Pyrimidine Derivatives XII
A Convenient Preparation of 6-Formylpyrimidinedione and 2- and 3-Formylpyridine Derivatives from Corresponding Nitrooxymethyl Derivatives

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The convenient preparation of 6-formylpyrimidinedione derivatives and 2- and 3-formylpyridine are described. Thus, 5-bromo-1,3-dimethyl- (**1a**), 5-bromo-3-methyl-1-(2-nitrooxyethyl)- (**1b**), and 5-bromo-3-methyl-1-(3-nitrooxypropyl)-2,4(1*H*,3*H*)-pyrimidine-dione (**1c**) were converted to the corresponding 6-formyl compounds **2a**, **2b**, and **2c**, respectively, in excellent yields by the reaction with triethylamine and 1,4-diazabicyclo[2.2.2]octane. These 6-formylpyrimidinedione derivatives are key intermediates for the preparation of 6-carbon-carbon substituted compounds, which are expected to be potential antitumor and antiviral agents. Similarly, 2-(and 3-)formylpyridine (**9a** (and **9b**)) were obtained by the reaction of 2-(and 3)nitrooxymethylpyridine (**8a** (and **8b**)) with 1,4-diazabicyclo[2.2.2]octane.

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Some C-6 substituted pyrimidines have been recently found to be active against HIV (Human Immunodeficiency Virus) [1] and other viruses [2]. Pyrimidines containing a carbon substituted at the C-6 position have been generally difficult to synthesize. A more general approach to various C-6 substituted pyrimidines would be from the 6-carboxaldehydes using the Wittig reaction [3] and epoxidation [4]. Although 6-formylpyrimidinediones are important intermediates for C-C bond formation at the C-6 position as previously mentioned, they have been prepared by the oxidation of 6-methyl derivatives with toxic selenium dioxide [5] and subsequently by several reaction steps after cyclization of various β-ketoseters with urea or thiourea derivatives [6]. Many papers have reported the preparation of 2- and 3-pyridinecarboxaldehyde, which were obtained by oxidation [7] of the corresponding hydroxymethyl- or methylpyridines, reduction [8] of pyridineamides or cyanopyridines, or other methods [9].

We described herein the convenient preparation of 6-formylpyrimidinediones from the corresponding 6-nitrooxymethyl derivatives, which are prepared in excellent yields from 6-bromomethyl compounds and are quite stable at room temperature [10]. Moreover, we found that nitrooxymethylpyridines were easily converted to the corresponding formylpyridines.

In a previous paper of this series [11], we briefly described that the reaction of 6-nitrooxymethylpyrimidinediones **1a**, **1b**, and **1c** with sodium methoxide exclusively gave 6-formyl and carbon-carbon cleaving products at the 6-position, respectively, based on the molar ratio of sodium methoxide. We propose that a nitrooxymethyl group must be converted to a formyl group by treatment with the appropriate bases, which are required to possess strong basicity and low nucleophilicity, by careful consideration of the proposed reaction mechanism [11].

Reaction with Tertiary Amines (Table I).

Triethylamine, well-known as a strong basic and low nucleophilic organic base, was first examined. When 5-bromo-1,3-dimethyl-6-nitrooxymethyl-2,4(1*H*,3*H*)-

