Purines, pyrimidines, and related fused systems

20.* Heterocyclizations of 6-alkynyl-1,3-dimethyllumazines. Synthesis of pyrrole and thiophene analogs of some natural pteridines

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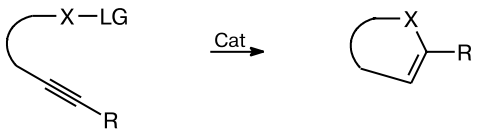
Sonogashira cross-coupling of 6-chloro-1,3-dimethyllumazine with terminal alkynes gave 6-alkynyl derivatives in good yields. Oxidative amination of the latter with primary alkylamines was accompanied by the pyrrole-ring closure to form 1-R′-2-R-6,8-dimethylpyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones. The addition of bromine to 6-alkynyllumazines afforded the corresponding dibromoalkenes whose treatment with sodium trithiocarbonate gave rise to 2-R-6,8-dimethylthieno[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones. The latter compounds are close analogs of the metabolite of molybdenum cofactor (molybdopterine).

Key words: 6-chloro-1,3-dimethyllumazine, alkynes, metal complex catalysis, Sonogashira reaction, 6-(alkyn-1-yl)-1,3-dimethyllumazines, oxidative amination, pyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones, thieno[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones.

Various acetylene derivatives became readily accessible due to considerable recent progress in metal complex catalysis.[2,3] These compounds are finding ever increasing use in organic synthesis for performing various heterocyclization reactions.[4—9] In the general case, heterocyclization proceeds according to Scheme 1 and requires a catalyst (a base, transition metal complex, or electrophile).

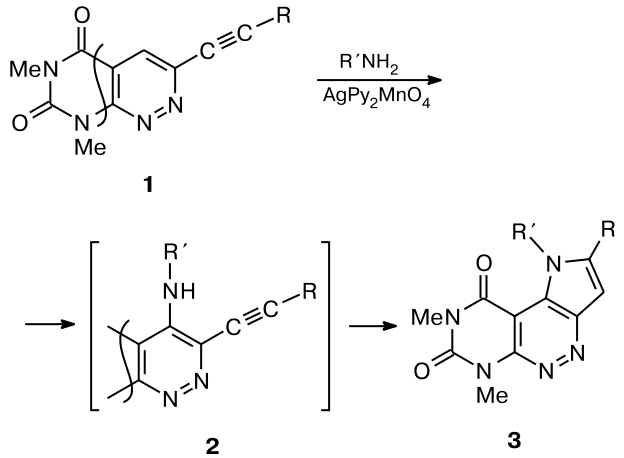
Scheme 1



X = N, O, S; LG = H or another leaving group;
Cat is a catalyst

Recently,[1] we have demonstrated that oxidative S_N^H-amination of 3-(alkyn-1-yl)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (**1**) with primary alkylamines afforded *o*-aminoacetylenes **2**, which underwent spontaneous cyclization to give 1-R′-2-R-6,8-dimethylpyrrolo[3′,2′:3,4]pyrimido[4,5-*c*]pyridazine-7,9(6*H*,8*H*)-diones (**3**) (Scheme 2). We believed that this method of the pyrrole-ring annelation would be particularly useful in the synthesis of isomeric pyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones (**4**), which can be considered as analogs of natural pteridines, for example, of the yellow pigment russupteridine (**5**)[10] and the metabolite of molybdenum cofactor, *viz.*, urothione (**6**).[11]

Scheme 2



1 **2** **3**

We used 6-chloro-1,3-dimethyllumazine (**7**) as the starting compound.[12] Its reactions with terminal alkynes

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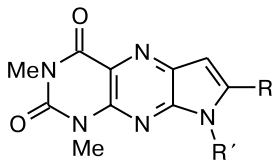

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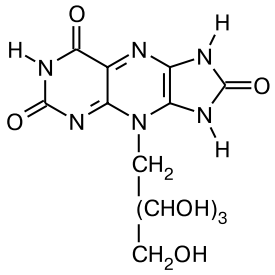

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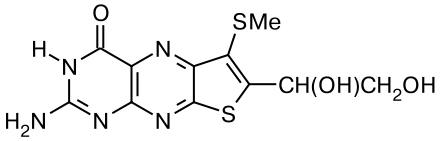
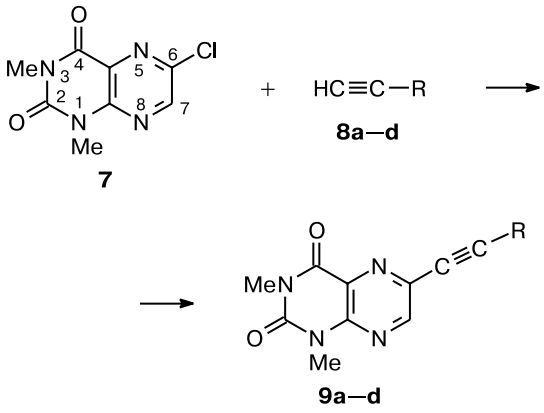


