Purines, pyrimidines, and related fused systems
21.* Oxidative amination of 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione

V. V. Goryunenko, A. V. Gulevskaya, and A. F. Pozharskii*

Rostov State University,
7 pr. Zorge, 344090 Rostov-on-Don, Russian Federation.
Fax: +7 (863 2) 22 3958. E-mail: AGulevskaya@chimfak.rsu.ru

Oxidative amination of 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione with primary alkylamines and potassium amide in liquid ammonia gives rise to the corresponding 4-amino derivatives as the major products. The reactions with acyclic secondary amines are accompanied by annelation of the pyrrole moiety to the starting heterosystem to form 1-R-3-R´-6,8-dimethylpyrrolo[2´,3´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones. The reaction with piperidine as the aminating agent occurs exclusively as aminodehalogenation. The Sonogashira cross-coupling of 4-amino-3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones with terminal alkynes affords 1-R-2-R´-6,8-dimethylpyrrolo[3´,2´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones.

Key words: 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione, oxidative amination, 4-amino(alkylamino)-3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones, 6,8-dimethylpyrrolo[2´,3´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones, alkynes, metal complex catalysis, Sonogashira reaction, 6,8-dimethylpyrrolo[3´,2´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones.

Recently,[2] we have demonstrated that oxidative amination of 3-(alk-1-yn-1-yl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (**1**) with primary alkylamines initially affords *vic*-(alkylamino)alkynes **2**, which undergo spontaneous cyclization to give 6,8-dimethylpyrrolo[3´,2´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones (**3**) (Scheme 1). Attempts to prepare N(1)-unsubstituted pyrroles **3** failed because compounds **1** do not react with potassium amide in liquid ammonia in the presence of $KMnO_4$ due apparently to insufficient electrophilicity of the C(4) atom and too low boiling point of the solvent.

Compounds **2** and then pyrroles **3** can also be synthesized, in principle, by condensation of 4-amino-3-chloropyridazinouracils **4** with alk-1-ynes. We expected that this change in the order of introduction of the amino and alkynyl residues into the pyridazinouracil molecule would make pyrroles **3** containing the free NH group more accessible.

We intended to prepare previously unknown *vic*-chlorohetarylamines **4** by oxidative amination of 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**5a**). It appeared that chloride **5a** reacts with potassium amide in liquid ammonia and with primary amines in the presence of $KMnO_4$ or the complex $AgPy_2MnO_4$ at −78—20 °C (depending on boiling point of the amine) to give 4-amino derivatives **4a—f** in 63—80% yields (Scheme 2); the reaction time is 10—15 min. Under the same conditions, the reaction with cyclohexylamine proceeds more slowly (24 h), is more complicated, and gives a mixture of 3-chloro-4-cyclohexylaminopyridazine **4g** (in 30% yield), 3-cyclohexylamino derivative **6a** (4%), and pyrrole **7a** (25%). In the case of other primary amines (R^1 = Et, Pr, or Bu), an increase in the reaction time to 24 h also resulted in the appearance of the corresponding 3-alkylamino derivatives **6b—d** (~1%) and pyrroles **7b—d** (5—7%) in the reaction mixture, the yields of amines **4c,d,f** remaining virtually unchanged.

The reactions of 3-chloropyridazinouracil **5a** with secondary amines in the presence of an oxidant proceed differently. For example, the reaction with piperidine affords exclusively aminodehalogenation product **8** (Scheme 3). Diethyl-, dipropyl-, and dibutylamines react with compound **5a** to form predominantly pyrroles **7b—d**. The reaction with diethylamine gives pyrrole **7b** (in 43% yield) along with enamine **9** (15%).

The structures of compounds **4** and **9** were established based on their spectroscopic characteristics and results of elemental analysis. The IR spectra of 4-amino deriva-

