

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

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**Abstract**-The reaction of the  $\beta$ -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,<sup>1</sup> with 5,10-dideazatetrahydrofolic acid (DDATHF) and its 6*R*-enantiomer (lometrexol), as antifolates, having been of particular interest.<sup>2</sup> Although, a large number of studies in this area have been reported,<sup>3</sup> almost all of the preparation for 6-substituted pyrido[2,3-*d*]pyrimidines, other than those of Wamhoff,<sup>6a</sup> Hirota,<sup>6b</sup> and Yoon,<sup>6c</sup> have involved the formation of a fused pyridine ring using 6-aminouracils with malonaldehyde derivatives<sup>4</sup> or their equivalents<sup>5</sup> such as  $\beta$ -amino- and  $\beta$ -alkoxyacroleins. We have previously described the utilization of  $\beta$ -methylsulfanylacroleins as an efficient three-carbon unit for the synthesis of 5-phenylpyrimidines,<sup>7a,b</sup> 5-benzylpyrimidines (trimethoprim),<sup>7c</sup> and imidazo[4,5-*b*]pyridines.<sup>7d</sup> 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  $\beta$ -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**),<sup>7d,8</sup> 77% (**2b**), 99% (**2c**), and 96% (**2d**) yields, respectively; these sulfides then underwent a Vilsmeier reaction to produce the required  $\beta$ -methylsulfanylacroleins (**3**) in 72 (**3a**),<sup>7d</sup> 98 (**3b**), 70 (**3c**), and 49% (**3d**) yields, respectively, according to our reported procedure<sup>7</sup> (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.<sup>7d</sup> The addition of Lewis acids instead of *p*-TsOH was

Scheme 1

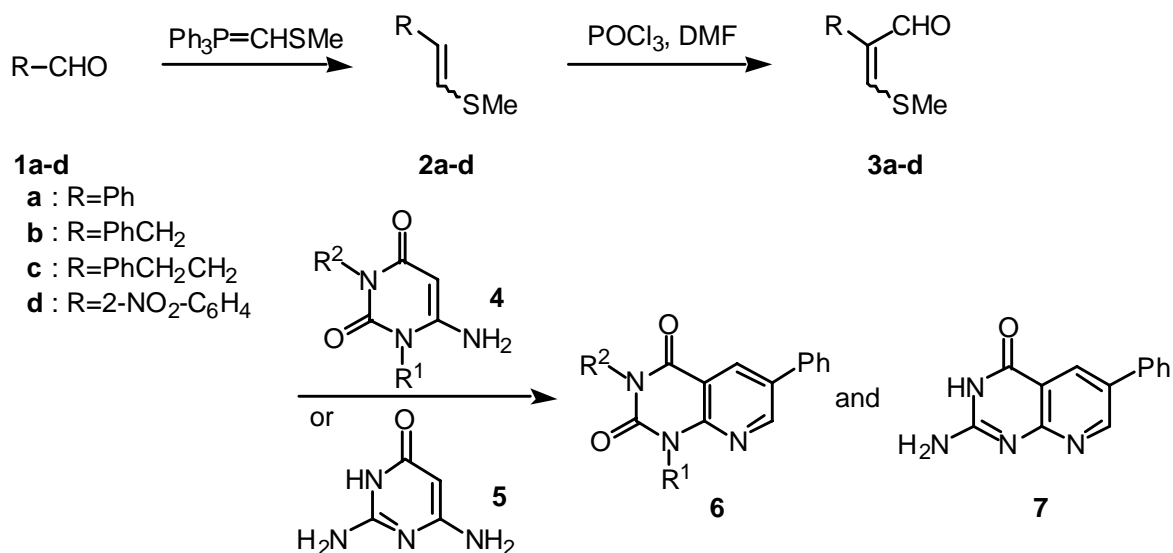
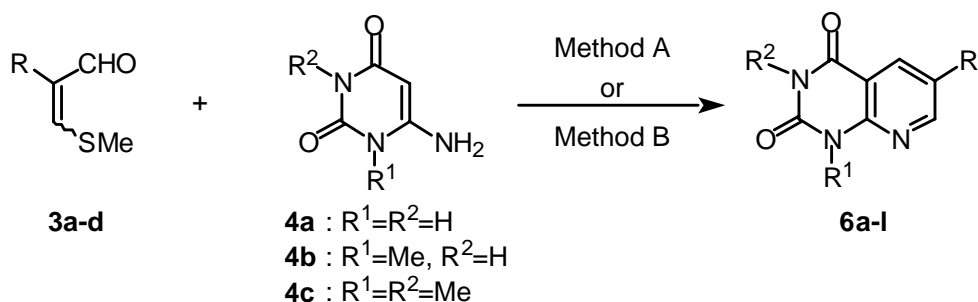


