New, Convenient Synthesis of 2-Alkyl- and 2-Vinylpyrazolo[3,4-*d*]-pyrimidine Derivatives (1)

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Treatment of 1,3-dimethyl-6-hydrazinouracil with the appropriate dimethylformamide dialkylacetal afforded the corresponding 2-alkyl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)diones. The reaction of 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)uracils with dimethylformamide dimethylacetal or triethyl orthoformate gave the corresponding 5,7-dimethyl-2-vinylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones, respectively. Similarly, treatment of 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)uracils with triethyl orthopropionate yielded the corresponding 5,7-dimethyl-3-ethyl-2-vinylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones.

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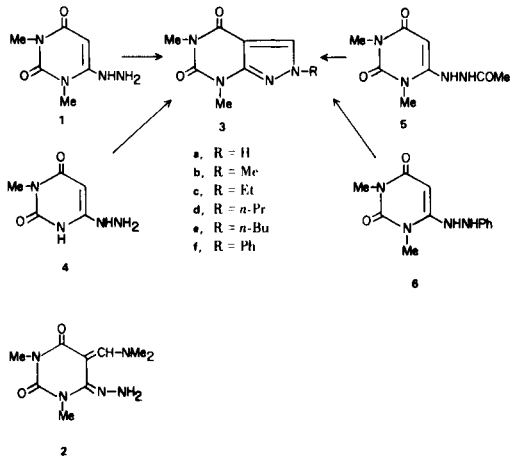
Recently, considerable interest has been devoted on the derivatives of pyrazolo[3,4-*d*]pyrimidine as potential purine antagonists (2), and several synthetic routes to this ring system have been developed (3-10). We now wish to report new, convenient synthetic approaches to 2-alkyl- and 2-vinyl derivatives of pyrazolo[3,4-*d*]pyrimidine which is isomeric with theophylline.

Synthesis of 2-Alkyl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones.

Heating 1,3-dimethyl-6-hydrazinouracil (**1**) (11) with an excess of dimethylformamide dimethylacetal (DMFDMA) at 150° for 1.5 hours afforded a good yield of 2,5,7-trimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (**3b**), which was identical with an authentic sample (5) (12). Likewise, treatment of **1** with other dimethylformamide dialkylacetals under the same conditions described above gave the corresponding 2-alkylpyrazolo[3,4-*d*]pyrimidine derivatives (**3c-e**).

The conversion of **1** into **3b-e** apparently involves the initial formation of 5-dimethylaminomethylene intermediate (**2**) followed by cyclization accompanying the loss of dimethylamine to give 5,7-dimethylpyrazolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)dione (**3a**) (5) and subsequent alkylation (13). In fact, the reaction of **1** with DMFDMA at the diminished temperature (90°) afforded the second intermediate **3a** and subsequent treatment of **3a** with DMFDMA at the elevated temperature (150°) furnished **3b**. Compound **3b** could also be prepared by the reaction of 6-hydrazino-3-methyluracil (**4**) (14) or 6-acetylhydrazino-1,3-dimethyluracil (**5**) (15) with DMFDMA at 150° for 1.5 hours, respectively (Table I). When 1,3-dimethyl-6-phenylhydrazinouracil (**6**) (6) was used as a starting material, 5,7-dimethyl-2-phenylpyrazolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)dione (**3f**) (6) was obtained in high yield (Scheme I).

Scheme I



In general, 2-alkylpyrazolo[3,4-*d*]pyrimidines have been prepared either by the construction of 2-alkylpyrazole precursors followed by pyrimidine ring closure or by the alkylation of preformed pyrazolo[3,4-*d*]pyrimidines (3) (5-6), however, we considered that the reaction of **1** with dimethylformamide dialkylacetals offering a strikingly simple route to these derivatives since the cyclization and alkylation could be achieved in a single operation.

Synthesis of 5,7-Dimethyl-2-vinylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones.

The key intermediates, 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)uracils (**7a-e**), were prepared by the condensation of **1** with the respective acetophenones according to the reported procedure (16).

