HETEROCYCLES, Vol. 57, No. 11, 2002, pp. 2081 - 2090, Received, 29th July, 2002

A NEW SYNTHESIS OF 6-SUBSTITUTED PYRIDO[2,3-*d*]PYRIMIDINES

Takeshi Kuwada,[2] Kenichi Harada,[1] Junko Nobuhiro,[1] Tominari Choshi,[1] and Satoshi Hibino*[1]

Graduate School of Pharmacy and Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan,[1] Process Chemistry Laboratory, Medicinal Research Laboratory, Taisho Pharmaceutical Co. Ltd., 1-403 Yoshino-cho, Saitama, Saitama 330-8530, Japan[2]

Abstract-The reaction of the β-methylsulfanylacroleins, derived from alkenyl sulfides by the Vilsmeier reaction, with 6-aminouracils or 2,6-diaminouracil, provides a new synthetic route to the 6-substituted pyrido[2,3-*d*]pyrimidines by two methods, the reaction mechanisms of which were examined by a deuterium-labeled thioacrolein.

6-Substituted pyrido[2,3-*d*]pyrimidines, 5-deazapteridines, have attracted much attention due to their biological activities,[1] with 5,10-dideazatetrahydrofolic acid (DDATHF) and its 6*R*-enantiomer (lometrexol), as antifolates, having been of particular interest.[2] Although, a large number of studies in this area have been reported,[3] almost all of the preparation for 6-substituted pyrido[2,3-*d*]pyrimidines, other than those of Wamhoff,[6a] Hirota,[6b] and Yoon,[6c] have involved the formation of a fused pyridine ring using 6-aminouracils with malonaldehyde derivatives[4] or their equivalents[5] such as β-amino- and β-alkoxyacroleins. We have previously described the utilization of β-methylsulfanylacroleins as an efficient three-carbon unit for the synthesis of 5-phenylpyrimidines,[7a,,b] 5-benzylpyrimidines (trimethoprim),[7c] and imidazo[4,5-*b*]pyridines.[7d] In the present work, we describe a new synthesis of 6-substituted pyrido[2,3-*d*]pyrimidines (**6** and **7**) based on the reaction of β-methylsulfanylacroleins (**3**) with 6-aminouracils (**4**) or 2,6-diamino-4-pyrimidinone (**5**) (Scheme 1), together with a consideration of its reaction mechanisms. The alkenyl sulfides (**2a-d**) were easily arranged by a Wittig reaction of the corresponding aldehydes (**1a-d**) with methylsulfanylmethylenetriphenylphosphorane in 89% (**2a**),[7d,8] 77% (**2b**), 99% (**2c**), and 96% (**2d**) yields, respectively; these sulfides then underwent a Vilsmeier reaction to produce the required β-methylsulfanylacroleins (**3**) in 72 (**3a**),[7d] 98 (**3b**), 70 (**3c**), and 49% (**3d**) yields, respectively, according to our reported procedure[7] (Scheme 1).

The acroleins (**3a-d**) were subjected to a reaction with 6-aminouracils (**4**) by two methods, A and B

(Table 1). Method A: A reaction of the acroleins (**3**) with 6-aminouracils (**4**) was carried out by heating in benzene at the reflux temperature in the presence of *p*-toluenesulfonic acid (*p*-TsOH) under the conditions of the imidazo[4,5-*b*]pyridine synthesis.[7d] The addition of Lewis acids instead of *p*-TsOH was

Scheme 1

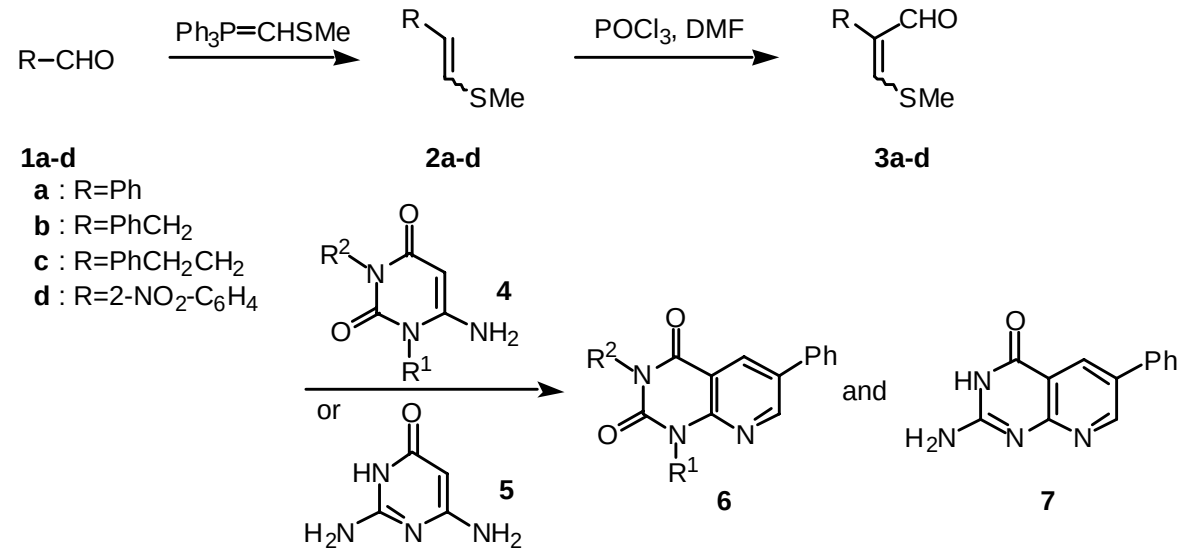
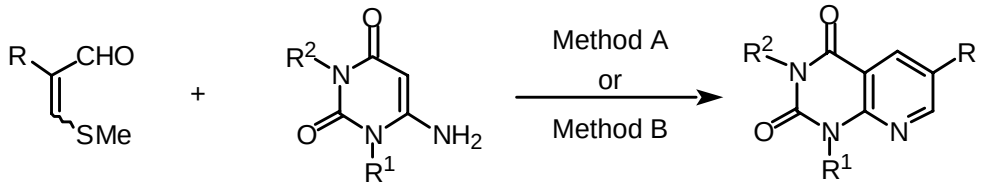