Table 1



Run	Starting Materials		Products ( <b>6a-l</b> )			Yield (%) of <b>6a-l</b>	
	<b>3a-d</b>	<b>4a-c</b>	R	R <sup>1</sup>	R <sup>2</sup>	Method A <sup>a)</sup>	Method B <sup>b)</sup>
1	<b>3a</b>	+ <b>4a</b>	<b>6a</b> Ph	H	H	53	75
2	<b>3a</b>	+ <b>4b</b>	<b>6b</b> Ph	Me	H	69	99
3	<b>3a</b>	+ <b>4c</b>	<b>6c</b> Ph	Me	Me	64	92
4	<b>3b</b>	+ <b>4a</b>	<b>6d</b> PhCH <sub>2</sub>	H	H	25	80
5	<b>3b</b>	+ <b>4b</b>	<b>6e</b> PhCH <sub>2</sub>	Me	H	44	96
6	<b>3b</b>	+ <b>4c</b>	<b>6f</b> PhCH <sub>2</sub>	Me	Me	68	92
7	<b>3c</b>	+ <b>4a</b>	<b>6g</b> PhCH <sub>2</sub> CH <sub>2</sub>	H	H	26	78
8	<b>3c</b>	+ <b>4b</b>	<b>6h</b> PhCH <sub>2</sub> CH <sub>2</sub>	Me	H	30	82
9	<b>3c</b>	+ <b>4c</b>	<b>6i</b> PhCH <sub>2</sub> CH <sub>2</sub>	Me	Me	54	85
10	<b>3d</b>	+ <b>4a</b>	<b>6j</b> 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	H	H	- <sup>c)</sup>	77
11	<b>3d</b>	+ <b>4b</b>	<b>6k</b> 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Me	H	- <sup>c)</sup>	85
12	<b>3d</b>	+ <b>4c</b>	<b>6l</b> 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Me	Me	- <sup>c)</sup>	88

a) heating in benzene in the presence of *p*-TsOH.

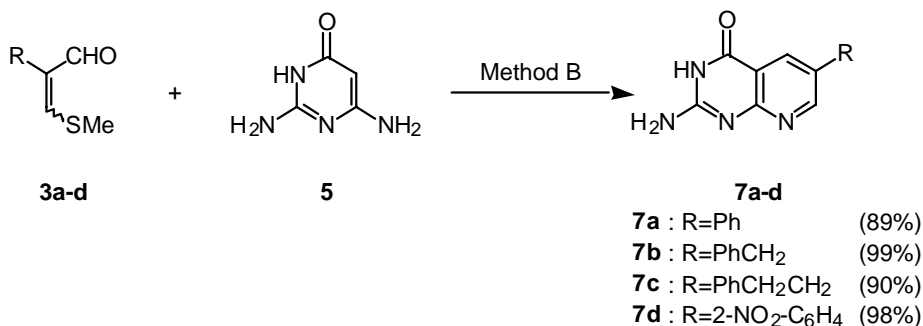
b) heating in an aqueous AcOH (60%).

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).