Heating **7a** with an excess of DMFDMA at 90° for 30 minutes provided 5,7-dimethyl-2-(1-phenylvinyl)pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (**9a**) in good yield. The structure of **9a** was assigned by the elemental analysis and molecular weight determination by mass spectrometry, and confirmed by nmr spectrum. The nmr spectrum revealed two protons of the 1-phenylvinyl group at the position 2 and a single aromatic proton at the position 3. This reaction was equally applicable to other 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)uracils (**7b-e**) to give the corresponding 2-vinylpyrazolo[3,4-*d*]-pyrimidine derivatives (**9b-e**).

Table I

2-Alkyl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones

Compound (a)	M.p. (°C)	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
3a	280-281 (b)	66	46.66	4.48	31.10	$C_7H_8N_4O_2$	46.87	4.52	30.98
3b	202-204 (c)	82 (d), 42 (e), 37 (f), 90 (g)	49.48	5.19	28.85	$C_8H_{10}N_4O_2$	49.21	5.05	29.08
3c	187-188	73	51.91	5.81	26.91	$C_9H_{12}N_4O_2$	51.80	5.73	27.12
3d	153-155	61	54.04	6.35	25.21	$C_{10}H_{14}N_4O_2$	53.68	6.39	24.89
3e	120-121	61	55.91	6.83	23.72	$C_{11}H_{16}N_4O_2$	55.62	6.83	23.46

(a) All compounds were recrystallized from ethanol. (b) Lit. (5) m.p. 277-279°. (c) Lit. (5) m.p. 202-203°. (d) From **1**. (3) From **4**. (f) From **5**. (g) From **3a**.

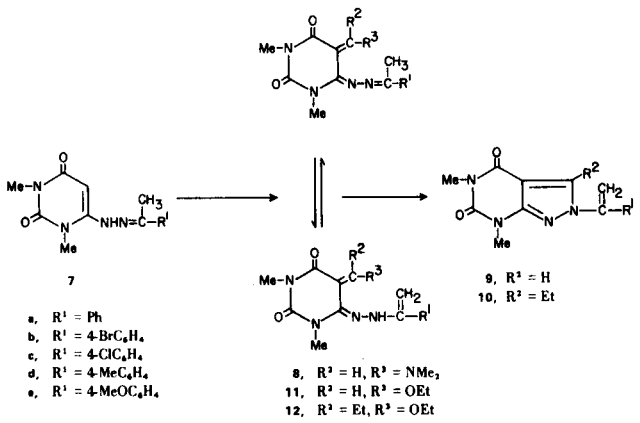
Table II

5,7-Dimethyl-2-vinylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones

Compound (a)	M.p. (°C)	Yield (%)	Synthetic method (b)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
9a	148-149	60	A	63.82	5.00	19.85	$C_{15}H_{14}N_4O_2$	63.59	5.13	19.98
		55	B							
		7	C							
9b	198-200	60	A	49.85	3.62	15.52	$C_{15}H_{13}BrN_4O_2$	49.69	3.57	15.57
		74	B							
		36	C							
9c	210	98	A	56.85	4.14	17.69	$C_{15}H_{13}ClN_4O_2$	56.93	4.21	17.82
		99	B							
		10	C							
9d	200-201	98	A	64.85	5.44	18.91	$C_{16}H_{16}N_4O_2$	64.72	5.47	19.16
		96	B							
		7	C							
9e	186-188	33	A	61.53	5.16	17.94	$C_{16}H_{16}N_4O_3$	61.43	5.24	18.09
		55	B							
		3	C							
10a	134-135	44	D	65.79	5.85	18.05	$C_{17}H_{18}N_4O_2$	65.52	5.89	17.99
10b	135-136	56	D	51.95	4.58	14.60	$C_{17}H_{17}BrN_4O_2$	51.72	4.60	14.34
10c	153-154	32	D	59.19	4.97	16.26	$C_{17}H_{17}ClN_4O_2$	59.05	5.02	16.37
10d	130-131	26	D	66.65	6.22	17.27	$C_{18}H_{20}N_4O_2$	66.84	6.30	17.57
10e	126-127	15	D	63.51	5.92	16.46	$C_{18}H_{20}N_4O_3$	63.25	5.77	16.79

(a) All compounds were recrystallized from ethanol. (b) A, cyclization with DMFDMA; B, cyclization with triethyl orthoformate; C, cyclization with dimethylformamide-phosphorus oxychloride; D, cyclization with triethyl orthopropionate.