Chart 1

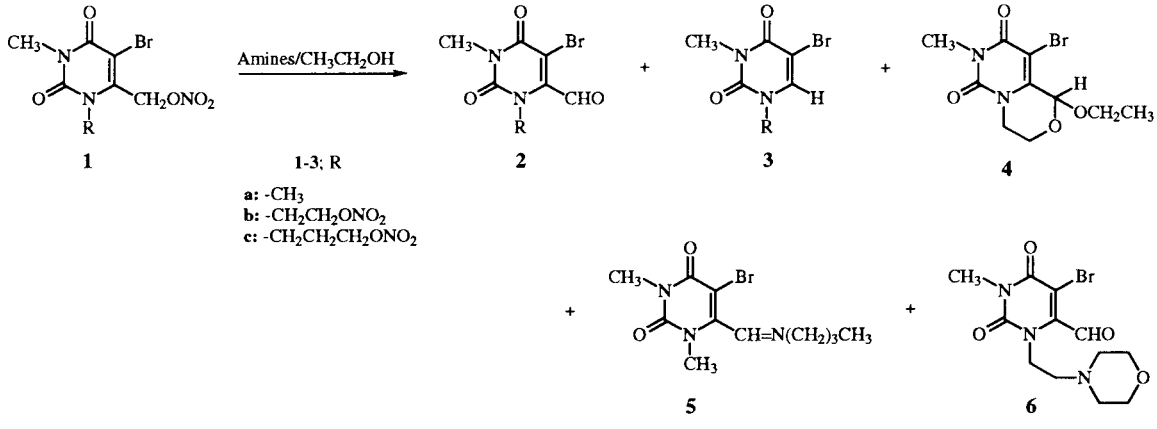


Table I

Reaction [a] of **1a**, **1b**, and **1c** with Tertiary Amine

Entry No.	Compound No. (equivalent, g)			Amine [b] (equivalent)		**2a-c** Yield [c] (g(%))		**2a-c** Ratio in %
1	**1a**	1.0,	0.88	A	1.5	0.68	(92)	100
2	**1a**	1.0,	0.88	A	3.0	0.58	(78)	100
3	**1b**	1.0,	0.74	A	2.0	0.59	(92)	100
4	**1c**	1.0,	0.77	A	2.0	0.65	(97)	100
5	**1a**	1.0,	0.44	B	0.5	0.31	(84)	100
6	**1a**	1.0,	0.44	B	1.0	0.34	(92)	100
7	**1a**	1.0,	0.88	B	1.5	0.59	(80)	100
8	**1b**	1.0,	1.10	B	1.0	0.87	(90)	100
9	**1b**	1.0,	1.10	B	1.5	0.82	(85)	100
10	**1c**	1.0,	1.15	B	1.0	0.87	(86)	100
11	**1c**	1.0,	1.15	B	1.5	0.83	(82)	100

[a] The reaction procedure and computation of the product ratio are described in the experimental. [b] A; Triethylamine, B; 1,4-Diazabicyclo[2.2.2]-octane. [c] Isolated yields are shown.

pyrimidinedione [12] (**1a**) was treated with 1.5 equivalents of triethylamine at room temperature for 3 hours in ethanol, 5-bromo-1,3-dimethyl-6-formyl-2,4(1*H*,3*H*)-pyrimidinedione [11] (**2a**) was obtained in 92% yield as the sole product. Similarly, compounds **1b** [10] and **1c** [10] were converted to the corresponding 6-formyl compounds **2b** [11] (92%) and **2c** [11] (97%) (entries 3 and 4). However, the yield of **2a** was reduced by treatment with 3.0 equivalents of triethylamine (entry 2). In the case of 1,4-diazabicyclo[2.2.2]octane, cyclic tertiary amines similar to triethylamine, corresponding 6-formyl compounds were obtained in nearly the same high yields as triethylamine while excess base caused a slight reduction in yields.

Reaction with Secondary Amines (Table II).

When **1a** was treated with 1.0 and 2.0 equivalents of dimethylamine, the 6-formyl compounds **2a** were isolated in 53 and 58% yield as sole product (entries 1 and 2), respectively. However, a mixture of the 6-formyl compound **2a** and carbon-carbon cleavage-products **3a** [11] was obtained by reaction with 4.0 equivalents of diethylamine (entry 3). Treatment of **1b** with 1.0 equivalent of diethylamine gave only the 6-formyl product in 69% (entry 4). When 2.0 and 4.0 equivalents of diethylamine were used, a mixture of 6-formyl **2b**, carbon-carbon cleaving **3b** [11], and bicyclic **4** [13] compounds were obtained. The yields of the carbon-carbon cleaving and bicyclic compounds increased with an increase in the molar ratio of the diethylamine (entries 5 and 6). As shown in entries 7 and 8, by reaction with piperidine, which has a stronger basicity than diethylamine, the yields of the carbon-carbon bond cleaving product were increased. Compound **1a** was completely converted to **3a** by reaction with 4.0 equivalents of piperidine. In the case of morpholine, which is weaker than diethylamine, complicated results occured. The obtained reaction products could not be computed for product ratio, because the characteristic signal peaks could not be identified. Excess morpholine (2.3 equivalents) gave 5-bromo-6-formyl-3-methyl-1-[2-(4-morpholino)ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (**6**).