Table 1



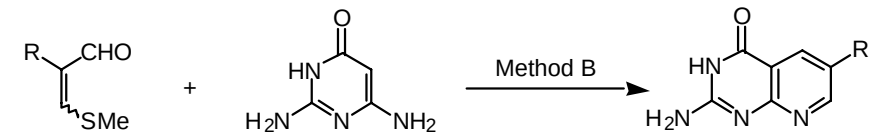
Run	Starting Materials			Products (**6a-l**)				Yield (%) of **6a-l**	
	3a-d		**4a-c**		R	R^1	R^2	Method A[a)]	Method B[b)]
1	**3a**	+	**4a**	**6a**	Ph	H	H	53	75
2	**3a**	+	**4b**	**6b**	Ph	Me	H	69	99
3	**3a**	+	**4c**	**6c**	Ph	Me	Me	64	92
4	**3b**	+	**4a**	**6d**	$PhCH_2$	H	H	25	80
5	**3b**	+	**4b**	**6e**	$PhCH_2$	Me	H	44	96
6	**3b**	+	**4c**	**6f**	$PhCH_2$	Me	Me	68	92
7	**3c**	+	**4a**	**6g**	$PhCH_2CH_2$	H	H	26	78
8	**3c**	+	**4b**	**6h**	$PhCH_2CH_2$	Me	H	30	82
9	**3c**	+	**4c**	**6i**	$PhCH_2CH_2$	Me	Me	54	85
10	**3d**	+	**4a**	**6j**	2-NO_2-C_6H_4	H	H	- [c)]	77
11	**3d**	+	**4b**	**6k**	2-NO_2-C_6H_4	Me	H	- [c)]	85
12	**3d**	+	**4c**	**6l**	2-NO_2-C_6H_4	Me	Me	- [c)]	88

a) heating in benzene in the presence of *p*-TsOH.
b) heating in an aqueous AcOH (60%).
c) Runs 10-12 by Method A were not examined.

not effective, and at least two equimolar amounts of 6-aminouracils was necessary. Although, yields of the pyrido[2,3-*d*]pyrimidines (**6a-i**) were generally low (25-69%), among them the reactions in Runs 2, 3, 6, and 9 using 1-methyl- (or 1,3-dimethyl)-6-aminouracil (**4b** or **4c**) gave **6b** (69%), **6c** (64%), **6f** (68%), and **6i** (54%) in moderate yields. By contrast, the reaction of the acroleins (**3**) with one equimolar amount of 6-aminouracils (**4**) was carried out by heating in an aqueous acetic acid at 120°C for 3 h (Method B) to obtain the pyrido[2,3-*d*]pyrimidines (**6a-l**) in good to excellent yields (75-92%). It was found that this reaction was relatively effective in the polar solvent.

In addition, the acroleins (**3**) were subjected to a reaction with 2,6-diamino-4-pyrimidinone (**5**) by Method B to provide the 6-substituted pyrido[2,3-*d*]pyrimidines (**7a-d**) in excellent yields (89-99%), respectively (Scheme 2).