Scheme II



The cyclization of **7a-e** to **9a-e** involves the initial formation of 5-dimethylaminomethylene intermediates (**8a-e**), followed by the tautomerization and subsequent cyclization by the elimination of dimethylamine. When **7a** was treated with DMFDMA at room temperature for 30 minutes, **8a** was isolated. The structure of **8a** was assigned by the elemental analysis as well as spectral data and established by its thermal cyclization to **9a** by reflux in dimethylformamide for 2 hours.

2-Vinylpyrazolo[3,4-*d*]pyrimidines **9a-e** could also be prepared by refluxing the compounds **7a-e** with triethyl orthoformate for 1 hour in similar yields. These cyclizations were also achieved by treatment with dimethylformamide-phosphorus oxychloride (Vilsmeier reagent) at 90° for 3 hours, albeit in lower yields. The former method is particularly suitable for the introduction of an alkyl group at the position 3 of 2-vinylpyrazolo[3,4-*d*]-pyrimidines. For example, refluxing of compounds **7a-e** with triethyl orthopropionate for 3 hours gave the desired 5,7-dimethyl-3-ethyl-2-(1-phenylvinyl)pyrazolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)diones (**10a-e**) (Table II). In the cases of **7b** and **7c**, a small amount of the corresponding 1,3-dimethyl-6-ethoxy-4-(α-methylbenzylidenehydrazino)-pyrimidine-2(1*H*,3*H*,4*H*)ones (**13a** and **13b**) were formed. The structures of **13** were established by the unequivocal synthesis. Namely, treatment of the appropriate **7** with phosphorus oxychloride at reflux for 1 hour gave 6-chloro-1,3-dimethyl-4-(α-methylbenzylidenehydrazino)-pyrimidine-2(1*H*,3*H*,4*H*)ones (**14a** and **14b**) and subsequent nucleophilic displacement with sodium ethoxide in ethanol led to the corresponding **13**.

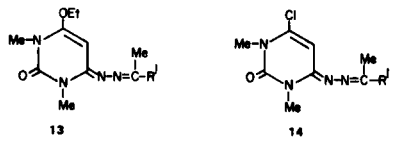


Table III

Uv Spectra of Pyrazolo[3,4-*d*]pyrimidines

Compound	λ max (ethanol) nm (log ε)	
3a	245 (3.99)	255 (3.96)
3b	238 (3.66)	263 (3.81)
9a	258 (3.78)	287 (3.81)
10a	245 (4.44)	282 (3.92)

The reaction of **7a-e** with ortho esters to give 2-vinylpyrazolo[3,4-*d*]pyrimidines (**9a-e** and **10a-e**) presumably proceeds through the initial formation of 5-ethoxymethylene intermediates (**11** or **12**), which cyclize *via* the tautomeric forms with the elimination of ethanol (Scheme II).

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Nmr spectra were determined with a Varian T-60 spectrometer at 60 MHz (tetramethylsilane as internal standard in deuteriochloroform) and uv spectra were recorded on a Hitachi 124 spectrophotometer (1 cm quartz cell). Identity of compounds was confirmed by comparison of ir spectra (Nujol mulls) with a Japan Spectroscopic Co. Ltd., Model IR-E spectrophotometer.

5,7-Dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (**3a**) (Table I).

A mixture of 1,3-dimethyl-6-hydrazinouracil (**1**) (11) (0.17 g., 0.001 mole) with DMFDMA (0.238 g., 0.002 mole) was heated at 90° for 30 minutes. After cooling, the precipitated solid was filtered off and recrystallized to give **3a**, identical with an authentic sample (5).