Table II

Reaction [a] of **1a** and **1b** with Secondary Amines

Entry (No.)	Compound No. (equivalent, g)			Amine [b] (equivalent)		Yield (g(%))			Products Ratio in % **2a/2b**	**3a/3b**	**4**
1	**1a**	1.0,	0.79	A	1.5	0.35	(53)	[c]	100	-	-
2	**1a**	1.0,	0.88	A	2.0	0.43	(58)	[c]	100	-	-
3	**1a**	1.0,	0.88	A	4.0	0.40			90	10	-
4	**1b**	1.0,	0.74	A	1.0	0.44	(69)	[c]	100	-	-
5	**1b**	1.0,	0.74	A	2.0	0.56			79	13	8
6	**1b**	1.0,	0.74	A	4.0	0.55			45	31	24
7	**1a**	1.0,	0.88	B	2.0	0.57			70	30	-
8	**1a**	1.0,	0.88	B	4.0	0.55	(84)	[c]	-	100	-

[a] The reaction procedure and computation of the product ratio are described in the experimental. [b] A: Diethylamine, B: Piperidine. [c] Isolated yields are shown.

Table III

Reaction [a] of **1a** with Butylamine

Entry (No.)	Compound No. (equivalent, g)			Butylamine (equivalent)	Yield (g)	Products Ratio in %			
						1a	**2a**	**3a**	**5**
1 [b]	**1a**	1.0,	0.29	0.5	0.26	33	46	-	21
2	**1a**	1.0,	0.29	0.5	0.21	-	77	-	23
3	**1a**	1.0,	0.29	1.0	0.26	-	44	-	56
4	**1a**	1.0,	0.29	2.0	0.25	-	10	12	78
5	**1a**	1.0,	0.29	4.0	0.25	-	3	28	69

[a] The reaction procedure and computation of the product ratio are described in the experimental. [b] The reaction was carried out at room temperature.

Table IV

Reaction [a] of **7a**, **7b**, **8a**, and **8b** with Sodium Methoxide

Entry (No.)	Compound No. (equivalent, g)			Sodium Methoxide (equivalent)	Yield (g)	Products Ratio in %	
						8a/8b	**9a/9b**
1	**7a**	1.0,	0.37	2.0	0.12	68	32
2	**7a**	1.0,	0.46	4.0	0.18	54	46
3	**8a**	1.0,	0.54	0.5	0.23	17	83
4	**8a**	1.0,	0.54	1.0	0.28	39	61
5	**8a**	1.0,	0.54	2.0	0.22	65	35
6	**7b**	1.0,	0.60	2.0	0.15	38	62
7	**7b**	1.0,	0.60	4.0	0.19	60	40
8	**8b**	1.0,	0.54	1.0	0.23	57	43
9	**8b**	1.0,	0.54	2.0	0.26	70	30

[a] The reaction procedure and computation of the product ratio are described in the experimental.

Reaction with Butylamine (Table III).

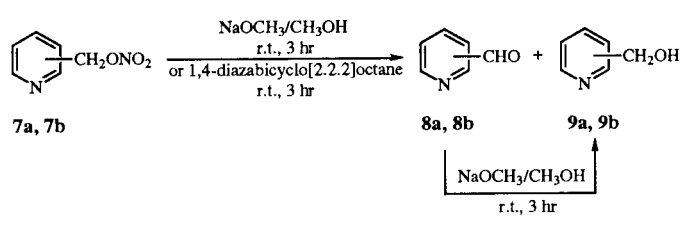
In all cases, a nucleophilic substitution reaction was observed for the formyl group producing compound **5**. When 0.5 equivalents of butylamine was used and reaction was carried out in ethanol at room temperature for 3 hours, 6-formyl **2a** and Mannich's base **5** were obtained along with starting material (entry 1). Therefore, in this case, reactions were carried out at 70-80° for 3 hours. The yields of **2a** decreased with an increase in the butylamine molar ratio, whereas the yields of **5** increased with an increase (entries 2, 3, 4 and 5).