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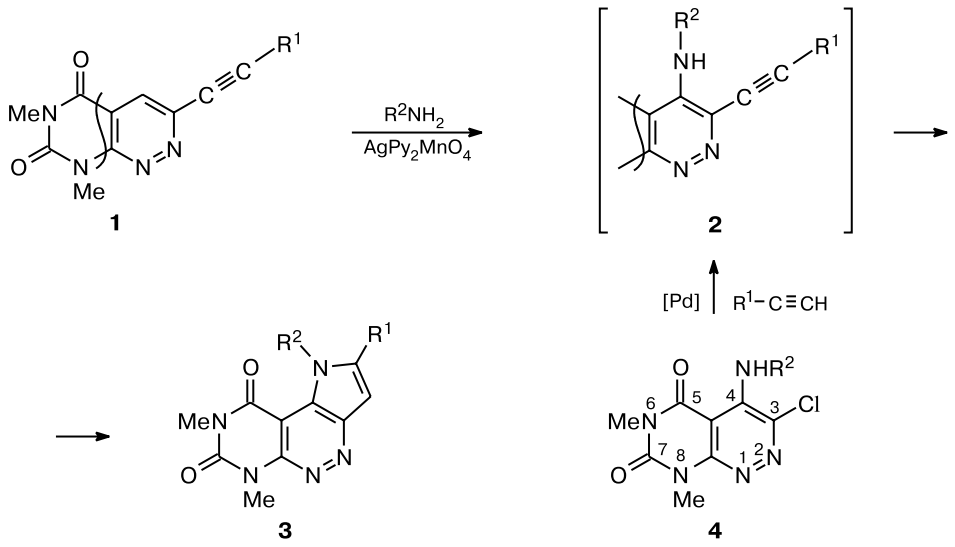
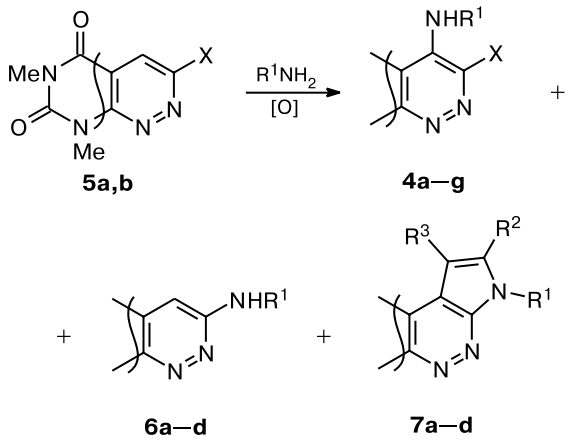
Scheme 1



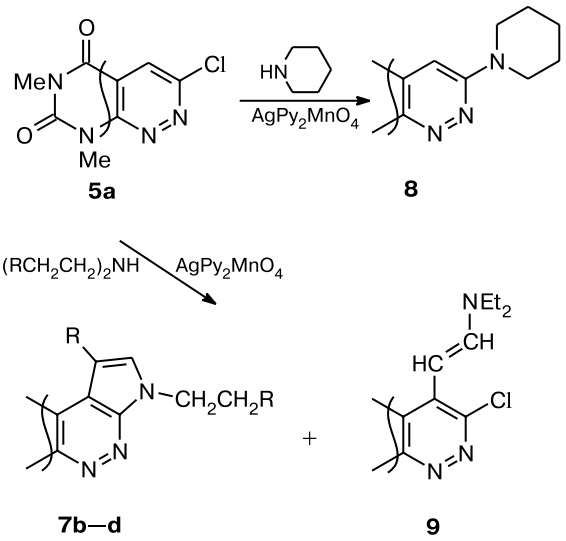
Scheme 2



4: X = Cl, R^1 = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Pr^i (**e**), Bu (**f**), *cyclo*-C_6H_{11} (**g**);
5: X = Cl (**a**), H (**b**);
6: R^1 = *cyclo*-C_6H_{11} (**a**), Et (**b**), Pr (**c**), Bu (**d**),
7: R^1 = *cyclo*-C_6H_{11}, R^2, R^3 = —$(CH_2)_4$— (**a**),
R^1 = Et, R^2, R^3 = H (**b**), R^1 = Pr, R^2 = H, R^3 = Me (**c**),
R^1 = Bu, R^2 = H, R^3 = Et (**d**)

Reagents and conditions: KNH_2—NH_3—$KMnO_4$ or R^1NH_2—$AgPy_2MnO_4$, –78—20 °C.

Scheme 3



7: R = H (**b**), Me (**c**), Et (**d**)

tives **4** (Table 1) have characteristic absorption bands of two carbonyl groups (ν(C=O) 1652—1718 cm^{-1}) and the N—H bond (ν(N—H) 3088—3207 cm^{-1}). The spectrum of compound **4a** shows bands corresponding to symmetrical and asymmetrical N—H stretching vibrations of the amino group (ν^{as} 3301 and ν^{s} 3407 cm^{-1}). In the ^{1}H NMR spectra of compounds **4b—g**, the signals for the NH proton of the alkylamino group are observed at low field at δ 9.86—10.05. In derivative **4a**, the protons of the NH_2 group are magnetically nonequivalent and give two signals at δ 5.79 and 8.86, which coalesce on heating of a solution in DMSO-d_6 to 60 °C. The spectroscopic characteristics of *vic*-chlorohetarylamines **4** are consistent with the data for 4-amino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones.[3]

In the ^{1}H NMR spectrum of enamine **9**, the signals for protons of the vinyl group appear as two doublets at δ 7.03 and 8.46 with the spin-spin coupling constants $^3J_{trans}$ = 13.4 Hz.[4] The mass spectrum has an intense molecular ion peak at *m*/*z* 323.