2-Alkyl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones (**3b-e**) (Table I).

A mixture of **1** (0.17 g., 0.001 mole) and the appropriate dimethylformamide dialkylacetal (3 ml.) was heated at 150° for 1.5 hours. The reaction mixture was evaporated *in vacuo* and the residue was diluted with ethanol. The separated crystals were filtered off and recrystallized to give the corresponding product **3b-e**.

Treatment of 6-hydrazino-3-methyluracil (**4**) (14) (0.156 g., 0.001 mole) or 6-acetylhydrazino-1,3-dimethyluracil (**5**) (15) with DMFDMA (3 ml.) under the same conditions described above afforded **3b**, respectively.

Similarly, compound **3b** was also obtained by refluxing **3a** (0.18 g., 0.001 mole) with DMFDMA (3 ml.) at 150° for 1.5 hours.

5,7-Dimethyl-2-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (**3f**).

A mixture of 1,3-dimethyl-6-phenylhydrazinouracil (**6**) (6) (0.25 g., 0.001 mole) and DMFDMA (0.3 ml.) was heated at 90° for 5 minutes. After cooling, the precipitated solid was filtered off, washed with methanol, and recrystallized from methanol to give **3f** (0.22 g., 86%), m.p. 286° (lit. (6) m.p. 285-287°).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.22; H, 4.53; N, 21.97.

1,3-Dimethyl-6-(α-methylbenzylidenehydrazino)uracils (**7a-e**).

1,3-Dimethyl-6-(α-methylbenzylidenehydrazino)uracils (**7a**, **7c**, and **7d**) were prepared previously (16). Other derivatives (**7b** and

7e) were obtained according to the reported procedure (16).

Compound **7h**.

This compound had m.p. 208-209° (40% from ethanol).

Anal. Calcd. for $C_{14}H_{15}BrN_4O_2$: C, 47.86; H, 4.31; N, 15.96. Found: C, 47.93; H, 4.54; N, 16.15.

Compound **7e**.

This compound had m.p. 209-211° (39% from ethanol).

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.44; H, 5.82; N, 18.52.

1,3-Dimethyl-5-dimethylaminomethylene-6-(α-methylbenzylidenehydrazino)uracil (**8a**).

A mixture of **7a** (0.272 g., 0.001 mole) and DMFDMA (1 ml.) was stirred at room temperature for 30 minutes. The crystals which separated were filtered off, washed with ethanol, and recrystallized from ethanol to give **8a** (0.14 g., 43%), m.p. 168-169°; ms: m/e 327 (M^+); nmr: δ 2.47 (3H, s, Me), 3.13 (6H, s, NMe_2), 3.32 (3H, s, N-Me), 3.53 (3H, s, N-Me), 7.23-7.90 (5H, m, C_6H_5), 8.07 (1H, s, =CH-).

Anal. Calcd. for $C_{17}H_{21}N_5O_2$: C, 62.36; H, 6.47; N, 21.39. Found: C, 62.64; H, 6.50; N, 21.66.

5,7-Dimethyl-2-vinylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones (**9a-e** and **10a-e**) (Table II).

Method A.

A mixture of the appropriate **7** (0.001 mole) and DMFDMA (3 ml.) was heated at 90° for 30 minutes. After cooling, the separated solid was filtered off, washed with ethanol, and recrystallized to give the corresponding product **9a-e**.

Compound **9a**.

This compound had ms: m/e 282 (M^+); nmr δ 3.40 (3H, s, N-Me), 3.60 (3H, s, N-Me), 5.27 (1H, s, =CH-), 5.83 (1H, s, =CH-), 7.43 (5H, s, C_6H_5), 7.90 (1H, s, C^3-H).

Method B.

A mixture of the appropriate **7** (0.001 mole) and triethyl orthoformate (5 ml.) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized to give the corresponding product **9a-e**.

Method C.

A suspension of the appropriate **7** (0.001 mole) in a mixture of dimethylformamide (0.146 g., 0.002 mole) and phosphorus oxychloride (0.306 g., 0.002 mole) was heated at 90° for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ice-water. The crystals which separated were filtered off, washed with water, dried, and recrystallized to give the corresponding product **9a-e**.