Reaction of Nitrooxymethylpyridines with Various Amines (Table IV).

In order to expand this preparation, 2-nitrooxymethylpyridine [14] (**7a**) and 3-nitrooxymethylpyridine [14] (**7b**) were examined. When **7a** and **7b** were treated with triethylamine at room temperature for 3 hours, a mixture of starting material and 2- (and 3-) formylpyridine were identified by ^{1}H-nmr spectra. Therefore, reaction time was prolonged for 2 days, however, the starting material still remained. The reaction was then carried out at 70-80° for 3 hours, and the resulting material showed several spots on a thin layer chromatograph plate, but they could not be isolated as pure materials. Compounds **7a** and **7b** were reacted with 1,4-diazabicyclo[2.2.2]octane in ethanol at room temperature for 3 hours. The target 2-formylpyridine (**8a**) was isolated in 84% yield as the sole product. Under the same reaction conditions **8b** was only obtained in 20% yield. Other organic bases have been examined, however, the resulting products are more complicated and could not be identified.

For the reactions of **7a** and **7b** with sodium methoxide, the results are summarized in Table IV. A mixture of formyl **8a** and **8b** and hydroxymethyl **9a** and **9b** compounds were obtained in all cases using 2.0 and 4.0 equivalents of sodium methoxide (entries 1, 2, 6, and 7). In order to confirm whether compound **8** could be converted to **9**, compounds **8a** and **8b** were treated with sodium methoxide. It was determined that the formyl compounds were able to be converted to the hydroxymethyl derivatives and the yields of **9** decreased with an increase in the molar ratio of sodium methoxide (entries 3, 4, 5, 8, and 9).

Chart 2



Conclusions.

6-Nitrooxymethylpyrimidinedione derivatives and 2- and 3-nitrooxymethylpyridines were converted to the corresponding formyl compounds, by reaction with triethylamine or 1,4-diazabicyclo[2.2.2]octane, respectively. The resulting 6-formylpyrimidinedione derivatives are key intermediates for the preparation of 6-carbon-carbon substituted compounds, which are potential antitumor and antiviral agents.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were taken using a JASCO IR-810 spectrophotometer. The uv spectra were measured on a Shimadzu UV-3100PC spectrophotometer. The nmr spectra were taken on a Hitachi R-600 (60 MHz for ^{1}H) and a JEOL JNM FX-90Q (90 MHz for ^{1}H, 22.5 MHz for ^{13}C) Fourier-transform spectrometer, and were measured in deuteriochloroform solution unless otherwise mentioned. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard. The ms were obtained using a JEOL JMS-DX-303 instrument equipped with a JMA-DA-5000 data processor.

General Reaction Procedure and Computation of the Products Ratio (Tables I, II, and III).

A solution of the starting material and base in ethanol (15-20 ml) was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* at room temperature. The residue was suspended in water (20 ml), acidified to *p*H 5, and then the mixture was extracted with chloroform (3 times). The combined extract was dried over magnesium sulfate and filtered. The filtrate was passed through a short silica gel column (Wako-gel C-200, 5 g, inner diameter 17 mm) eluted with a mixture of chloroform-acetonitrile (gradient from 9:1 to 8:2). The eluent was concentrated to dryness *in vacuo*. A part of the residue was dissolved in chloroform and the ^{1}H-nmr spectrum was recorded. Integration intensities of characteristic peaks [C(6)-CH_2-ONO_2 for **1a** (5.67), **1b** (5.77), and **1c** (5.72); C(6)-CHO for **2a** (10.18), **2b** (10.17), and **2c** (10.20); C(6)-H for **3a** (7.53), **3b** (7.49), and **3c** (7.54); C(1)-H for **4** (5.59); C(6)-CH=N-Bu for **5**] were computed and the mean values from three experiments are shown.