6

8a,b,d in DMF under an argon atmosphere in the presence of palladium complexes and catalytic amounts of CuI and K_2CO_3 afforded 6-(alkyn-1-yl) derivatives **9a,b,d** in 56—79% yields (Scheme 3). Cross-coupling of **7** with volatile trimethylsilylacetylene **8c** giving rise to **9c** was carried out in a sealed tube in the absence of a solvent using the Pd_2dba_3/PPh_3 system as the catalyst (dba is dibenzylideneacetone as the ligand) and Et_3N as the base.

Scheme 3



7 + HC≡C—R **8a—d** → **9a—d**

8, 9: R = Ph (**a**), *n*-C_6H_{13} (**b**), $SiMe_3$ (**c**), 1-piperidinocyclohexyl (**d**)

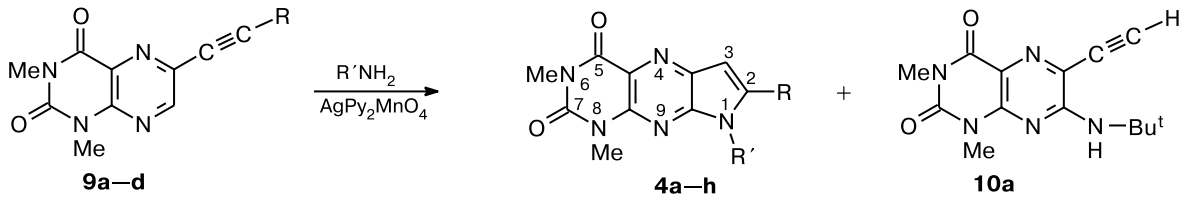
Reagents and conditions: Pd_2dba_3—PPh_3, K_2CO_3, CuI, DMF, 90—100 °C, Ar.

The structures of hetarylacetylenes **9** were confirmed by the data of spectroscopy and elemental analysis (Tables 1 and 2). Compounds **9** are virtually colorless (λ_{max} 353—369 nm). Their IR spectra each have a low-intensity absorption band at 2167—2207 cm^{-1} (ν(C≡C)). The ^1H NMR spectra show singlets of two *N*-methyl groups at δ ~3.5 and ~3.7 and signals of the alkynyl fragment and the H(7) proton at δ 8.6—8.7. The mass spectra of hetarylacetylenes **9** show molecular ion peaks with the intensities of 30—100%.

Oxidative amination of 6-(alkyn-1-yl)lumazines **9a,b** with primary alkylamines in the presence of $AgPy_2MnO_4$ at 20 °C afforded 1-R′-2-R-6,8-dimethylpyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones (**4a—f**) in 32—75% yields (Scheme 4). Treatment of trimethylsilylacetylene **9c** with propylamine gave rise not to the expected pyrrole but to its desilylation product **4g** in 74% yield. Compounds **9a,b** did not react with KNH_2 in liquid ammonia in the presence of $KMnO_4$ at temperatures from −60 to −55 °C. Under these conditions, trimethylsilyl derivative **9c** underwent, apparently, desilylation and polymerization.

Evidently, the ease of oxidative amination and subsequent heterocyclization of hetarylacetylenes **9** depends on the bulkyness of the amine used and the nature of the substituent R. Thus, the reactions of **9a,b** with *tert*-butylamine required a longer reaction time and gave products in low yields (see Table 1). The reactions of *tert*-butylamine with compound **9c** afforded a mixture of pyrrole **4h** and *o*-aminoacetylene **10a** (R = H, R′ = Bu^t) in a ratio of 1 : 0.85, which we failed to separate.