Scheme 2



3a-d **5** **7a-d**

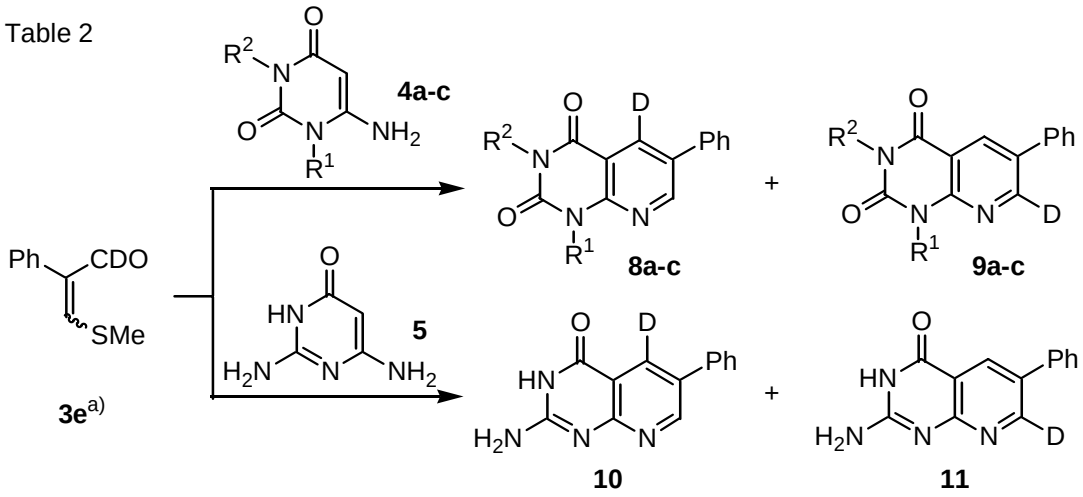
7a : R=Ph (89%)
7b : R=$PhCH_2$ (99%)
7c : R=$PhCH_2CH_2$ (90%)
7d : R=2-NO_2-C_6H_4 (98%)

To examine the reaction mechanism in this case, we repeated the reaction using *d*-labeled β-methylsulfanylacroleins (**3e**)[7d] (Table 2). The reaction of **3e** with 6-aminouracils (**4**) was carried out by Method A to furnish an inseparable mixture of 5- and 7-deuterated pyrido[2,3-*d*]pyrimidines (**8a-c** and **9a-c**) in the ratio of 1 : 1 to 1.5 : 1 (Runs 1-3). Furthermore, the reaction of **3e** with 6-aminouracils (**4**) by Method B gave a similar mixture of 5- and 7-deuterated pyrido[2,3-*d*]pyrimidines (**8a-c** and **9a-c**) in the ratio of 3 : 1 to 7 : 1 (Runs 4-6). In the reaction of **3e** with 2,6-diaminouracil (**5**) by Method B (Run 7), a 2 : 1 mixture of 5- and 7-deuterated pyrido[2.3-*d*]pyrimidines (**10** and **11**) was obtained. Each of the ratios of deuterated compounds (**8** and **9**) was determined by the relative intensity of two singlet signals at near δ 8.5 (C7-H) and δ 9.0 (C5-H) in the respective ^{1}H-NMR spectra. Moreover, the 2 : 1 ratio of **10** and **11** was measured by the relative intensities of C7-H (near at δ 9.3, singlet) and C5-H (near at δ 9.5, singlet) in the same way. Based on the results of this deuterium experiment, the C5-deuterated pyrido[2,3-*d*]pyrimidines (**8**) would result from pathways “a” and / or “b”, as depicted in Chart 1, whereas C7-deuterated pyrido[2,3-*d*]pyrimidines (**9**) would result from pathways “a” and / or “b”, as depicted in Chart 2. As a result, the pathway of Chart 1 appears to be more favorable than the pathway of Chart 2 under the conditions of Method B.

Regarding the related work, Breitmaier[5d] has proposed that the reaction of the β-aminoacrolein with 6-aminouracil (**4**) would proceed by route “b” of Chart 1 in 1973. Although the reactivity of β-

aminoacrolein might be somewhat different from that of β-methylsulfanylacroleins, another pathway similar to ours would be expected by this experiment.

Table 2



Run	Starting Materials			Methods	Ratio of deuterated Products b)	
	3e a)		4a-c and 5			
1	**3e**	+	**4a**	A	**8a** : **9a**	1 : 1
2	**3e**	+	**4b**	A	**8b** : **9b**	1 : 1
3	**3e**	+	**4c**	A	**8c** : **9c**	1.5 : 1
4	**3e**	+	**4a**	B	**8a** : **9a**	3 : 1
5	**3e**	+	**4b**	B	**8b** : **9b**	5 : 1
6	**3e**	+	**4c**	B	**8c** : **9c**	7 : 1
7	**3e**	+	**5**	B	**10** : **11**	2 : 1

a) **3e** was prepared by the method of reference 7d.
b) The ratio was determined by ^{1}H-NMR spectra.