General Reaction Procedure and Computation of the Products Ratio (Table IV).

A solution of starting material and sodium methoxide (2.0 m*M*/ml methanol) in methanol (entire volume, 20-30 ml) was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* at room temperature. The residue was dissolved in water (20 ml) and then the mixture was extracted with chloroform (3 times). The combined extract was treated as previously mentioned for Tables I, II, and III. Integration intensities of characteristic peaks [C(6)-H for **8a** (8.80), **9a** (8.42); C(4)-H for **8b** (8.17), **9b** (7.71)] were computed and the mean values from three experiments are shown.

5-Bromo-1,3-dimethyl-6-(*N*-butyliminomethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**5**).

A mixture of **1a** (0.58 g, 2.0 mmoles) and butylamine (0.08 g, 1.0 mmole) in methanol (20 ml) was refluxed for 3 hours. After removal of the solvent, some water was added to the residue and the mixture was extracted with chloroform (3 times). The combined extracts were dried over magnesium sulfate and filtered. The filtrate was concentrated into a small volume and chromatographed on a silica gel column. The chloroform eluent were collected and recrystallized from methanol to give 0.32 g (53%) of colorless needles, mp 82-84°, ir (potassium bromide): 1705, 1658 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ε): 210 (4.041), 299 (3.697); ^{1}H-nmr (deuteriochloroform): δ 0.97 (3H, t, J = 6.4 Hz, -CH_2-CH_3), 1.29 (2H, m, -CH_2CH_3), 1.65 (2H, m, -CH_2-CH_2-CH_3), 3.44 (3H, s, N-CH_3), 3.51 (3H, s, N-CH_3), 4.73 (2H, td, J = 6.7, 1.3 Hz, N-$CH_2CH_2CH_3$), 8.26 (1H, t, J = 1.3 Hz, -CH=N-); ms: EI m/z (r.i., %) 303 (M^+ for ^{81}Br, 30.6), 301 (M^+ for ^{79}Br, 30.8).

Anal. Calcd. for $C_{11}H_{16}BrN_3O_2$: C, 43.73; H, 5.34; Br, 26.44; N, 13.91. Found: C, 43.76; H, 5.18; Br, 25.88; N, 13.82.

5-Bromo-6-formyl-3-methyl-1-[2-(4-morpholino)ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (**6**).

A mixture of **1b** (0.45 g, 3.0 mmoles) and morpholine (0.70 g, 8 mmoles) in ethanol (20 ml) was stirred at room temperature for 3 hours. After removal of the solvent, some water was added to the residue and the mixture was extracted with chloroform (3 times). The combined extracts were dried over magnesium sulfate and filtered. The filtrate was concentrated into a small volume and chromatographed on a silica gel column. The eluent from chloroform were collected and recrystallized from ether-hexane to give 0.35 g (51%) of yellow needles, mp 132-134°, ir (potassium bromide): 1710, 1692, 1655 (C=O), 1583, 1460, 1330, 1120 cm^{-1}; uv (ethanol): λ max nm (log ε): 286 (4.029), 360 (2.299); ^{1}H-nmr (deuteriochloroform): δ 2.46 (6H, m, (-CH_2-)$_3$N), 3.45 (3H, s, N-CH_3), 3.64 (4H, t, J = 4.6 Hz, -CH_2-O-CH_2-), 4.31 (2H, t, J = 5.0 Hz, N(1)-CH_2-), 9.95 (1H, s, CHO); ms: EI m/z (r.i., %) 347 (M^+ for ^{81}Br, 15.8), 345 (M^+ for ^{79}Br, 15.9).

Anal. Calcd for $C_{12}H_{16}BrN_3O_4$: C, 41.64; H, 4.66; Br, 23.08; N, 12.14. Found: C, 41.82; H, 4.64; Br, 23.00; N, 12.25.

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