Scheme 4



9a—d → (R′NH_2, $AgPy_2MnO_4$) **4a—h** + **10a**

4	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R	Ph	Ph	Ph	Ph	*n*-C_6H_{13}	*n*-C_6H_{13}	H	H
R′	Pr^n	Pr^i	Bu^n	Bu^t	Pr^n	Bu^t	Pr^n	Bu^t

Table 1. Physicochemical characteristics and elemental analysis data for the compounds synthesized

Compound	R	R´	τ^a	Yield (%)	M.p. /°C	R_f	Found / Calculated (%)			Molecular formula
							C	H	N	
4a	Ph	Pr^n	10 min	75	156—157	0.40	65.57 65.33	5.30 5.44	19.83 20.06	$C_{19}H_{19}N_5O_2$
4b	Ph	Pr^i	1.5 h	68	182—184	0.35	65.16 65.33	5.32 5.44	20.23 20.06	$C_{19}H_{19}N_5O_2$
4c	Ph	Bu^n	6 h	65	136—138	0.30	66.25 66.12	5.69 5.79	19.43 19.28	$C_{20}H_{21}N_5O_2$
4d	Ph	Bu^t	7 days	38	209—211	0.30	66.33 66.12	5.58 5.79	19.23 19.28	$C_{20}H_{21}N_5O_2$
4e	*n*-C_6H_{13}	Pr^n	10 min	68	109—112	0.35	64.00 63.87	7.70 7.56	19.54 19.61	$C_{19}H_{27}N_5O_2$
4f	*n*-C_6H_{13}	Bu^t	7 days	32	182—183	0.25	64.83 64.69	7.53 7.82	18.72 18.87	$C_{20}H_{29}N_5O_2$
4g	H	Pr^n	10 min	74	180—182	0.30	57.30 57.14	5.27 5.49	25.76 25.64	$C_{13}H_{15}N_5O_2$
4i	Ph	Me	—	81	227—229	0.40	63.43 63.55	4.89 4.67	21.63 21.81	$C_{17}H_{15}N_5O_2$
9a	Ph	—	2 h	69	221—223	0.60	265.64 65.75	4.17 4.11	19.31 19.18	$C_{16}H_{12}N_4O_2$
9b	*n*-C_6H_{13}	—	2 h	79	84—87	0.65	64.03 64.00	6.55 6.67	18.93 18.67	$C_{16}H_{20}N_4O_2$
9c	$SiMe_3$	—	2 h	56	112—115	0.85	54.25 54.17	5.39 5.56	19.59 19.44	$C_{13}H_{16}N_4O_2Si$
9d	1-Piperidino-cyclohexyl	—	45 min	63	191—193	0.30	66.36 66.14	7.21 7.09	18.53 18.37	$C_{21}H_{27}N_5O_2$
11[b]	—	—	—	—	—	—	42.45 42.27	2.51 2.65	27.58 27.40	$C_9H_{10}N_5O_2Cl$
13	—	—	—	—	—	—	67.82 67.67	5.11 5.26	21.23 21.05	$C_{15}H_{14}N_4O$
14	—	—	—	—	—	—	63.79 63.91	5.50 5.33	16.75 16.57	$C_{18}H_{18}N_4O_3$
16a[c]	Ph	—	—	70	213—216	0.75	42.34 42.48	2.61 2.65	12.57 12.39	$C_{16}H_{12}Br_2N_4O_2$
16b[d]	*n*-C_6H_{13}	—	—	70	[e]	0.75	41.56 41.74	4.22 4.35	12.34 12.17	$C_{16}H_{20}Br_2N_4O_2$
16c[f]	$SiMe_3$	—	—	88	104—106	0.90	35.01 34.82	3.45 3.57	12.81 12.50	$C_{13}H_{16}Br_2N_4O_2Si$
17a[g]	Ph	—	—	61	316—319	0.60	59.29 59.26	3.42 3.70	17.41 17.28	$C_{16}H_{12}N_4O_2S$
17b[h]	*n*-C_6H_{13}	—	—	58	175—177	0.65	57.68 57.83	6.27 6.02	16.70 16.87	$C_{16}H_{20}N_4O_2S$

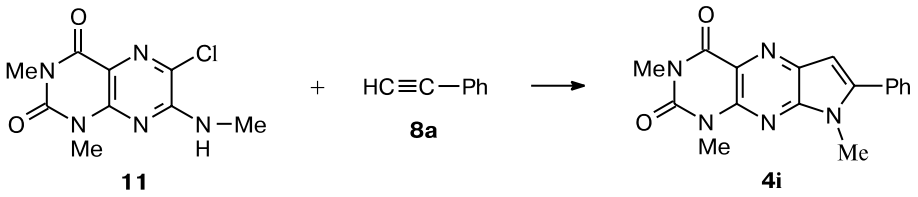
[a] Reaction time.
[b] Found (%): Cl, 13.75. Calculated (%): Cl, 13.89.
[c] Found (%): Br, 35.23. Calculated (%): Br, 35.40.
[d] Found (%): Br, 34.91. Calculated (%): Br, 34.78.
[e] The compound was prepared as an oil.
[f] Found (%): Br, 35.67. Calculated (%): Br, 35.71.
[g] Found (%): S, 10.04. Calculated (%): S, 9.88.
[h] Found (%): S, 9.47. Calculated (%): S, 9.64.

