137.61 (*ipso*-Ph); 150.26 (CON); 158.39 (C(4)); 163. 08 (C(2)); 165.63 ($\underline{C}O_2Et$); 171.61 (C(6)). The assignment of the signals in the ^{13}C NMR spectrum was made based on correlation peaks in the 2D HMBC spectrum.

Ethyl 6-methyl-4-[*N*-(4-tolyl)ureido]-2-trichloromethylpyrimidine-5-carboxylate (6b), yield 0.28 g (63%), m.p. 176—178 °C. Found (%): C, 47.32; H, 4.03; Cl, 24.72; N, 12.95. $C_{17}H_{17}Cl_3N_4O_3$. Calculated (%): C, 47.30; H, 3.97; Cl, 24.62; N, 12.98. MS (EI), *m/z* (I_{rel} (%)): 430 $[M]^+$ (3), 297 $[M - MeC_6H_4NCO]^+$ (6), 225 $[M - MeC_6H_4NCO - C_2H_4 - CO_2]^+$ (34), 217 $[M - MeC_6H_4NCO - Cl - OEt]^+$ (36), 133 $[MeC_6H_4NCO]^+$ (87), 78 (100). IR, (KBr), ν/cm^{-1}: 3232 (NH), 1712 (CO), 1680 (CO), 1576, 1528. ^{1}H NMR ($CDCl_3$), δ: 1.49 (t, 3 H, $\underline{Me}CH_2$, *J* = 7.0 Hz); 2.35 (s, 3 H, $\underline{Me}C_6H_4$); 2.87 (s, 3 H, Me); 4.54 (q, 2 H, CH_2, *J* = 7.0 Hz); 7.18 (d, 2 H, *m*-Ph, *J* = 8.0 Hz); 7.50 (d, 2 H, *o*-Ph, *J* = 8.0 Hz); 10.14 (br.s, 1 H, NH); 11.21 (br.s, 1 H, $\underline{NH}C_6H_4$).

5-Methyl-3-phenyl-7-trichloromethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7a). A mixture of urea **6a** (0.2 g, 0.48 mmol) and MeONa (2.4 mmol) in MeOH (5 mL) was stirred for 5 min, the homogeneous solution was acidified with AcOH, the precipitate that formed was filtered off, washed with hexane. Bicycle **7a** was obtained in a yield of 0.14 g (79%), m.p. 238—240 °C (benzene). Found (%): C, 45.22; H, 2.46; Cl, 28.68; N, 15.00. $C_{14}H_9Cl_3N_4O_2$. Calculated (%): C, 45.25; H, 2.44; Cl, 28.62; N, 15.08. MS (EI), *m/z* (I_{rel} (%)): 370 $[M]^+$ (46), 335 $[M - Cl]^+$ (20), 119 $[PhNCO]^+$ (100). IR, ($CHCl_3$), ν/cm^{-1}: 3392 (NH); 1744 (CO); 1692 (CO); 1592, 1572. ^{1}H NMR ($CDCl_3$), δ: 3.08 (s, 3 H, Me); 7.30 (d, 2 H, *o*-Ph, *J* = 8.0 Hz); 7.53 (m, 3 H, *m*-Ph, *p*-Ph); 8.80 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 24.56 (Me); 95.99 (CCl_3); 106.62 (C(4a)); 128.46 (*p*-Ph); 128.82, 128.98 (*o*-Ph, *m*-Ph); 135.10 (*ipso*-Ph); 149.83 (C(2)); 158.37 (C(8a)); 160.71 (C(4)); 164.90 (C(7)); 171.77 (C(5)). The assignment of the signals in the ^{13}C NMR spectrum was made based on comparison with the ^{13}C NMR spectrum of urea **6a**.

5-Methyl-3-(4-tolyl)-7-trichloromethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7b). A mixture of urea **6b** (0.1 g, 0.23 mmol) and MeONa (1.15 mmol) in MeOH (5 mL) was stirred for 5 min, the homogeneous solution was acidified with AcOH, the solvent was evaporated *in vacuo*. Chloroform (15 mL) was added to the residue, insoluble sodium acetate was filtered off, chloroform was evaporated *in vacuo*, the residue was recrystallizated from benzene. Bicycle **7b** was obtained in a yield of 0.08 g (90%), m.p. 231—233 °C. Found (%): C, 46.30; H, 2.69; Cl, 27.55; N, 14.31. $C_{15}H_{11}Cl_3N_4O_2$. Calculated (%): C, 46.72; H, 2.88; Cl, 27.58; N, 14.53. MS (EI), *m/z* (I_{rel} (%)): 384 $[M]^+$ (100), 349 $[M - Cl]^+$ (97), 316 $[M - MeCN - CO + H]^+$ (39), 133 $[MeC_6H_4NCO]^+$ (98). IR, ($CHCl_3$), ν/cm^{-1}: 3392 (NH); 1744 (CO); 1712 (CO); 1592, 1584, 1524. ^{1}H NMR ($CDCl_3$), δ: 2.42 (s, 3 H, $\underline{Me}C_6H_4$); 3.05 (s, 3 H, Me); 7.15 (d, 2 H, *o*-C_6H_4, *J* = 8.0 Hz); 7.36 (d, 2 H, *m*-C_6H_4, *J* = 8.0 Hz); 8.88 (br.s, 1 H, NH).

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