Table 1. Physicochemical characteristics of 4-amino-3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones **4**

Compound	R	M.p./°C	^{1}H NMR, δ (*J*/Hz)				IR, ν/cm^{-1}		
			Me(6)	Me(8)	NH	R	ring	C=O	N—H
4a	H	225—228 (decomp.)	3.42	3.73	5.79, 8.86	—	1558, 1612	1665, 1705	3301, 3407
4b	Me	197—199	3.39	3.70	9.92	3.46 (d, 2 H, NH<u>Me</u>, *J* = 5.9)	1518, 1585	1652, 1718	3181
4c	Et	150—152	3.39	3.71	9.86	1.35 (t, 3 H, CH_2<u>Me</u>, *J* = 7.3); 3.95 (m, 2 H, C<u>H</u>$_2$Me)	1572, 1599	1652, 1705	3114
4d	Pr^n	116—118	3.40	3.71	9.94	1.03 (t, 3 H, CH_2CH_2<u>Me</u>, *J* = 7.4); 1.70 (m, 2 H, CH_2C<u>H</u>$_2$Me); 3.87 (m, 2 H, C<u>H</u>$_2CH_2$Me)	1519, 1585	1665, 1705	3181
4e	Pr^i	136—138	3.39	3.71	9.95	1.34 (d, 6 H, CH<u>Me</u>$_2$, *J* = 6.6); 4.91 (m, 1 H, C<u>H</u>Me$_2$)	1519, 1558, 1585	1652, 1705	3168
4f	Bu	80—82	3.40	3.71	9.92	0.97 (t, 3 H, $CH_2(CH_2)_2$<u>Me</u>, *J* = 7.3); 1.46 (m, 2 H, $(CH_2)_2$C<u>H</u>$_2$Me); 1.69 (m, 2 H, CH_2C<u>H</u>$_2C_2H_5$); 3.90 (m, 2 H, C<u>H</u>$_2C_3H_7$)	1518, 1585	1665, 1705	3207
4g	*cyclo*-C_6H_{11}	178—180	3.40	3.71	10.05	1.36 (m, 6 H); 1.77, 2.06 (both m, 2 H each); 4.55 (m, 1 H)	1518, 1558, 1611	1678, 1718	3088

The structures of compounds **6**—**8** were confirmed by comparing with samples of these compounds prepared earlier.[3,5—7]

It should be noted that the reactivity of 3-chloro derivative **5a** toward amines is similar to that of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**5b**).[3,5,6] Both molecules possess the properties of bifunctional electrophiles and are subjected to the nucleophilic attack both at the C(3) and C(4) atoms, the attack at position 4 prevailing in their reactions with nucleophiles due to higher π-deficiency of this position and higher stability of the corresponding σ complex.[3]

The results of our study elucidate particular details of the mechanism of formation of pyrroles **7** from pyridazinouracils **5a**,**b** and dialkylamines (Scheme 4). Thus, the earlier assumption that the reaction involves imines **10**, which are generated *in situ* from dialkylamines,[5] was experimentally confirmed. However, the question as to which of two atoms, C(3) or C(4), in molecule **5b** is subjected to the primary nucleophilic attack remained open. The formation of enamine **9** in the reaction of chloride **5a** with diethylamine indicates that heterocyclization starts with the attack on position 4 and follows the path *a*. The addition of diethylamine at the C=N bond of intermediate **11** giving rise to *gem*-diamine **12** followed by elimination of ethylamine from the latter affords enamine **9**.

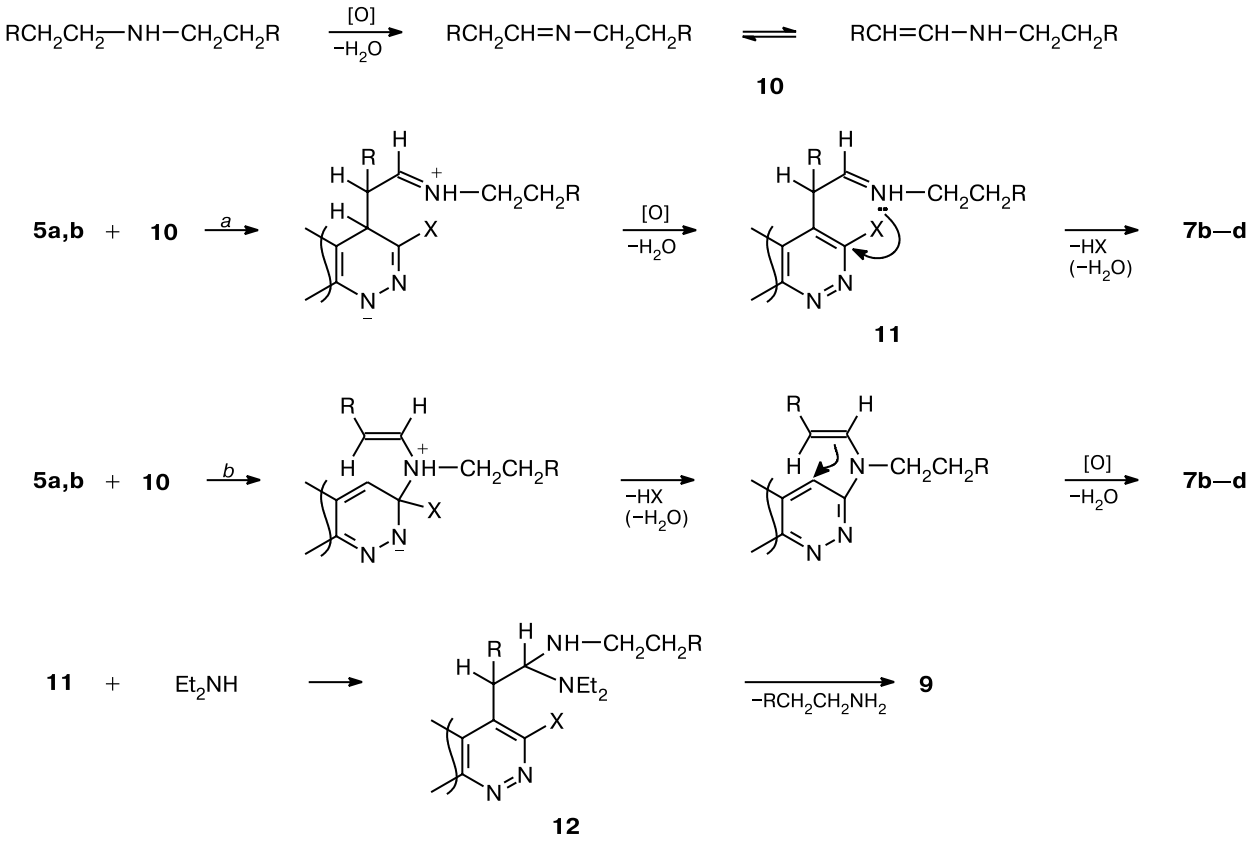
Annelation of the pyrrole moiety in the reactions of compound **5a** with primary amines can be represented by analogous Scheme 5.