Apparently, the transformation **9** → **4** resulted from spontaneous heterocyclization of intermediate *o*-aminohetarylacetylenes **10**. This is evidenced by the fact that cross-coupling of 6-chloro-7-methylaminolumazine **11** with phenylacetylene performed under the above-described conditions afforded exclusively pyrrole **4i** in 81%

Table 2. Spectroscopic data for 6-(alkyn-1-yl)-1,3-dimethyllumazines **9**

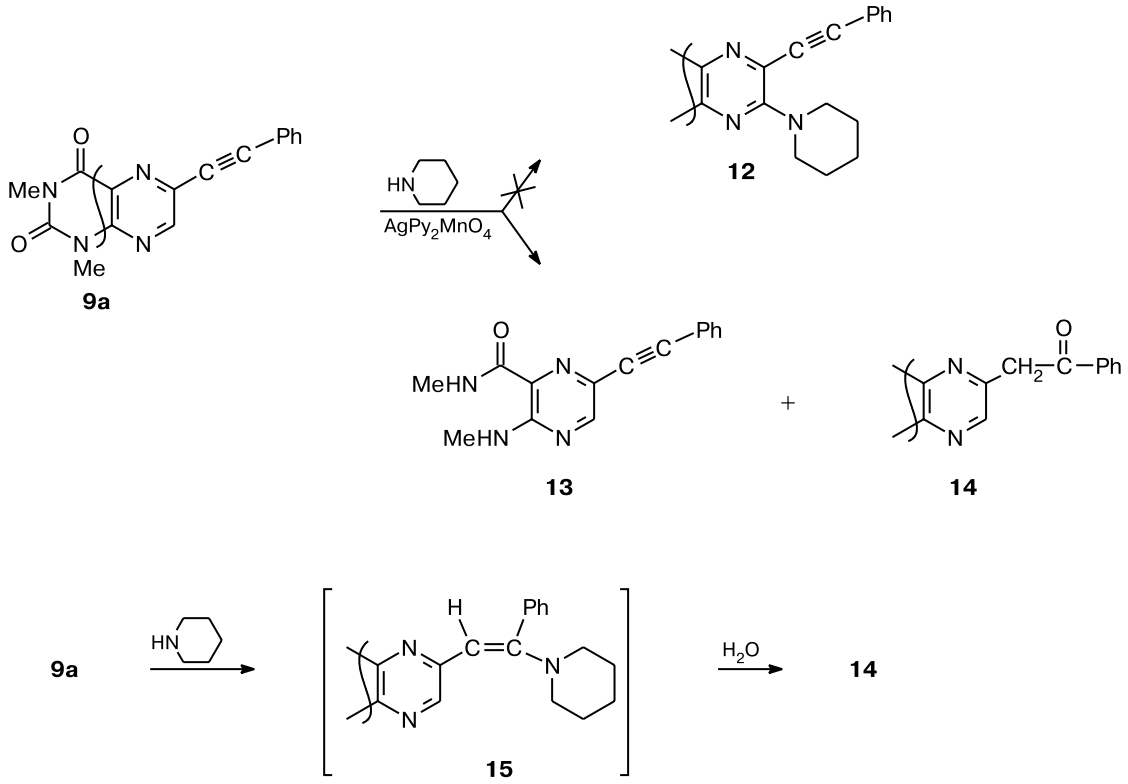
Compound	MS, *m/z*	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)			IR, ν/cm^{-1}		UV, λ_{max}/nm (logε)
		N—Me	H(7)	R	C=O	C≡C	
9a	292	3.54; 3.71	8.75	7.39 (m, 3 H, Ph); 7.60 (m, 2 H, Ph)	1671, 1720	2207	259 (4.05), 297 (4.41), 303 (4.41), 369 (4.41)
9b	300	3.52; 3.68	8.60	0.88 (t, 3 H, Me, *J* = 6.8); 1.26—1.32 (m, 4 H, $(CH_2)_3(C\underline{H}_2)Me$); 1.40—1.46 (m, 2 H, $(CH_2)_2C\underline{H}_2C_3H_7$); 1.56—1.65 (m, 2 H, $CH_2C\underline{H}_2C_4H_9$); 2.45 (t, 2 H, $C\underline{H}_2C_5H_{11}$, *J* = 7.2)	1673, 1720	2200	277 (4.26), 281 (4.26), 358 (3.93)
9c	288	3.51; 3.68	8.65	0.26 (s, 9 H, $SiMe_3$)	1673, 1723	2167	285 (4.29), 357 (3.99)
9d	381	3.48; 3.65	8.61	1.23—1.80 (m, 12 H, H_γ, H_β piperidino and cyclohexyl); 2.06 (m, 4 H, cyclohexyl); 2.61 (m, 4 H, H_α piperidino)	1692, 1727	2212	259 (4.22), 282 (4.26), 353 (3.97)