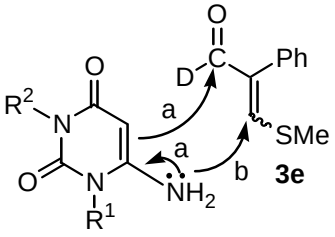


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Chart 1

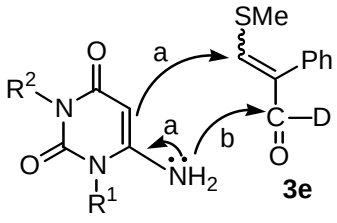

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Chart 2

In summary, a new synthesis of 6-substituted pyrido[2.3-*d*]pyrimidines using β-methylsulfanylacroleins (**3**) has been established by two methods, together with the study of the reaction mechanisms by the deuterium-labeled experiment. It was demonstrated that the 2-substituted β-methylsulfanylacroleins (**3**) are a useful three-carbon component in the synthesis of the fused pyridine ring system.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR

spectra were recorded with a Horiba FT-720 spectrophotometer. ^{1}H-NMR spectra were taken by JEOL PMX60Si and JNM AL-300 spectrometers using $SiMe_4$ as an internal standard. MS spectra and HRMS were recorded on Shimadzu QP-5050 and GC-MS 9020DF spectrometers (EI). Silica gel (60-100 mesh, Merck Art 7734) was used for the column chromatography.

1-Methylsulfanyl-3-phenylpropene (2b)

n-BuLi (1.60 M in hexane, 31.2 mL, 49.9 mmol) was added to the ice-cooled suspension of methylsulfanylmethyltriphenylphosphonium chloride (17.9 g, 49.9 mmol) in THF (90 mL) under N_2 atmosphere, and then the solution was stirred at the same temperature for 30 min. After addition of a solution of phenylacetaldehyde (5.0 g, 41.6 mmol) in THF (10 mL), the mixture was stirred at rt for 14 h. The reaction mixture was quenched with sat. NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, 200g) using EtOAc-hexane (3:7) as an eluent to give the alkene (**2b**) (5.3 g, 77%). bp 101-102^{o}C/2.0 torr. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (1.5H, s), 2.20 (1.5H, s), 3.33 (1H, d, *J*=6 Hz), 3.47 (1H, d, *J*=6 Hz), 5.22-6.12 (2H, m), 7.13 (5H, m). MS *m/z*: 164 (M^+). *Anal*. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36. Found: C, 73.18; H, 7.41.

1-Methylsulfanyl-4-phenylbut-1-ene (2c)

The same procedure as above was carried out using **1c** (5.0 g, 28 mmol) to give the alkene (**2c**) (6.5 g, 99%). bp 108-110^{o}C/2.5 torr. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (1.5H, s), 2.18 (1.5H, s), 2.33-2.87 (4H, m), 5.09-6.03 (2H, m), 7.30 (5H, m). MS *m/z*: 178 (M^+). *Anal*. Calcd for $C_{11}H_{14}S$: C, 74.10; H, 7.91. Found: C, 74.04; H, 7.90.

1-Methylsulfanyl-2-(2-nitrophenyl)ethane (2d)

The same procedure as above was carried out using **1d** (3.0 g, 19.9 mmol) to give the alkene (**2d**) (3.8 g, 98%). IR (naet) υ: 1521, 1349 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, d, *J*=2 Hz), 6.42 (1H, d, *J*=10 Hz), 6.90 (1H, d, *J*=10 Hz), 7.13-8.03 (4H, m). MS *m/z*: 195 (M^+). *Anal*. Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65. Found: C, 55.31; H, 4.77.

2-Benzyl-3-methylsulfanylacrolein (3b)

$POCl_3$ (3.4 mL, 37.4 mmol) was added to an ice-cooled solution of DMF (30 mL) under N_2 atmosphere, and then the solution was stirred at rt for 30 min. After addition of 1-methylsulfanyl-2-phenylpropene (**2b**) (5.0 g, 31.2 mmol) in DMF (5 mL) under ice-cooled water, the mixture was stirred at rt for 14 h. The mixture was poured into ice water. The whole was neutralized with 10% NaOH solution and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over, Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, 200 g) using EtOAc-hexane (3:7) as an eluent to give the acrolein (**3b**) (5.9 g, 98%). bp 145-147^{o}C/2.5 torr. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.58 (2H, s), 7.13-7.28 (6H, m), 9.23 (1H, s). IR (naet) υ: 1725 cm^{-1}. MS *m/z*: 192 (M^+). *Anal*. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29. Found: C, 68.65; H, 6.34.

3-Methylsulfanyl-2-(2-phenylethyl)acrolein (3c)

The same procedure as above was carried out using **2c** (6.8 g, 38.0 mmol) to give the alkene (**3c**) (5.5 g, 70%). bp 176-177^{o}C/6.0 torr. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.62 (4H, s), 7.11 (1H, s), 7.15 (5H, s), 9.15 (1H, s). IR (naet) υ: 1666 cm^{-1}. MS *m/z*: 206 (M^+). *Anal*. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84. Found: C, 69.80; 6.90.

