

HETEROCYCLES, Vol. 89, No. 9, 2014, pp. 2168 - 2176. © 2014 The Japan Institute of Heterocyclic Chemistry  
Received, 8th July, 2014, Accepted, 29th July, 2014, Published online, 6th August, 2014  
DOI: 10.3987/COM-14-13058

## A SIMPLE SYNTHESIS OF 4-HYDROXY-3,4-DIHYDROPYRIDO[3,4-*d*]PYRIMIDINE-2(1*H*)-THIONE DERIVATIVES BY THE REACTION OF 3-ISOTHIOCYANATOPYRIDIN-4-YL KETONES WITH PRIMARY AMINES

**Kazuhiro Kobayashi,\* Hiroki Inouchi, and Manami Konishi**

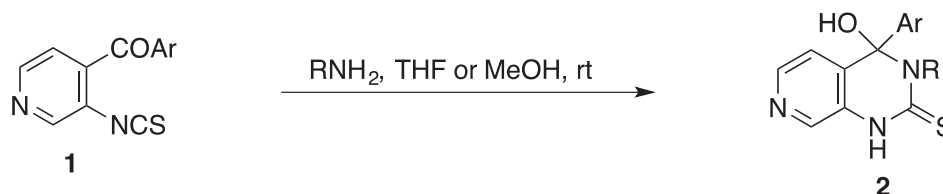
Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

**Abstract** – The reaction of aryl(3-isothiocyanatopyridin-4-yl)methanones, prepared easily from commercially available 3-aminopyridine, with primary amines at room temperature afforded 3-substituted 4-aryl-4-hydroxy-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thiones in good yields. These ketones could be converted to new tricyclic heterocyclic systems, 2,3-dihydro-5*H*-pyrido[3,4-*d*]thiazolo[3,2-*a*]pyrimidine and 3,4-dihydro-2*H*,6*H*-pyrido[3',4':4,5]-pyrimido[2,1-*b*][1,3]thiazine, upon treatment with 2-bromoethanamine hydrobromide and 3-bromopropaneamine hydrobromide, respectively, in the presence two equivalents of triethylamine.

3,4-Dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione derivatives are interesting heterocycles, because some compounds having this structure have reported to exhibit biological activity<sup>1</sup> and have been elaborated to more complex fused heterocyclic systems.<sup>2</sup> However, no reports have been so far recorded for the general preparation of 3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione derivatives. On the other hand, we have recently described syntheses of 1,7-naphthyridine<sup>3a</sup> and 3*H*-pyrrolo[2,3-*c*]pyridin-3-ol derivatives<sup>3b</sup> utilizing aryl(3-isocyanopyridin-4-yl)methanones, which can be easily prepared starting with commercially available 3-aminopyridine. We envisaged that conversion of these isocyanides to the corresponding isothiocyanates and their reaction with primary amines would give 3-substituted 4-aryl-4-hydroxy-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thiones.<sup>4</sup> This paper describes the results of our study, which provide a facile synthetic entry to 3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione derivatives (**2**) and (**3**) from aryl(3-isothiocyanatopyridin-4-yl)methanones (**1**). We have also found that

the use of 2-bromoethanamine and 3-bromopropanamine has proven to result in two-ring annulation leading to the corresponding tricyclic heterocyclic systems (**4**) and (**5**).

The synthesis of **2** from **1** was carried out under the conditions shown in Scheme 1. The respective known isocyanides could be easily converted to the requisite starting materials (**1**) under the conditions reported by Fujiwara *et al.*<sup>5</sup> When these isothiocyanato ketones (**1**) were treated with primary amines in THF (or MeOH for benzenamine) at room temperature, the addition of amines to the isothiocyanato carbon of **1** followed by ring closure of the resulting thiourea intermediates proceeded smoothly and cleanly to afford, after evaporation of the solvent and the subsequent recrystallization of the crude products, the corresponding desired products (**2**). The progress of the reactions could be readily monitored by TLC on silica gel. The results obtained using series of **1** and primary amines are summarized in Table 1. The yields of **2** were generally good. The reaction of **1a** with benzenamine in THF gave a *ca.* 1:1 mixture of two products, **2d** and a structurally undefined product, probably 4-phenyl-2-(phenylimino)-1,4-dihydro-2*H*-1,3-benzothiazin-4-ol as judged by <sup>1</sup>H NMR analyses. The thiourea intermediate could not be observed by TLC analyses for the confirmation of the progress of the reaction sequence in each case as it rapidly underwent intramolecular ring closure to form **2**. The thiocarbonyl group appears to stabilize the hemiaminal structure in these products.