Another important aspect of oxidative amination of chloride **5a** is that it is accompanied by the competitive nucleophilic substitution of the Cl and H atoms. An analogous competition between S_N^{ipso} and S_N^H reactions and even complete predominance of the latter is known for 2-chloropteridine,[8] 3-bromo-4-dimethylaminopyridine,[9] 4-bromo-1-methyl-2-nitroimidazole,[10] bromonaphthyridines,[11] *etc*.[12] The isomer of compound **5a**, *viz*., 6-chloro-1,3-dimethyllumazine, also exhibits dual reactivity with respect to primary alkylamines.[13] In both cases, the reason is the lower π-deficiency of the C atom bearing the Cl substituent and higher stability of the σ complex corresponding to the addition of a nucleophile to the unsubstituted C atom (the C(4) atom in molecule **5a** and the C(7) atom in 6-chloro-1,3-dimethyllumazine).

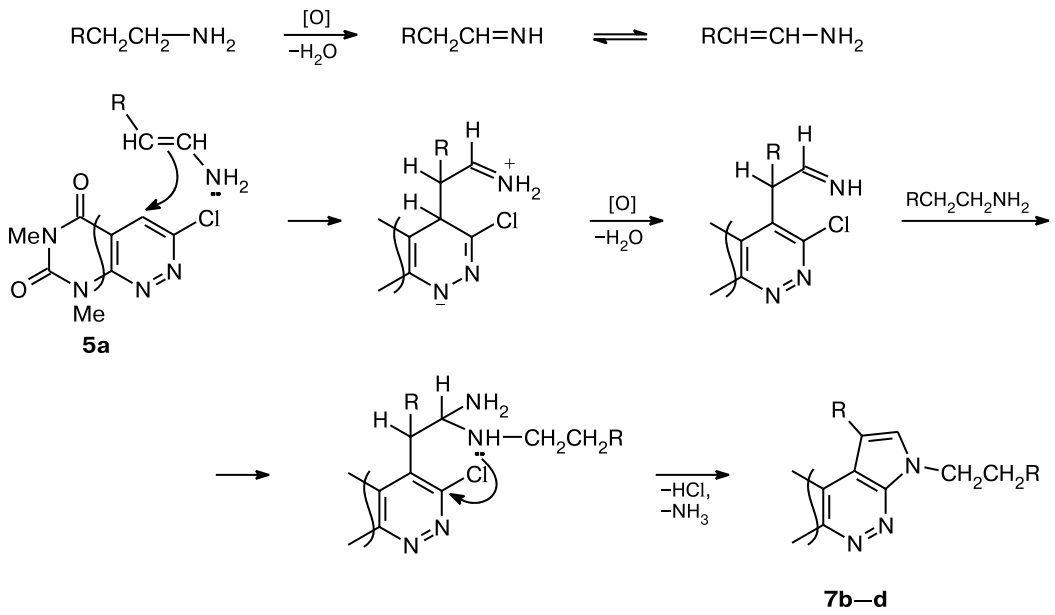
We found that under conditions of the Sonogashira reaction, 4-amino-3-chloropyridazinouracils **4a** reacts with phenylacetylene to give a complex mixture of products in 1 h, from which only pyrrole **3a** was isolated in 21% yield. The reaction of 4-propylamino derivative **4d** with phenylacetylene proceeds more selectively, but its result depends on the reaction time. Judging from the TLC data, the starting compound disappeared already after 30 min, but the reaction afforded a mixture of *vic*-aminohetarylacetylene **2b** and pyrrole **3b** in a ratio of 7 : 1 (according to the NMR spectroscopic data) in a total yield of 72%. An increase in the reaction time to 5 h led to the formation of pyrrole **3b** as the only product (84%) (Scheme 6).