3-Methylsulfanyl-2-(2-nitrophenyl)acrolein (3d)

$POCl_3$ (9.3 mL, 99.9 mmol) was added to an ice-cooled solution of DMF (20 mL) under N_2 atmosphere, and then the solution was stirred at rt for 30 min. After addition of the alkene (**2d**) (3.9 g, 20.0 mmol) in DMF (5 mL) at the same temperature, the mixture was heated at 90^{o}C for 14 h. The mixture was poured into ice water. The whole was neutralized with 10% NaOH solution and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, 150 g) using EtOAc-hexane (3:7) as an eluent to give the acrolein (**3d**) (2.2 g, 49%). ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s), 7.38 (1H, d, *J*=9 Hz), 7.55 (1H, t, *J*=9 Hz), 7.62-7.69 (2H, m), 8.14 (1H, d, *J*=9 Hz), 9.42 (1H, s). IR (naet) υ: 1671, 1527, 1349 cm^{-1}. MS *m/z*: 223 (M^+). *Anal*. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06. Found: C, 53.75; H, 4.18.

General procedure of 6-substituted pyrido[2,3-*d*]pyrimidines (6)

6-Phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6a)

Method A: The suspension mixture of 4-aminouracil (**4**) (732 mg, 5.8 mmol), the acrolein (**3**) (513 mg, 2.9 mmol), and *p*-TsOH (300 mg, 1.7 mmol) in benzene (40 mL) using the water separater was heated at 100^{o}C for 14 h. The reaction mixture was quenched with 30% aqueous $KHCO_3$ solution (30 mL), and the whole was extracted with 5% MeOH-$CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc-hexane (3:7) as an eluent to give the pyridopyrimidine (**6a**) (362 mg, 53%). mp 338^{o}C (decomp) (AcOH-H_2O). ^{1}H-NMR (DMSO-d_6) δ: 7.43 (1H, t, *J*=7 Hz), 7.52 (1H, t, *J*=7 Hz), 7.77 (2H, d, *J*=7 Hz), 8.44 (1H, d, *J*=2 Hz), 8.96 (1H, d, *J*=2 Hz), 11.56 (1H, s), 11.83 (1H, s). IR (KBr) υ: 1733, 1684 cm^{-1}. MS *m/z*: 239 (M^+). *Anal*. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.30; H, 3.85; N, 17.62.

Method B: The mixture of 4-aminouracil (**4**) (283 mg, 2.2 mmol) and the acrolein (**3**) (400 mg, 2.2 mmol) in an aqueous 60% AcOH (10 mL) using the water separater was heated at 120^{o}C for 3 h. The reaction mixture was diluted with H_2O, and extracted with 5% MeOH-$CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, g) using EtOAc-hexane (3:7) as an eluent to give the pyridopyrimidine (**6a**) (402 mg, 75%).

1-Methyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6b)

Method A: The same procedure as above was carried out using **3b** (350 mg, 2.0 mmol) to give the alkene (**6b**) (343 mg, 69%). **Method B**: The same procedure as above was carried out using **3b** (500 mg, 2.8

mmol) to give the alkene (**6b**) (700 mg, 99%). mp 314-315°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 3.35 (3H, s), 7.43 (1H, t, *J*=7 Hz), 7.52 (2H, t, *J*=7 Hz), 7.78 (2H, d, *J*=7 Hz), 8.48 (1H, d, *J*=2 Hz), 8.98 (1H, d, *J*=2 Hz), 12.11 (1H, s). IR (KBr) υ: 1728, 1680 cm^{-1}. MS *m/z*: 253 (M^+). *Anal*. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.32; H, 4.46; N, 16.48.

1,3-Dimethyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6c)

Method A: The same procedure as above was carried out using **3c** (430 mg, 2.4 mmol) to give the alkene (**6c**) (412 mg, 64%). **Method B**: The same procedure as above was carried out using **3c** (500 mg, 2.8 mmol) to give the alkene (**6c**) (689 mg, 92%). mp 158-159°C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 3.56 (3H, s), 3.58 (3H, s), 7.36-7.80 (5H, m), 8.63 (1H, d, *J*=2 Hz), 8.87 (1H, d, *J*=2 Hz). IR (KBr) υ: 1709, 1662 cm^{-1}. MS *m/z*: 267 (M^+). *Anal*. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.31; H, 5.01; N, 15.80.

6-Benzylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6d)

Method A: The same procedure as above was carried out using **3d** (380 mg, 2.0 mmol) to give the alkene (**6d**) (125 mg, 25%). **Method B**: The same procedure as above was carried out using **3d** (500 mg, 2.6 mmol) to give the alkene (**6d**) (526 mg, 80%). mp 210-211₀C (EtOAc). ₁H-NMR (DMSO-d_6) δ: 3.97 (2H, s), 7.13-7.33 (5H, m), 7.93 (1H, d, *J*=2 Hz), 8.47 (1H, d, *J*=2 Hz). IR (KBr) υ: 1709 1662 cm^{-1}. MS *m/z*: 253 (M^+). *Anal*. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.49; H, 4.50; N, 16.38.