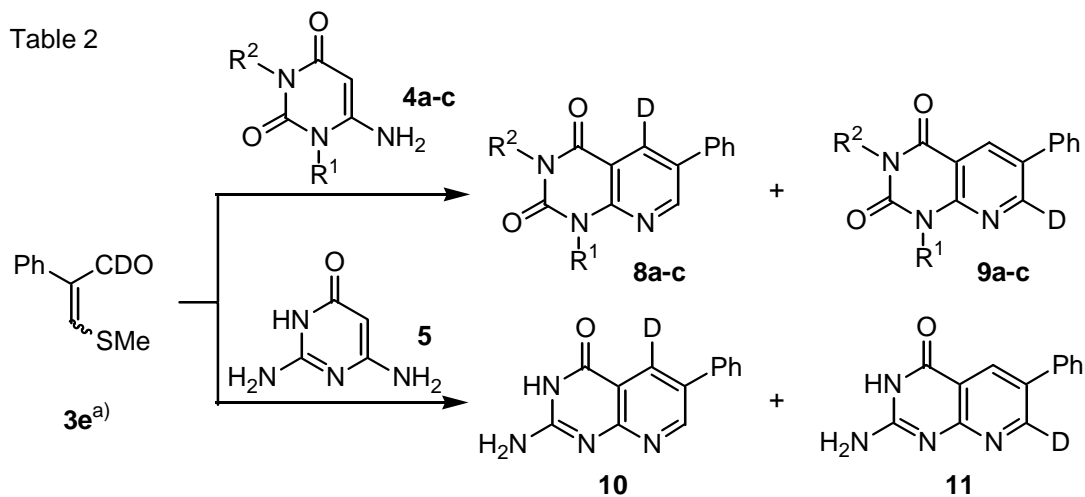
Scheme 2



To examine the reaction mechanism in this case, we repeated the reaction using *d*-labeled  $\beta$ -methylsulfanylacroleins (**3e**)<sup>7d</sup> (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  $\delta$  8.5 (C7-H) and  $\delta$  9.0 (C5-H) in the respective <sup>1</sup>H-NMR spectra. Moreover, the 2 : 1 ratio of **10** and **11** was measured by the relative intensities of C7-H (near at  $\delta$  9.3, singlet) and C5-H (near at  $\delta$  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<sup>5d</sup> has proposed that the reaction of the  $\beta$ -aminoacrolein with 6-aminouracil (**4**) would proceed by route “b” of Chart 1 in 1973. Although the reactivity of  $\beta$ -

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



Run	Starting Materials		Methods	Ratio of deuterated Products <sup>b)</sup>	
	3e <sup>a)</sup>	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 <sup>1</sup>H-NMR spectra.

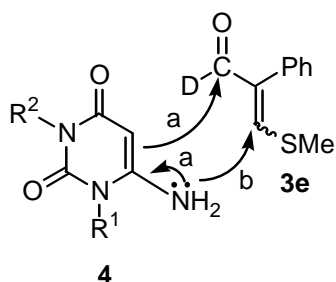


Chart 1

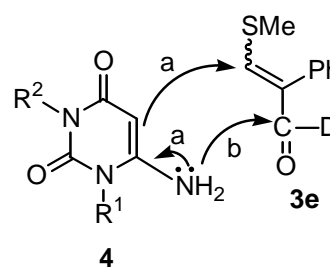


Chart 2

In summary, a new synthesis of 6-substituted pyrido[2,3-*d*]pyrimidines using  $\beta$ -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  $\beta$ -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. <sup>1</sup>H-NMR spectra were taken by JEOL PMX60Si and JNM AL-300 spectrometers using SiMe<sub>4</sub> 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<sub>2</sub> 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<sub>4</sub>Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, 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°C/2.0 torr. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>). *Anal.* Calcd for C<sub>10</sub>H<sub>12</sub>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°C/2.5 torr. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>). *Anal.* Calcd for C<sub>11</sub>H<sub>14</sub>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) ν: 1521, 1349 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sup>+</sup>). *Anal.* Calcd for C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>S: C, 55.37; H, 4.65. Found: C, 55.31; H, 4.77.

### 2-Benzyl-3-methylsulfanylacrolein (3b)

POCl<sub>3</sub> (3.4 mL, 37.4 mmol) was added to an ice-cooled solution of DMF (30 mL) under N<sub>2</sub> 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<sub>2</sub>SO<sub>4</sub>, 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°C/2.5 torr. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.33 (3H, s), 3.58 (2H, s), 7.13-7.28 (6H, m), 9.23 (1H, s). IR (naet) ν: 1725 cm<sup>-1</sup>. MS *m/z*: 192 (M<sup>+</sup>). *Anal.* Calcd for C<sub>11</sub>H<sub>12</sub>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°C/6.0 torr. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.62 (4H, s), 7.11 (1H, s), 7.15 (5H, s), 9.15 (1H, s). IR (naet) ν: 1666 cm<sup>-1</sup>. MS *m/z*: 206 (M<sup>+</sup>). *Anal.* Calcd for C<sub>12</sub>H<sub>14</sub>OS: C, 69.86; H, 6.84. Found: C, 69.80; 6.90.