Scheme 5



Reagents and conditions: Pd_2dba_3—PPh_3, K_2CO_3, CuI, DMF, 90—100 °C, Ar.

Scheme 6



yield (Scheme 5). However, treatment of acetylene **9a** with piperidine in the presence of an oxidizer gave rise not to the expected amino derivative **12** but to carboxamide **13** as the product of uracil-ring opening (7.5% yield) and ketone **14** (10%) (Scheme 6). The formation of the latter can be considered as a result of hydrolysis of enamine **15**. The ability of acetylenes to add amines giving enamines is well known.[13] As regards the transformation of pteridinedione **9a** into compound **13**, it should be noted that the uracil-ring opening under the action of nucleophiles is one of the most widespread reactions of uracil-containing compounds.[14]

The physicochemical characteristics of pyrroles **4** are given in Tables 1 and 3. Pyrroles **4** are pale-yellow compounds (λ_{max} 343—381 nm). Their IR spectra have absorption bands at 1650—1710 cm^{-1} (ν(C=O)). The ^1H NMR spectra show a signal for the H(3) proton of the pyrrole ring at δ 6.54—6.82 characteristic of fused pyrroles.[15] The protons of the α-CH_2 groups and the α-CH substituent at N(1) in compounds **4** are deshielded by the N(9) aza group and are observed at low field (δ 4.18—4.67). The mass spectra of pyrroles **4** show molecular ion peaks, which are most intense in the spectra of **4a—c,g**.

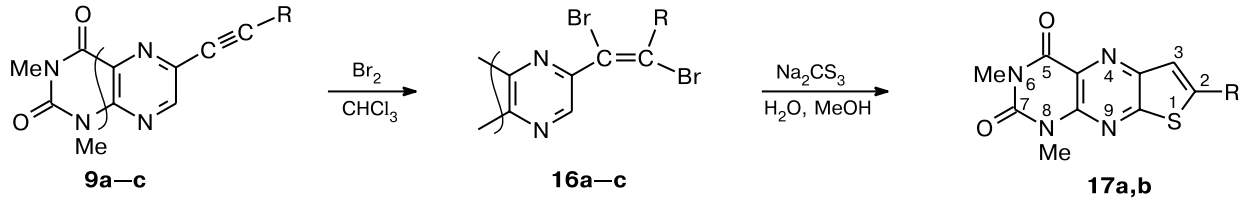
As mentioned above, the structure of urothione is based on thieno[3,2-*g*]pteridine. We attempted to annelate the thiophene ring to 6-alkynyllumazines **9** according to a procedure reported recently.[16] This method involves

Table 3. Spectroscopic data for 1-R′-2-R-6,8-dimethylpyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones **4a—g,i**