6-Benzyl-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6e)

Method A: The same procedure as above was carried out using **3e** (400 mg, 2.1 mmol) to give the alkene (**6e**) (245 mg, 44%). **Method B**: The same procedure as above was carried out using **3e** (500 mg, 2.6 mmol) to give the alkene (**6e**) (667 mg, 96%). mp 212-213°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 3.20 (3H, s), 3.96 (2H, s), 7.15 (5H, s), 7.97 (1H, d, *J*=3 Hz), 8.42 (1H, d, *J*=3 Hz). IR (KBr) υ: 1719, 1655 cm^{-1}. MS *m/z*: 267 (M^+). *Anal*. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.51; H, 5.21; N, 15.56.

6-Benzyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6f)

Method A: The same procedure as above was carried out using **3f** (400 mg, 2.1 mmol) to give the alkene (**6f**) (398 mg, 68%). **Method B**: The same procedure as above was carried out using **3f** (500 mg, 2.6 mmol) to give the alkene (**6f**) (673 mg, 92%). mp 142-143.5°C (EtOAc). ^{1}H-NMR (DMSO-d_6) δ: 3.40 (3H, s), 3.63 (3H, s), 3.97 (2H, s), 7.13 (5H, s), 8.13 (1H, d, *J*=3 Hz), 8.38 (1H, d, *J*=3 Hz). IR (KBr) υ: 1717, 1664 cm^{-1}. MS *m/z*: 281 (M^+). *Anal*. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.30; H, 5.42; N, 15.00.

6-(Phenylethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6g)

Method A: The same procedure as above was carried out using **3g** (410 mg, 2.0 mmol) to give the alkene (**6g**) (138 mg, 26%). **Method B**: The same procedure as above was carried out using **3g** (500 mg, 2.4 mmol) to give the alkene (**6g**) (505 mg, 78%). mp 292-293°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 2.89-2.95 (4H, m), 7.18 (1H, t, *J*=7 Hz), 7.24 (2H, t, *J*=7 Hz), 7.29 (2H, d, *J*=7 Hz), 8.12 (1H, d, *J*=2 Hz), 8.43 (1H,

d, *J*=2 Hz), 11.43 (1H, s), 11.60 (1H, s). IR (KBr) υ: 1730, 1675 cm^{-1}. MS *m/z*: 267 (M^+). *Anal*. Calcd for $C_{15}H_{15}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.53; H, 5.05; N, 15.65.

1-Methyl-6-(phenylethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6h)

Method A: The same procedure as above was carried out using **3h** (400 mg, 1.9 mmol) to give the alkene (**6h**) (164 mg, 30%). **Method B**: The same procedure as above was carried out using **3h** (500 mg, 2.4 mmol) to give the alkene (**6h**) (559 mg, 82%). mp 224-225°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 2.88-3.04 (4H, m), 3.29 (3H, s), 7.18 (1H, t, *J*=7 Hz), 7.23 (2H, t, *J*=7 Hz), 7.28 (2H, d, *J*=7 Hz), 8.15 (1H, d, *J*=2.2 Hz), 8.44 (1H, d, *J*=2.2 Hz), 11.88 (1H, s). IR (KBr) υ: 1726, 1672 cm^{-1}. MS *m/z*: 281 (M^+). *Anal*. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.52; H, 5.45; N, 14.81.

1,3-Dimethyl-6-(phenylethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6i)

Method A: The same procedure as above was carried out using **3i** (410 mg, 2.0 mmol) to give the alkene (**6i**) (317 mg, 54%). **Method B**: The same procedure as above was carried out using **3i** (500 mg, 2.4 mmol) to give the alkene (**6i**) (608 mg, 85%). mp 113-114°C ($CHCl_3$-hexane). ^{1}H-NMR (DMSO-d_6) δ: 3.05 (4H, s), 3.54 (3H, s), 3.75 (3H, s), 7.00-7.43 (5H, m), 8.25 (1H, d, *J*=3 Hz), 8.38 (1H, d, *J*=3 Hz). IR (KBr) υ: 1710, 1668 cm^{-1}. MS *m/z*: 295 (M^+). *Anal*. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.36; H, 5.94; N, 14.10.

6-(2-Nitrophenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6j)

Method B: The same procedure as above was carried out using **3j** (500 mg, 2.2 mmol) to give the alkene **6j** (490 mg, 77%). mp 351-357°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 3.61-7.70 (2H, m), 7.81 (1H, t, *J*=9 Hz), 8.10 (1H, d, *J*=9 Hz), 8.20 (1H, d, *J*=9 Hz), 8.60 (1H, d, *J*=3 Hz). IR (KBr) υ: 1750 1700, 1520, 1335 cm^{-1}. MS *m/z*: 284 (M^+). *Anal*. Calcd for $C_{13}H_8N_4O_4$: C, 54.93; H, 2.84; N, 19.71. Found: C, 55.04; H2.89; N, 19.65.