Scheme 1

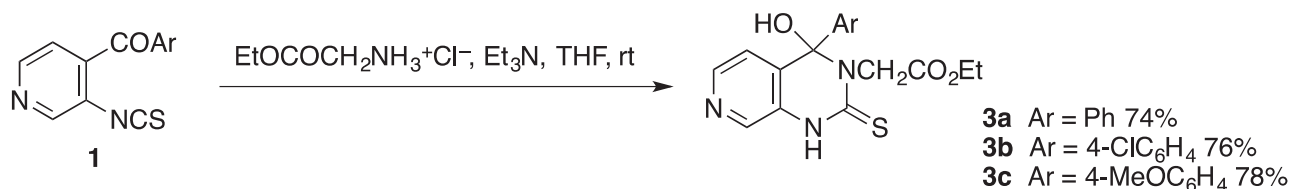
**Table 1.** Preparation of 4-hydroxy-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione derivatives (**2**)

Entry	<b>1</b>	R	Solvent	<b>2</b>	Yield/% <sup>a</sup>
1	<b>1a</b> (Ar = Ph)	Me	THF	<b>2a</b>	76
2	<b>1a</b>	Bn	THF	<b>2b</b>	78
3	<b>1a</b>	MeO(CH <sub>2</sub> ) <sub>2</sub>	THF	<b>2c</b>	88
4	<b>1a</b>	Ph	MeOH	<b>2d</b>	73
5	<b>1b</b> (Ar = 4-ClC <sub>6</sub> H <sub>4</sub> )	Et	THF	<b>2e</b>	81
6	<b>1c</b> (Ar = 4-MeOC <sub>6</sub> H <sub>4</sub> )	Me	THF	<b>2f</b>	76
7	<b>1c</b>	4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	THF	<b>2g</b>	72

<sup>a</sup> Yields of isolated products.

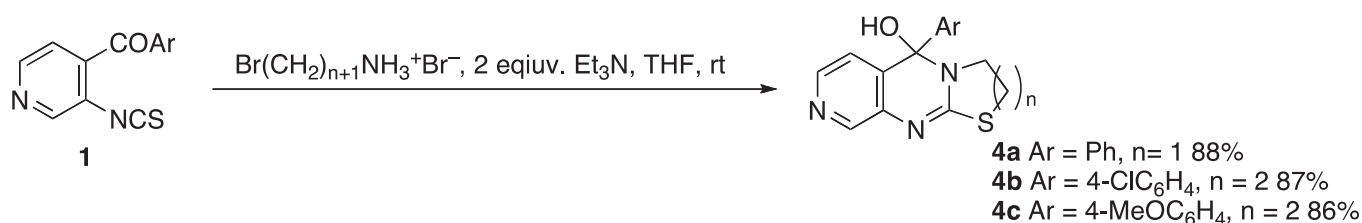
The 3-ethoxycarbonylmethyl derivatives (**3**) could also be readily prepared by employing essentially the same procedure for the preparation of **2** as shown in Scheme 2. Thus, the treatment of **1** with glycine ethyl ester hydrochloride in THF in the presence of an equivalent of triethylamine afforded, after

evaporation of the solvent followed by washing the resulting residual solid with water and recrystallization, the desired products (**3**) in relatively good yields.