Pyrrole **3b** is identical to a sample prepared earlier.[2] Its structure was confirmed by X-ray diffraction analysis (Fig. 1). The IR spectrum of compound **3a** has a narrow ν(N—H) band at 3380 cm^{-1}. In the ^{1}H NMR spectrum, a

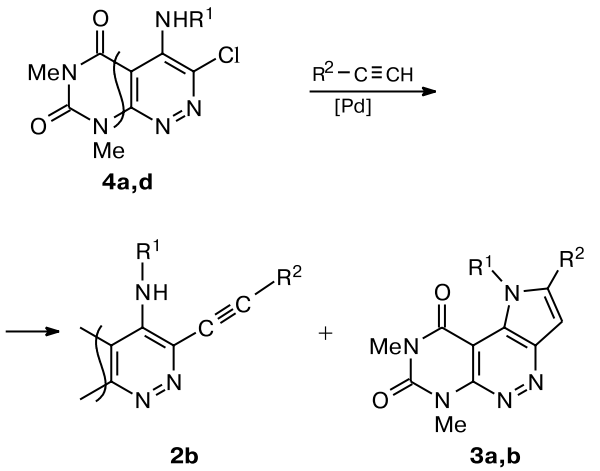
Scheme 4



Scheme 5



Scheme 6



3: R^1 = H, R^2 = Ph (**a**); R^1 = Pr, R^2 = Ph (**b**)

Reagents and conditions: $Pd_2(dba)_3$—PPh_3, K_2CO_3, CuI, DMF, 90—100 °C, Ar.

signal for the proton of the NH group appears as a broadened singlet at δ 10.00.

Therefore, compounds **4** can serve as the starting material in the synthesis of 6,8-dimethylpyrrolo[3′,2′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones, including those unsubstituted at the N(1)—H group.

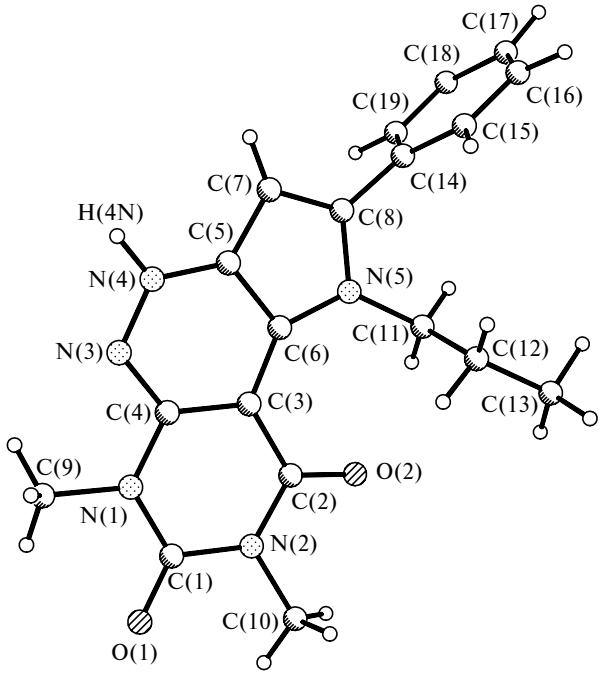


Fig. 1. Molecular structure of 6,8-dimethyl-2-phenyl-1-propylpyrrolo[3′,2′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione **3b** (the crystallographic numbering of atoms is given).

Experimental

The IR spectra were recorded on a Specord IR-71 instrument in Nujol mulls. The ^{1}H NMR spectra were measured on a Bruker-250 spectrometer (250 MHz, solutions in $CDCl_3$). The mass spectra were obtained on an MX-1321A spectrometer. Chromatography was carried out on Al_2O_3 (Brockmann activity III—IV) using chloroform as the eluent; visualization was performed with iodine vapor. Melting points were measured in glass capillaries and are uncorrected.

The physicochemical characteristics of compounds **4** are given in Table 1. The results of elemental analysis are listed in Table 2.

4-Amino-3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (4a). Metallic potassium (0.06 g, 1.6 mmol) was dissolved in liquid ammonia (35 mL) at −70 °C. 3-Chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione[14] (**5a**) (227 mg, 1 mmol) was added to the resulting solution of potassium amide. The reaction mixture was stirred for 10 min, $KMnO_4$ (0.35 g, 2.2 mmol) was added, and cooling was discontinued. After 10 min, ammonium sulfate (0.3 g) was added to the reaction mixture (to decompose unconsumed KNH_2) and the mixture was concentrated to dryness. The residue was extracted with $CHCl_3$ in a Soxlet apparatus. The extract was concentrated to dryness and the residue was recrystallized from Pr^iOH to give compound **4a** in a yield of 192 mg (79%) as colorless crystals.