1-Methyl-6-(2-nitrophenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6k)

Method B: The same procedure as above was carried out using **3k** (500 mg, 2.2 mmol) to give the alkene (**6k**) (567 mg, 85%). mp 253-254°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 3.71 (3H, s), 7.47 (1H, d, *J*=9 Hz), 7.64 (1H, t, *J*=9 Hz), 7.76 (1H, t, *J*=9 Hz), 8.10 (1H, d, *J*=9 Hz), 8.39 (1H, d, *J*=3 Hz), 8.62 (1H, d, *J*=3 Hz). IR (KBr) υ: 1710 1698, 1510, 1320 cm^{-1}. MS *m/z*: 298 (M^+). *Anal*. Calcd for $C_{14}H_{10}N_4O_4$: C, 56.38; H, 3.38; N, 18.78. Found: C, 56.46; H, 3.50; N, 18.63.

1,3-Dimethyl-6-(2-nitrophenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6l)

Method B: The same procedure as above was carried out using **3l** (500 mg, 2.2 mmol) to give the alkene (**6l**) (615 mg, 88%). mp 238-240°C (AcOH). ^{1}H-NMR (DMSO-d_6) δ: 3.31 (3H, s), 3.60 (3H, s), 7.63-7.73 (2H, m), 7.84 (1H, t, *J*=9 Hz), 8.13 (1H, d, *J*=9 Hz), 8.33 (1H, d, *J*=3 Hz), 8.75 (1H, d, *J*=3 Hz). IR (KBr) υ: 1710 1695, 1520, 1350 cm^{-1}. MS *m/z*: 312 (M^+). *Anal*. Calcd for $C_{14}H_{10}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.76; H, 3.99; N, 17.69.

General Procedure of 2-amino-6-substituted pyrido[2,3-*d*]pyrimidines (7)

2-Amino-6-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (7a)

The mixture of 2.4-diamino-6-hydroxypyrimidine (369 mg, 2.8 mmol) and the acrolein (500 mg, 2.8 mmol) in an aqueous 60% AcOH (15 mL) using the water separater was heated at 120°C for 3 h. The reaction mixture was diluted with H_2O, and the resulted precipitation was filtrated to give the pyridopyrimidine (**7a**) (594 mg, 89%). mp 416-420°C (AcOH). ^{1}H-NMR (DMSO-d_6-CF_3COOD) δ: 7.44-7.53 (3H, m), 7.81 (2H, d, *J*=6 Hz), 8.72 (1H, d, *J*=3 Hz), 9.03 (1H, d, *J*=3 Hz). IR (KBr) υ: 3100 cm^{-1}. *Anal*. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.71; H, 4.35; N, 23.34.

2-Amino-6-benzylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (7b)

The same procedure as above was carried out using **3b** (500 mg, 2.6 mmol) to give the alkene (**7b**) (650 mg, 99%). mp 379-392°C (AcOH). ^{1}H-NMR (DMSO-d_6-CF_3COOD) δ: 4.06 (2H, s), 7.18-7.30 (5H, m), 8.41 (1H, d, *J*=3 Hz), 8.66 (1H, d, *J*=3 Hz), 14.1 (2H, br s). IR (KBr) υ: 3150 cm^{-1}. *Anal*. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.80; H, 4.88; N, 22.06.

2-Amino-6-(phenylethyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (7c)

The same procedure as above was carried out using **3c** (500 mg, 2.4 mmol) to give the alkene (**7c**) (582 mg, 90%). mp 376-379°C (AcOH). ^{1}H-NMR (DMSO-d_6-CF_3COOD) δ: 2.88-3.03 (4H, m), 7.14-7.28 (5H, m), 8.50 (2H, s). IR (KBr) υ: 3100 cm^{-1}. *Anal*. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.73; H5.44; N, 21.09.

2-Amino-6-(2-nitrophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (7d)

The same procedure as above was carried out using **3d** (500 mg, 2.2 mmol) to give the alkene (**7d**) (621 mg, 98%). mp 457-461°C (AcOH). ^{1}H-NMR (DMSO-d_6-CF_3COOD) δ: 7.67 (1H, d, *J*=9 Hz), 7.76 (1H, t, *J*=9 Hz), 7.88 (1H, t, *J*=9 Hz), 8.22 (1H, d, *J*=9 Hz), 8.55 (1H, d, *J*=3 Hz), 8.83 (1H, d, *J*=3 Hz). IR (KBr) υ: 3120 cm^{-1}. *Anal*. Calcd for $C_{13}H_9N_5O_3$: C, 55.13; H, 3.20; N, 24.73. Found: C, 55.36; H, 3.34; N, 24.56.