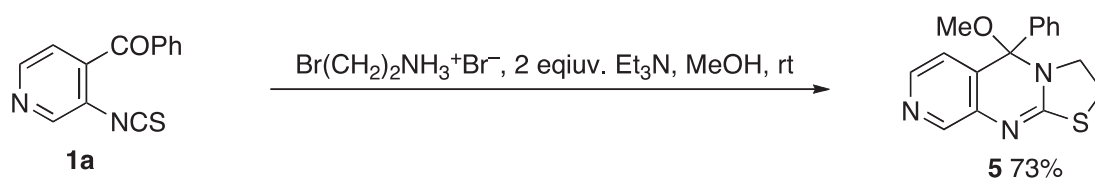
Scheme 2

In order to demonstrate the efficiency of the present procedure, we investigated the reaction of **1** with 2-bromoethanamine hydrobromide or 3-bromopropanamine hydrobromide in the presence of two equivalents of triethylamine in THF, expecting the production of tricyclic derivatives (**4**) (Scheme 3). The successive formation of dihydropyrimidine ring followed by thiazolidine or 1,3-thiazinane ring formations proceeded smoothly and cleanly to yield the desired tricyclic derivatives (**4**) in high yields. Each of these products could be obtained in a pure form by a purification procedure similar to that for **3**.



Scheme 3

It should be also noted that 5-methoxy-5-phenyl-2,3-dihydro-5*H*-pyrido[3,4-*d*]thiazolo[3,2-*a*]pyrimidine (**5**) was formed by reacting **1a** with 2-bromoethanamine hydrobromide in the presence of two equivalents of triethylamine in methanol at room temperature in relatively good yield as depicted in Scheme 4.



Scheme 4

In conclusion, we have developed an efficient ring annulation procedure leading to the 4-hydroxy-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione system. The overall efficiency of this method, the ease of access to the starting materials, the simplicity of operation, the mild reaction

conditions, the applicability to the preparation of new tricyclic ring systems, and the relatively high yields, makes it valuable in organic synthesis. Work on the synthesis of new heterocyclic systems utilizing aryl(3-isothiocyanatopyridin-4-yl)methanones is now in progress in our laboratory.

## EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Spectrum65 FTIR spectrophotometer.  $^1\text{H}$  NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400FT NMR spectrometer operating at 400 MHz.  $^{13}\text{C}$  NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF<sub>254</sub>. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

**Starting Materials.** *n*-BuLi was supplied by Asia Lithium Corporation. Aryl(3-isocyanopyridin-4-yl)methanones were prepared by the procedure previously reported by us.<sup>3</sup> All other chemicals used in this study were commercially available.

**Aryl(3-isothiocyanatopyridin-4-yl)methanones 1.** These compound were prepared by reacting the respective aryl(3-isocyanopyridin-4-yl)methanones with sulfur in the presence of catalytic amount of selenium and excess Et<sub>3</sub>N in THF under conditions reported by Fujiwara *et al.*<sup>5</sup>

**(3-Isouthiocyanatopyridin-4-yl)phenylmethanone (1a):** yield: 78%; a yellow oil;  $R_f$  0.35 (AcOEt/hexane 1:3); IR (neat) 2056, 1670  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (dd,  $J = 5.0, 0.9$  Hz, 1H), 7.53 (dd,  $J = 8.2, 7.3$  Hz, 2H), 7.68 (tt,  $J = 7.3, 1.4$  Hz, 1H), 7.81 (dd,  $J = 8.2, 1.4$  Hz, 2H), 8.62 (d,  $J = 5.0$  Hz, 1H), 8.68 (s, 1H). Anal. Calcd for  $\text{C}_{13}\text{H}_8\text{N}_2\text{OS}$ : C, 64.98; H, 3.36; N, 11.66. Found: C, 64.71; H, 3.41; N, 11.53.

**(4-Chlorophenyl)(3-isouthiocyanatopyridin-4-yl)methanone (1b):** yield: 78%; an orange solid; mp 80–82 °C (hexane/Et<sub>2</sub>O); IR (KBr) 2090, 1662  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (d,  $J = 5.0$  Hz, 1H), 7.51 (d,  $J = 8.7$  Hz, 2H), 7.75 (d,  $J = 8.7$  Hz, 2H), 8.63 (d,  $J = 5.0$  Hz, 1H), 8.69 (s, 1H). Anal. Calcd for  $\text{C}_{13}\text{H}_7\text{ClN}_2\text{OS}$ : C, 56.83; H, 2.57; N, 10.20. Found: C, 56.82; H, 2.70; N, 10.10.