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

POCl<sub>3</sub> (9.3 mL, 99.9 mmol) was added to an ice-cooled solution of DMF (20 mL) under N<sub>2</sub> 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°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<sub>2</sub>SO<sub>4</sub>, 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%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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) ν: 1671, 1527, 1349 cm<sup>-1</sup>. MS *m/z*: 223 (M<sup>+</sup>). *Anal.* Calcd for C<sub>10</sub>H<sub>9</sub>NO<sub>3</sub>S: 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 separator was heated at 100°C for 14 h. The reaction mixture was quenched with 30% aqueous KHCO<sub>3</sub> solution (30 mL), and the whole was extracted with 5% MeOH-CHCl<sub>3</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, 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°C (decomp) (AcOH-H<sub>2</sub>O). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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) ν: 1733, 1684 cm<sup>-1</sup>. MS *m/z*: 239 (M<sup>+</sup>). *Anal.* Calcd for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: 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 separator was heated at 120°C for 3 h. The reaction mixture was diluted with H<sub>2</sub>O, and extracted with 5% MeOH-CHCl<sub>3</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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) ν: 1728, 1680 cm<sup>-1</sup>. MS *m/z*: 253 (M<sup>+</sup>). *Anal.* Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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) ν: 1709, 1662 cm<sup>-1</sup>. MS *m/z*: 267 (M<sup>+</sup>). *Anal.* Calcd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: 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 210-211°C (EtOAc). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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) ν: 1709 1662 cm<sup>-1</sup>. MS *m/z*: 253 (M<sup>+</sup>). *Anal.* Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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) ν: 1719, 1655 cm<sup>-1</sup>. MS *m/z*: 267 (M<sup>+</sup>). *Anal.* Calcd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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) ν: 1717, 1664 cm<sup>-1</sup>. MS *m/z*: 281 (M<sup>+</sup>). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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)  $\nu$ : 1730, 1675  $\text{cm}^{-1}$ . MS  $m/z$ : 267 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ : 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).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 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)  $\nu$ : 1726, 1672  $\text{cm}^{-1}$ . MS  $m/z$ : 281 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$ : 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 ( $\text{CHCl}_3$ -hexane).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 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)  $\nu$ : 1710, 1668  $\text{cm}^{-1}$ . MS  $m/z$ : 295 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2$ : 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).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 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)  $\nu$ : 1750 1700, 1520, 1335  $\text{cm}^{-1}$ . MS  $m/z$ : 284 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{13}\text{H}_8\text{N}_4\text{O}_4$ : C, 54.93; H, 2.84; N, 19.71. Found: C, 55.04; H, 2.89; 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).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 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)  $\nu$ : 1710 1698, 1510, 1320  $\text{cm}^{-1}$ . MS  $m/z$ : 298 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_4$ : 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).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 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)  $\nu$ : 1710 1695, 1520, 1350  $\text{cm}^{-1}$ . MS  $m/z$ : 312 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_4$ : 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 separator was heated at 120°C for 3 h. The reaction mixture was diluted with H<sub>2</sub>O, and the resulted precipitation was filtrated to give the pyridopyrimidine (**7a**) (594 mg, 89%). mp 416-420°C (AcOH). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>-CF<sub>3</sub>COOD) 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) ν: 3100 cm<sup>-1</sup>. *Anal.* Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>O: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>-CF<sub>3</sub>COOD) 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) ν: 3150 cm<sup>-1</sup>. *Anal.* Calcd for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>-CF<sub>3</sub>COOD) δ: 2.88-3.03 (4H, m), 7.14-7.28 (5H, m), 8.50 (2H, s). IR (KBr) ν: 3100 cm<sup>-1</sup>. *Anal.* Calcd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.73; H, 5.44; 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>-CF<sub>3</sub>COOD) 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) ν: 3120 cm<sup>-1</sup>. *Anal.* Calcd for C<sub>13</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub>: C, 55.13; H, 3.20; N, 24.73. Found: C, 55.36; H, 3.34; N, 24.56.

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