3-Chloro-6,8-dimethyl-4-methylaminopyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (4b). A solution of compound **5a** (0.4 g, 1.8 mmol) in methylamine (40 mL) was stirred at a temperature from −65 to −55 °C for 10 min and then $KMnO_4$ (0.28 g, 1.8 mmol) was added. The reaction mixture was stirred at the

Table 2. Results of elemental analysis of the compounds synthesized

Compound	Found / Calculated (%)				Molecular formula
	C	H	Cl	N	
3a	62.73	4.04	—	22.68	$C_{16}H_{13}N_5O_2$
	62.54	4.23		22.80	
4a	39.56	3.38	14.86	29.13	$C_8H_8ClN_5O_2$
	39.75	3.51	14.70	28.99	
4b	42.44	4.17	14.02	27.51	$C_9H_{10}ClN_5O_2$
	42.27	3.91	13.90	27.40	
4c	44.68	4.59	13.28	26.04	$C_{10}H_{12}ClN_5O_2$
	44.53	4.45	13.17	25.97	
4d	46.69	5.08	12.66	24.76	$C_{11}H_{14}ClN_5O_2$
	46.56	4.94	12.52	24.69	
4e	46.38	5.12	12.37	24.53	$C_{11}H_{14}ClN_5O_2$
	46.56	4.94	12.52	24.69	
4f	48.25	5.33	11.77	23.71	$C_{12}H_{16}ClN_5O_2$
	48.40	5.38	11.93	23.53	
4g	52.06	5.72	10.84	21.76	$C_{14}H_{18}ClN_5O_2$
	51.93	5.56	10.97	21.67	
6d	54.66	6.29	—	26.80	$C_{12}H_{17}N_5O_2$
	54.75	6.46		26.62	
9	51.85	5.61	11.16	21.49	$C_{14}H_{18}ClN_5O_2$
	51.93	5.56	10.97	21.67	

same temperature for 15 min and concentrated to dryness. The residue was worked up as described above and compound **4b** was obtained in a yield of 298 mg (66%) as colorless crystals.

3-Chloro-4-ethylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (4c). ***A.*** Compound **4c** was prepared analogously to **4b** from compound **5a** (0.4 g, 1.8 mmol), ethylamine (40 mL), and $AgPy_2MnO_4$ (0.28 g, 1.8 mmol) at a temperature from −5 to 0 °C. The yield was 267 mg (55%).

B. A mixture of compound **5a** (0.4 g, 1.8 mmol) and $AgPy_2MnO_4$ (0.28 g, 1.8 mmol) in ethylamine (40 mL) was stirred at a temperature from −5 to 0 °C for 24 h and concentrated to dryness. The residue was extracted with boiling $CHCl_3$ (40 mL). The extract was concentrated to ~5 mL and chromatographed on a column (1.5×50 cm) with Al_2O_3 in $CHCl_3$. 3-Ethyl-6,8-dimethylpyrrolo[2′,3′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (**7b**) was isolated from the first yellow fraction with R_f 0.6 in a yield of 23 mg (5%) as bright-yellow needles, m.p. 225—227 °C (*cf.* lit. data[5]). Compound **4c** was isolated from the colorless fraction with R_f 0.45 in a yield of 281 mg (58%) as colorless crystals (after recrystallization from Pr^iOH). 3-Ethylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**6b**) was isolated from the yellow fraction with R_f 0.2 in a yield of 4 mg (1%) as yellow crystals (after recrystallization from Pr^iOH), m.p. 211—213 °C (*cf.* lit. data[6]).

3-Chloro-6,8-dimethyl-4-propylaminopyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (4d). ***A.*** A solution of compound **5a** (227 mg, 1 mmol) in propylamine (40 mL) was stirred at 20 °C for 15 min and then $AgPy_2MnO_4$ (385 mg, 1 mmol) was added. The reaction mixture was stirred at 20 °C for 15 min and concentrated to dryness. The residue was extracted with $CHCl_3$ (30 mL) and the extract was concentrated to ~5 mL and chromatographed on a column with Al_2O_3 in $CHCl_3$. A colorless fraction with R_f 0.55 was collected. The product was recrystallized from Pr^iOH. Compound **4d** was obtained in a yield of 218 mg (77%) as colorless crystals.

B. The reaction was carried out analogously to the method *A* but the reaction mixture was kept at 20 °C for 24 h and concentrated to dryness. The residue was extracted with $CHCl_3$ (30 mL). Three fractions were isolated on a column (1.5×50 cm) with Al_2O_3 in $CHCl_3$. 1,6,8-Trimethyl-3-propylpyrrolo[2′,3′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (**7c**) was isolated from the yellow fraction with R_f 0.65 in a yield of 20 mg (7%) as bright-yellow needles, m.p. 174—175 °C (*cf.* lit. data[5]). Compound **4d** was isolated from the colorless fraction with R_f 0.55 in a yield of 207 mg (73%) as colorless crystals (after recrystallization from Pr^iOH). 6,8-Dimethyl-3-propylaminopyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**6c**) was isolated from the yellow fraction with R_f 0.26 in a yield of 3 mg (1%) as yellow crystals (after recrystallization from Pr^iOH), m.p. 161—162 °C (*cf.* lit. data[6]).

3-Chloro-4-isopropylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (4e) was prepared analogously to **4d** (method *A*) from compound **5** (0.5 g, 2.2 mmol), isopropylamine (70 mL), and $AgPy_2MnO_4$ (0.83 g, 2.2 mmol). The yield was 495 mg (80%).