Compound	MS, *m/z*	^1H NMR ($CDCl_3$), δ (*J*/Hz)					IR, ν(C=O) /cm^{-1}	UV, λ_{max}/nm (logε)
		N—Me	H(3)	R′		R		
				NCH_2(NCH)	Other groups			
4a	349	3.57; 3.78	6.82	4.29 (t, 2 H, *J* = 7.4)	0.76 (t, 3 H, Me, *J* = 7.5); 1.69 (m, 2 H, $CH_2C\underline{H}_2Me$)	7.52 (s, 5 H, Ph)	1673, 1708	266 (4.41), 344 (4.04), 378 (4.14)
4b	349	3.58; 3.79	6.76	4.67 (sept, 1 H, *J* = 6.9)	1.71 (d, 6 H, $CH\underline{Me}_2$, *J* = 6.8)	7.47—7.54 (m, 5 H, Ph)	1665, 1703	261 (4.37), 343 (3.99), 378 (4.07)
4c	363	3.57; 3.78,	6.81	4.33 (t, 2 H, *J* = 7.3)	0.80 (t, 3 H, Me, *J* = 7.3); 1.17 (m, 2 H, $(CH_2)_2C\underline{H}_2Me$); 1.63 (m, 2 H, $CH_2C\underline{H}_2C_2H_5$)	7.50—7.55 (m, 5 H, Ph)	1659, 1705	266 (4.37), 344 (3.99), 378 (4.11)
4d	363	3.57; 3.78	6.64	—	1.66 (s, 9 H, Bu^t)	7.43 (s, 5 H, Ph)	1653, 1703	270 (4.30), 340 (3.97), 371 (3.96)
4e	357	3.55; 3.75	6.54	4.18 (t, 2 H, *J* = 7.4)	0.94 (t, 3 H, Me, *J* = 7.4); 1.81 (m, 2 H, $CH_2C\underline{H}_2Me$)	0.89 (t, 3 H, Me, *J* = 6.9); 1.31—1.48 (m, 8 H, $CH_2(C\underline{H}_2)_4Me$); 2.78 (t, 2 H, $C\underline{H}_2C_5H_{11}$, *J* = 7.6)	1660, 1700	270 (4.18), 340 (3.96), 365 (3.91)
4f	371	3.55; 3.72	6.59	—	1.91 (s, 9 H, Bu^t)	0.89 (t, 3 H, Me, *J* = 7.0); 1.29—1.48 (m, 6 H, $(CH_2)_2(C\underline{H}_2)_3Me$); 1.70—1.82 (m, 2 H, $CH_2C\underline{H}_2C_4H_9$); 3.00 (t, 3 H, $C\underline{H}_2C_5H_{11}$, *J* = 7.7)	1660, 1700	271 (4.21), 339 (3.95), 366 (3.90)
4g	273	3.55; 3.75	6.82 (d, 1 H, *J* = 3.8)	4.22 (t, 2 H, *J* = 7.1)	0.93 (t, 3 H, Me, *J* = 7.4); 1.91 (m, 2 H, $CH_2C\underline{H}_2Me$)	7.53* (d, 1 H, *J* = 3.8)	1660, 1699	262 (4.09), 343 (3.98)
4i	321	3.57; 3.79	6.85	—	3.81 (c, 3 H, Me)	7.50—7.60 (m, 5 H, Ph)	1665, 1711	267 (4.40), 343 (3.98), 381 (4.14)

* The chemical shift of H(2).

Scheme 7



16, 17: R = Ph (**a**), *n*-C_6H_{13} (**b**), $SiMe_3$ (**c**)

the addition of bromine to the triple bond of hetarylacetylene followed by vicarious nucleophilic substitution of hydrogen under the action of sodium trithiocarbonate.

We found that 6-alkynyllumazines **9a—c** readily added bromine in a solution in $CHCl_3$ to give dibromovinyl derivatives **16a—c** (Scheme 7, Table 4). The reactions of compounds **9a,b** afforded the only stereoisomer (apparently, the *E* isomer). The reaction of **9c** with bromine gave a mixture of *E*- and *Z*-dibromides **16c** in a ratio of 2.7 : 1. The resulting mixture was not separated because both isomers can be used in the reaction with Na_2CS_3.

The reactions of compounds **16a,b** with sodium trithiocarbonate in an aqueous-methanolic solution afforded 2-R-6,8-dimethylthieno[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones (**17a,b**) in 58—61% yields. The reaction of **16c** with Na_2CS_3 gave rise to a complex mixture of products due, apparently, to rapid desilylation of the starting compound followed by polymerization.

Thienopteridines **17** (see Table 4) are yellow compounds (λ_{max} 374—392 nm). Their IR spectra have absorption bands of the C=O groups at 1657—1717 cm^{-1}. The ^1H NMR spectra show signals for the protons of two N—Me groups (δ 3.5 and 3.8) and the substituent R as well as a signal for the H(3) proton at δ 7.26—7.79 characteristic of fused thiophenes.[15] The mass spectra of compounds **16** have two molecular ion peaks corresponding to the ^{32}S and ^{34}S isotopes with the intensity ratio of 100 : 4. The intensities of the $[M - S]^+$ and $[M - SH]^+$ ions typical of the fragmentation of thiophenes are < 5%.[15]

To summarize, we developed an efficient approach to pyrrolo- and thieno[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones involving the synthesis of 6-alkynylpteridines under the conditions of the Sonogashira reaction followed by nucleophilic substitution of hydrogen in alkynyl derivatives or their dibromination products.