REFERENCES

1. (a) E. M. Grivsky, S. Lee, C. W. Siegel, and C. A. Nichol, *J. Med. Chem*., 1980, **23**, 327. (b) J. J. McGuire and J. K. Coward, In "*Folates and Pterines*", Vol. 1, ed. by R. L. Blakley and S. J. Benkovic, John Wiley & Sons, N. Y., 1984, pp. 135-190. (c) J. A. Montgomery and J. R. Piper, In "*Folates Antagonists as Therapeutic Agents*", Vol. 1, ed. by F. M. Sirotnak, J. J. Burchall, W. W. Ensminger, and J. A. Montgomery, Academic Press, Orlando, Florida, 1984. (d) L. K. A. Rahman and S. R. Chhabra, *Med. Res. Rev*., **8**, 95 (1988). (e) A. Rosowsky, H. Fu, and S. F. Queener, *J. Heterocycl. Chem*., 2000, **37**, 921 and related references cited therein.
2. (a) E. C. Taylor, P. J. Harrington, S. R. Fletcher, G. P. Beardsley, and R. G. Moran, *J. Med. Chem*., 1985, **28**, 914. (b) E. C. Taylor, R. G. Moran, S. W. Baldwin, C. Shih, *J. Biol. Chem.*, 1989, **264**, 21047. (c) E. C. Taylor, *J. Heterocycl. Chem*., 1990, **27**, 1. (d) E. C. Taylor and B. Liu, *J. Org. Chem*., 2001, **66**, 3726 and related references cited therein.
3. (a) E. Lunt and C. G. Newton, "*Comprehensive Heterocyclic Chemistry*", Vol. 3, ed. by A. R.

Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, pp. 199-232 and 260-261 (b) T. J. Delia, "*The Chemistry of Heterocyclic Compounds*", Vol. 24, Part 4, ed. by E. C. Taylor, Interscience Publishers, New York, 1992. (c) H. Wamhoff, J. Dzenis, and K. Hirota, "*Advances in Heterocyclic Chemistry*", Vol. 55, ed. by A. R. Katritzky, Academic Press, San Diego, 1992, pp. 129-259. (d) I. Durucasu, *Heterocycles*, 1993, **35**, 1527.

4. (a) R. Bernetti, F. Mancini, and C. C. Price, *J. Org. Chem*., 1962, **27**, 2863. (b) T.-C. Lee and G. Salemnick, *ibid*., 1975, **40**, 3608. (c) C. Temple, Jr., R. D. Elliott, and J. A. Montgomery, *ibid.*, 1982, **47**, 761. (d) E. C. Taylor, D. C. Palmer, T. J. George, S. R. Fletcher, C. P. Tseng, and P. J. Harrington, *ibid*., 1983, **48**, 4852. (e) E. C. Taylor and C.-M. Yoon, *Synth. Commun*., 1988, **18**, 1187. (f) E. C. Taylor and G. S. K. Wong, *J. Org. Chem*., 1989, **54**, 3618. (g) A. Gangjee and R. Devraj, *J. Heterocycl. Chem*., 1991, **28**, 1747. (h) E. C. Taylor, S. R. Otiv, and I. Durucasu, *ibid*., 1993, **36**, 1883.
5. (a) B. S. Hurlbert and B. F. Valenti, *J. Med. Chem*., 1968, **11**, 708. (b) E. Stark and E. Breitmaier, *Tetrahedron*, 1973, **29**, 2209. (c) G. M. Coppola, G. E. Hardtmann, and B. S. Huegi, *J. Heterocycl. Chem.*, 1974, **11**, 51. (d) E. Stark, E. Kraas, F.-S. Tjoeng, G. Jung, and E. Breitmaier, *Chem. Ber*., 1974, **107**, 2537. (e) E. C. Taylor and P. M. Harrington, *J. Org. Chem*., 1990, **55**, 3222.
6. (a) B. Walsh and H. Wamhoff, *Chem. Ber*., 1989, **122**, 1673. (b) K. Hirota, H. Kuki, and Y. Maki, *Heterocycles*, 1994, **37**, 563. (c) K. Y. Rho, J. H. Kim, S. H. Kim, and C. M. Yoon, *ibid*., 1998, **48**, 2521.
7. (a) S. Kano, Y. Yuasa, S. Shibuya, and S. Hibino, *Heterocycles*, 1982, **19**, 1079. (b) S. Hibino, K. Nomi, Y. Shintani, E. Sugino, H. Fujioka, S. Kadowaki, and M. Otagiri, *Drug Design and Delivery*, 1989, **5**, 49. (c) K. Harada, T. Choshi, E. Sugino, K. Sato, and S. Hibino, *Heterocycles*, 1994, **38**, 1119. (d) K. Harada, T. Choshi, E. Sugino, K. Sato, and S. Hibino, *ibid*., 1996, **42**, 213.
8. M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Am. Chem. Soc*., 1966, **88**, 5747.