4-Butylamino-3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (4f). ***A.*** Compound **4f** was prepared analogously to **4d** from compound **5a** (227 mg, 1 mmol), butylamine (40 mL), and $AgPy_2MnO_4$ (385 mg, 1 mmol). The product was recrystallized from MeOH. The yield was 192 mg (64%).

B. A mixture of compound **5** (227 mg, 1 mmol), butylamine (40 mL), and $AgPy_2MnO_4$ (385 mg, 1 mmol) was kept at ~20 °C for 24 h and concentrated to dryness. After extraction with $CHCl_3$ and chromatography on a column with Al_2O_3 in $CHCl_3$, three fractions were collected. 3-Butyl-1-ethyl-6,8-dimethylpyrrolo[2′,3′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (**7d**) was isolated from the first yellow fraction with R_f 0.7 in a yield of 19 mg (6%) as bright-yellow needles, m.p. 118—119 °C (*cf.* lit. data[5]). Compound **4f** was isolated from the colorless fraction with R_f 0.60 in a yield of 178 mg (60%) as colorless crystals (after recrystallization from Pr^iOH). 3-Butylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**6d**) was isolated from the yellow fraction with R_f 0.25 in a yield of 3 mg (1%) as yellow crystals (after recrystallization from Pr^iOH), m.p. 148—150 °C. IR, ν/cm^{-1}: 3329 (N—H); 1712, 1670 (C=O). ^{1}H NMR, δ: 0.95 (t, 6 H, $(CH_2)_3\underline{Me}$, J = 7.3 Hz); 1.43 (m, 2 H, $(CH_2)_2C\underline{H}_2Me$); 1.66 (m, 2 H, $CH_2C\underline{H}_2CH_2Me$); 3.43 (m, 2 H, $C\underline{H}_2CH_2CH_2Me$); 3.46 (s, 3 H, N(6)Me); 3.77 (s, 3 H, N(8)Me); 4.87 (m, 1 H, NH); 7.31 (s, 1 H, H(4)).

Reaction of 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione 5a with cyclohexylamine and an oxidant. A solution of compound **5a** (227 mg, 1 mmol) in cyclohexylamine (40 mL) was stirred at 20 °C for 15 min and then $AgPy_2MnO_4$ (385 mg, 1 mmol) was added. The reaction mixture was stirred at 20 °C for 24 h and concentrated to dryness. After extraction with $CHCl_3$ and chromatography on a column with Al_2O_3 in $CHCl_3$, three fractions were collected. 3-Cyclohexyl-6,8-dimethyl-1,2-tetramethylenepyrrolo[2′,3′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (**7a**) was isolated from the yellow fraction with R_f 0.70 in a yield of 92 mg (25%) as yellow crystals (after recrystallization from Pr^iOH), m.p. 222—225 °C (*cf.* lit. data[7]). Compound **4g** was isolated from the colorless fraction with R_f 0.50 in a yield of 97 mg (30%) as colorless crystals (after recrystallization from Pr^iOH). Compound **6a** was isolated from the yellow fraction with R_f 0.30 in a yield of 12 mg (4%) as yellow crystals (after recrystallization from Pr^iOH), m.p. 210—211 °C (*cf.* lit. data[6]).

6,8-Dimethyl-3-piperidinopyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (8). A solution of compound **5a** (227 mg, 1 mmol) in piperidine (25 mL) was stirred at 20 °C for 15 min and then $AgPy_2MnO_4$ (385 mg, 1 mmol) was added. The reaction mixture was stirred at 20 °C for 24 h and concentrated to dryness. After extraction with hot $CHCl_3$, chromatography on a column with Al_2O_3 in $CHCl_3$, and recrystallization from Pr^iOH, compound **8** was obtained in a yield of 194 mg (68%) as bright-yellow crystals, m.p. 154—156 °C (*cf.* lit. data[3]).

Reaction of compound 5a with diethylamine and an oxidant. A solution of compound **5a** (227 mg, 1 mmol) in diethylamine (50 mL) was stirred at 20 °C for 15 min and then $AgPy_2MnO_4$ (385 mg, 1 mmol) was added. The reaction mixture was stirred at 20 °C for 2 weeks and concentrated to dryness. After extraction with $CHCl_3$ and chromatography on a column with Al_2O_3 in $CHCl_3$, two fractions were collected. 3-Ethyl-6,8-dimethylpyrrolo[2′,3′;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (**7b**) was isolated from the first yellow fraction with R_f 0.6 in a yield of 111 mg (43%) as bright-yellow needles (after recrystallization from Pr^iOH), m.p. 225—227 °C (*cf.* lit. data[5]). Compound **9** was isolated from the orange fraction with R_f 0.30 in a yield of 24 mg (15%) as orange crystals (after recrystallization from Pr^iOH), m.p. 135—137 °C. IR, ν/cm^{-1}: 1705, 1652 (C=O). ^{1}H NMR, δ: 1.31 (t, 6 H, $N(CH_2\underline{Me})_2$, J = 7.3 Hz); 3.40 (s, 3 H,

N(6)Me); 3.46 (q, 4 H, $N(C\underline{H}_2Me)_2$, J = 7.3 Hz); 3.72 (s, 3 H, N(8)Me); 7.03 and 8.46 (both d, 1 H each, CH, J = 13.4 Hz). MS, m/z (I_{rel} (%), peaks with I < 10% are omitted): 324 $[M + 1]^+$ (15), 323 $[M]^+$ (88), 308 $[M - Me]^+$ (10), 288 $[M - Cl]^+$ (33), 266 (11), 253 (73), 251 $[M - NEt_2]^+$ (89), 240 (11), 84 (100), 71 (23), 70 (20), 56 (55), 42 (10).