Experimental

The IR spectra were recorded on a Specord IR-71 instrument in Nujol mulls. The ^1H NMR spectra were measured on

Table 4. Spectroscopic data for 6-(2-R-1,2-dibromovinyl-1)-1,3-dimethyllumazines **16** and 2-R-6,8-dimethylthieno[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones **17**

Compound	MS, *m/z*	^1H NMR ($CDCl_3$), δ (*J*/Hz)			IR, ν(C=O) /cm^{-1}	UV, λ_{max}/nm (logε)
		N—Me	H arom.	R		
16a	—	3.55, 3.75	8.86	7.37—7.47 (m, 3 H, Ph); 7.54—7.58 (m, 2 H, Ph)	1680, 1727	—
16b	—	3.52, 3.71	8.67	0.89 (t, 3 H, Me, *J* = 6.7); 1.30—1.50 (m, 6 H, $CH_2(C\underline{H}_2)_3C_2H_5$); 1.60—1.75 (m, 2 H, $CH_2C\underline{H}_2C_4H_9$); 2.85 (t, 2 H, $C\underline{H}_2C_5H_{11}$, *J* = 7.6)	1677, 1721	—
16c	—	3.53, 3.71 (*E*) 3.53, 3.71 (*Z*)	8.78 (*E*), 8.63 (*Z*)	0.03 (s, 9 H, $SiMe_3$) (*E*); 0.43 (s, 9 H, $SiMe_3$) (*Z*)	1673, 1721	—
17a	324	3.58, 3.79	7.79	7.45—7.52 (m, 3 H, Ph); 7.72—7.75 (m, 2 H, Ph)	1660, 1713	259 (4.28), 291 (4.42), 392 (4.19)
17b	332	3.55, 3.74	7.26	0.87 (t, 3 H, Me, *J* = 7.0); 1.28—1.42 (m, 6 H, $(CH_2)_2(C\underline{H}_2)_3Me$); 1.71—1.82 (m, 2 H, $CH_2C\underline{H}_2C_4H_9$); 2.96 (t, 3 H, $C\underline{H}_2C_5H_{11}$, *J* = 7.5)	1673, 1717	276 (4.32), 329 (3.57), 374 (3.90)

Bruker-250 (250 MHz) and Unity-300 (300 MHz) spectrometers with Me_4Si as the internal standard. The UV spectra were recorded on a Specord M-40 instrument in $CHCl_3$. The mass spectra were obtained on an MKh-1321A spectrometer. Chromatography was carried out on Al_2O_3 (Brockmann activity III—IV) using chloroform as the eluent; visualization was carried out with iodine vapor. The melting points were measured in glass tubes on a PTP instrument (an instrument for measurements of melting points manufactured at the Khimlaborpribor Joint-Stock Company, Russia) and were not corrected.

The physicochemical characteristics and elemental analysis data for the compounds synthesized are given in Table 1. The spectroscopic data are listed in Tables 2—4.

Synthesis of 6-(alkyn-1-yl)-1,3-dimethyllumazines (9a,b,d) (general procedure). A mixture of compound **7** (1 mmol), alkyne **8** (1.25 mmol), K_2CO_3 (1.5 mmol), Pd_2dba_3 (0.02 mmol), PPh_3 (0.16 mmol), and CuI (0.05 mmol) in anhydrous DMF (3 mL) was stirred at 90—100 °C under argon (reactions times are given in Table 1). The reaction mixture was concentrated to dryness and 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 $CHCl_3$. The colorless fraction was collected (R_f are listed in Table 1). The product was recrystallized from Pr^iOH.

1,3-Dimethyl-6-trimethylsilylethynyllumazine (9c). A mixture of compound **7** (227 mg, 1 mmol), trimethylsilylacetylene (0.2 mL, 1.2 mmol), Pd_2dba_3 (20 mg, 0.02 mmol), CuI (10 mg, 0.05 mmol), PPh_3 (42 mg, 0.16 mmol), and Et_3N (7 mL) was heated in a sealed tube under argon at 100 °C for 2 h and then treated as described above. The product was recrystallized from MeOH.

Synthesis of 1-R´-2-R-6,8-dimethylpyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones (4a—g) (general procedure). A solution of compound **9** (1 mmol) in amine (30—40 mL) was stirred at 20 °C for 15 min and then $AgPy_2MnO_4$ (1 mmol) was added. The completion of the reaction was monitored by chromatography (reaction times are given in Table 1). The reaction mixture was concentrated to dryness and 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 $CHCl_3$. The first yellow fraction was collected (R_f are listed in Table 1). The product was recrystallized from Pr^iOH.