Method D.

A mixture of the appropriate **7** (0.001 mole) and triethyl orthopropionate (3 ml.) was refluxed for 3 hours. After cooling, the precipitates were filtered off, washed with ethanol, and recrystallized to give the corresponding product **10a-e**.

Compound **10a**.

This compound had ms: m/e 310 (M^+); nmr δ 1.17 (3H, t, Me), 2.87 (2H, q, $-CH_2-$), 3.40 (3H, s, N-Me), 3.50 (3H, s, N-Me), 5.53 (1H, s, =CH-), 6.00 (1H, s, =CH-), 7.00-7.50 (5H, m, C_6H_5).

Thermal Cyclization of **8a**.

A mixture of **8a** (0.327 g., 0.001 mole) and dimethylformamide (3 ml.) was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The crystals which separated were filtered off and recrystallized to give **9a** (0.21 g., 75%).

1,3-Dimethyl-6-ethoxy-4-(α-methylbenzylidenehydrazino)-pyrimidine-2(1*H*,3*H*,4*H*)ones (**13a-b**).

Method A.

Compounds **13a** and **13b** were obtained as minor products in the reaction of the appropirate **7** with triethyl orthopropionate. These were isolated after evaporation of the filtrate which removed **10b** or **10c** followed by recrystallization from ethanol, respectively.

Compound **13a**.

This compound had m.p. 183-185° (16%).

Anal. Calcd. for $C_{16}H_{19}BrN_4O_2$: C, 50.64; H, 5.06; N, 14.78. Found: C, 50.57; H, 5.23; N, 15.02.

Compound **13b**.

This compound had m.p. 168-170° (3%).

Anal. Calcd. for $C_{16}H_{19}ClN_4O_2$: C, 57.37; H, 5.72; N, 16.74. Found: C, 57.72; H, 5.62; N, 16.48.

Method B.

A solution of the appropriate 6-chloro-1,3-dimethyl-4-(α-methylbenzylidenehydrazino)pyrimidine-2(1*H*,3*H*,4*H*)one (**14**) (0.0001 mole) in absolute ethanol (5 ml.) dissolving metallic sodium (0.00015 g.-atom) was refluxed for 3.5 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with water. The insoluble crystals were filtered off, washed with water, dried, and recrystallized to give the corresponding product **13a-b**; compound **13a**, 70%, and compound **13b**, 74%.

6-Chloro-1,3-dimethyl-4-(α-methylbenzylidenehydrazino)-pyrimidine-2(1*H*,3*H*,4*H*)ones (**14a-b**).

A mixture of the appropriate **7** (0.002 mole) and phosphorus oxychloride (20 ml.) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was poured onto ice-water. The aqueous suspension was basified with diluted aqueous ammonia. The precipitates were filtered off, washed well with water, dried, and recrystallized from ethanol to give the corresponding product **14a-b**.

Compound **14a**.

This compound had m.p. 164-165° (100%).

Anal. Calcd. for $C_{14}H_{14}BrClN_4O$: C, 45.34; H, 3.81; N, 15.12. Found: C, 45.33; H, 3.94; N, 15.08.

Compound **14b**.

This compound had m.p. 157-158° (98%).

Anal. Calcd. for $C_{14}H_{14}Cl_2N_4O$: C, 51.68; H, 4.34; N, 17.23. Found: C, 51.78; H, 4.31; N, 17.29.

The uv spectra of representative pyrazolo[3,4-*d*]pyrimidine derivatives prepared in this study were listed in Table III.

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(12) When this reaction was carried out in a large scale, a trace amount of the isomeric 1,5,7-trimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione, identical with an authentic sample (5), was also obtained from the filtrate which removed **3b**.

(13) When this reaction was carried out at room temperature for 2.5 hours, the crystals (m.p. 191-193°) which assumed to be the first intermediate **2** could be obtained, however, its purification was unsuccessful.

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