1,6,8-Trimethyl-3-propylpyrrolo[2´,3´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (7c). A solution of compound **5a** (227 mg, 1 mmol) in dipropylamine (30 mL) was stirred at 20 °C for 15 min and then $AgPy_2MnO_4$ (385 mg, 1 mmol) was added. The reaction mixture was stirred at 20 °C for 2 weeks and worked up as described above. After recrystallization from Pr^iOH, compound **7c** was obtained in a yield of 201 mg (71%) (R_f 0.65) as bright-yellow needles, m.p. 174—175 °C (*cf.* lit. data[5]).

3-Butyl-1-ethyl-6,8-dimethylpyrrolo[2´,3´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-dione (7d) was prepared analogously to **7c**, R_f 0.7, the yield was 155 mg (50%), bright-yellow needles, m.p. 118—119 °C (*cf.* lit. data[5]).

Synthesis of 1-R-2-R^1-6,8-dimethylpyrrolo[3´,2´;3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones (3a,b) (general procedure). A mixture of compound **4** (1 mmol), alkyne (1.5 mmol), K_2CO_3 (210 mg, 1.5 mmol), Pd_2dba_3 (18 mg, 0.02 mmol), PPh_3 (42 mg, 0.16 mmol), and CuI (10 mg, 0.05 mmol) in anhydrous DMF (3 mL) was stirred at 90—100 °C for 5 h under argon and concentrated to dryness. The residue was extracted with $CHCl_3$. The extract was concentrated to ~5 mL, chromatographed on a column with Al_2O_3, and eluted with $CHCl_3$. A pale-yellow fraction with R_f ~0.1—0.4 was collected. The product was recrystallized from MeOH. Compounds **3a** and **3b** were obtained in 21 and 84% yields, respectively.

Compound **3a**, cream-colored crystals, m.p. 272—274 °C. IR, ν/cm^{-1}: 3380 (N—H); 1713, 1687 (C=O). ^{1}H NMR, δ: 3.54 (s, 3 H, N(8)Me); 3.98 (s, 3 H, N(6)Me); 7.00 (s, 1 H, H(3)); 7.46—7.76 (m, 5 H, Ph); 10.00 (br.s, 1 H, NH).

Compound **3b**, pale-yellow crystals, m.p. 175—178 °C (*cf.* lit. data[2]).

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References

1. A. V. Gulevskaya, Dang Van Shee, and A. F. Pozharskii, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 1328 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 1403].
2. V. V. Goryunenko, A. V. Gulevskaya, and A. F. Pozharskii, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 422 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, ...441].
3. D. V. Besedin, A. V. Gulevskaya, and A. F. Pozharskii, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1161 [*Russ. Chem. Bull.*, 1999, **48**, 1150 (Engl. Transl.)].
4. R. M. Silverstein and G. C. Bassler, *Spectrometric Identification of Organic Compounds*, Wiley, New York, 1968, p. 144.
5. A. V. Gulevskaya, D. V. Besedin, A. F. Pozharskii, and Z. A. Starikova, *Tetrahedron Lett.*, 2001, **42**, 5981.
6. D. V. Besedin, A. V. Gulevskaya, and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 2000, 1403 [*Chem. Heterocycl. Compd.,* 2000, **36**, 1213 (Engl. Transl.)].
7. A. V. Gulevskaya, O. V. Serduke, A. F. Pozharskii, and D. V. Besedin, *Tetrahedron*, 2003, **59**, 7669.
8. H. Hara and H. C. van der Plas, *J. Heterocycl. Chem.,* 1982, **19**, 1527.
9. M. P. Groziak and L. M. Melcher, *Heterocycles*, 1987, **26**, 2905.
10. B. D. Palmer and W. A. Denny, *J. Chem. Soc., Perkin Trans. 1,* 1989, 95.
11. H. C. van der Plas, *Khim. Geterotsikl. Soedin.*, 1987, 1011 [*Chem. Heterocycl. Compd.,* 1987, **23**, 1015 (Engl. Transl.)].
12. O. N. Chupakhin, V. N. Charushin, and H. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, 1994.
13. A. V. Gulevskaya, A. F. Pozharskii, A. I. Chernyshev, and V. V. Kuz´menko, *Khim. Geterotsikl. Soedin.*, 1992, 1202 [*Chem. Heterocycl. Compd.,* 1992, **28**, 1015 (Engl. Transl.)].
14. S. Nishigaki, M. Ichiba, and K. Senga, *J. Org. Chem.*, 1983, **48**, 1628.

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