1,6,8-Trimethyl-2-phenylpyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)-dione (4i). A mixture of compound **11** (128 mg, 0.5 mmol), phenylacetylene (0.15 mL, 0.75 mmol), K_2CO_3 (105 mg, 0.75 mmol), Pd_2dba_3 (9 mg, 0.01 mmol), PPh_3 (20 mg, 0.08 mmol), and CuI (5 mg, 0.025 mmol) in anhydrous DMF (3 mL) was stirred under argon at 90—100 °C for 2 h. The reaction mixture was concentrated to dryness and 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 $CHCl_3$. The bright-yellow fraction with R_f 0.40 was collected. The product was recrystallized from Pr^iOH. The physicochemical characteristics of compound **4i** are given in Tables 1 and 3.

Reaction of 1,3-dimethyl-6-(2-phenylethyn-1-yl)lumazine (9a) with piperidine in the presence of an oxidizer. A solution of compound **9a** (292 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 kept at 20 °C for one week and then 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 $CHCl_3$. The yellow fraction with R_f 0.70 was collected and concentrated to obtain *N*-methylamide of 3-methylamino-6-(2-phenylethynyl)pyrazine-2-carboxylic acid (**13**) in a yield of 20 mg (7.5%) as yellow crystals, m.p. 101—103 °C (from Pr^iOH). IR, ν/cm^{-1}: 3400, 3380, 3313 (N—H); 2207 (C≡C); 1656 (C=O). ^1H NMR ($CDCl_3$), δ: 2.97 (d, 3 H, NHMe, J = 5.1 Hz); 3.06 (d, 3 H, NHMe, J = 5.0 Hz); 7.32—7.57 (m, 5 H, Ph); 7.91 (m, 1 H, NH); 8.38 (s, 1 H, H(7)); 8.86 (m, 1 H, NH).

6-Benzoylmethyl-1,3-dimethyllumazine (**14**) was obtained from the orange fraction with R_f 0.50 in a yield of 31 mg (10%) as orange crystals with t.decomp. 165 °C (from Pr^iOH). IR, ν/cm^{-1}: 1703, 1659, 1650 (C=O). ^1H NMR ($CDCl_3$), δ: 3.54 (s, 3 H, N(1)Me); 3.75 (s, 3 H, N(3)Me); 4.72 (s, 2 H, CH_2); 7.47—7.65 (m, 3 H, Ph); 8.02—8.05 (m, 2 H, Ph); 8.67 (s, 1 H, H(7)).

6-Chloro-1,3-dimethyl-7-methylaminolumazine (11). A solution of compound **7** (454 mg, 2 mmol) in methylamine (50 mL) was stirred at the temperature from −65 to −55 °C for 10 min. Then $KMnO_4$ (306 mg, 2 mmol) was added. The reaction mixture was stirred at this temperature for 10 min and then concentrated to dryness. The residue was extracted with hot Pr^iOH (30 mL). The extract was concentrated to dryness and the product was recrystallized from Pr^iOH. Compound **11** was obtained in a yield of 400 mg (78%) as colorless crystals, m.p. > 300 °C. IR, ν/cm^{-1}: 3353 (N—H); 1708, 1649 (C=O). ^1H NMR ($CDCl_3$), δ: 3.15 (d, 3 H, NHMe, J = 4.8 Hz); 3.46 (s, 3 H, N(1)Me); 3.62 (s, 3 H, N(3)Me); 6.01 (br.s, 1 H, NH).

Synthesis of 6-(2-R-1,2-dibromovinyl-1)-1,3-dimethyllumazines (16) (general procedure). Bromine (1.3 mmol) was added portionwise to a solution of compound **9** (1 mmol) in $CHCl_3$ (3 mL). The reaction mixture was stirred at ~20 °C for 2 h 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 $CHCl_3$. The yellow fraction with R_f 0.75 was collected. The product was recrystallized from Pr^iOH.

Synthesis of 2-R-6,8-dimethylthieno[3,2-*g*]pteridine-5,7(6*H*,8*H*)-diones (17) (general procedure). A solution of compound **16** (1 mmol) in MeOH (30 mL) was heated to boiling, a 30% Na_2CS_3 solution (5 mL) was added, and the mixture was stirred at this temperature for 1 h (in the case of compound **16b**, at 20 °C for 30 min). The completion of the reaction was monitored by chromatography. The reaction mixture was concentrated to dryness and 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 $CHCl_3$. The colorless fraction was collected (R_f are given in Table 1). The product was recrystallized from Pr^iOH.

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