**(3-Isouthiocyanatopyridin-4-yl)(4-methoxyphenyl)methanone (1c):** yield: 84%; a yellow oil;  $R_f$  0.45 ( $\text{CH}_2\text{Cl}_2$ ); IR (neat) 2053, 1660  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.91 (s, 3H), 6.99 (d,  $J = 8.8$  Hz, 2H), 7.33 (d,  $J = 4.9$  Hz, 1H), 7.79 (d,  $J = 8.8$  Hz, 2H), 8.60 (d,  $J = 4.9$  Hz, 1H), 8.65 (s, 1H). Anal. Calcd for  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ : C, 62.21; H, 3.73; N, 10.36. Found: C, 62.10; H, 3.79; N, 10.18.

**General Procedure for the Preparation of 4-Hydroxy-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thiones (2).** To a stirred solution of **1** (1.0 mmol) in THF or MeOH (3 mL) at rt was added a primary amine (1.0 mmol). For MeNH<sub>2</sub> and EtNH<sub>2</sub>, MeOH solutions were used. After complete consumption of the starting material was confirmed by TLC analyses (SiO<sub>2</sub>; AcOEt/hexane 1:1), the mixture was concentrated by evaporation to give a residual solid, which was recrystallized from hexane/THF to give **2**.

**4-Hydroxy-3-methyl-4-phenyl-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2a):** a white solid; mp 182–183 °C (decomp); IR (KBr) 3178, 3124, 1101 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 3.02 (s, 3H), 6.93 (d, *J* = 5.0 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.35–7.41 (m, 4H), 7.92 (br s, 1H), 8.08 (d, *J* = 5.0 Hz, 1H), 8.35 (s, 1H), 11.22 (br s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 35.24, 85.67, 121.34, 125.31, 128.34, 128.71, 129.06, 130.89, 135.85, 143.44, 143.74, 174.01; MS *m/z* 271 (M<sup>+</sup>, 100). Anal. Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>OS: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.73; H, 4.74; N, 15.20.

**4-Hydroxy-4-phenyl-3-(phenylmethyl)-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2b):** a white solid; mp 209–210 °C (decomp) (hexane/CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3173, 3112, 1194 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 4.65 (d, *J* = 15.5 Hz, 1H), 5.20 (d, *J* = 15.5 Hz, 1H), 7.08–7.35 (m, 11H), 7.99 (s, 1H), 8.14 (d, *J* = 4.6 Hz, 1H), 8.38 (s, 1H), 11.44 (br s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 51.07, 86.93, 120.89, 125.46, 125.85, 126.91, 127.46, 128.44, 128.54, 129.07, 131.66, 133.83, 138.70, 143.71 (2C), 175.46. HR MS. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>OS (M+H): 348.1170. Found: *m/z* 348.1167. Anal. Calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>OS: C, 69.14; H, 4.93; N, 12.09. Found: C, 69.08; H, 5.18; N, 11.95.

**4-Hydroxy-3-(2-methoxyethyl)-4-phenyl-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2c):** a white solid; mp 194–195 °C (decomp) (hexane/CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3195, 3132, 1111 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.41 (s, 3H), 3.43–3.50 (m, 2H), 4.10–4.16 (m, 1H), 4.62–4.67 (m, 1H), 6.39 (s, 1H), 7.03 (d, *J* = 4.9 Hz, 1H), 7.31–7.46 (m, 5H), 8.23 (d, *J* = 4.9 Hz, 1H), 8.25 (s, 1H), 9.00 (br s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 48.71, 59.03, 69.45, 86.05, 121.37, 125.79, 128.21, 128.82, 128.84, 132.21, 135.19, 143.17, 144.77, 174.84. HR MS. Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub>S (M+H): 316.1119. Found: *m/z* 316.1105. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S: C, 60.93; H, 5.43; N, 13.32; S, 10.17. Found: C, 60.77; H, 5.41; N, 13.30; S, 10.06.

**4-Hydroxy-3,4-diphenyl-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2d):** a white solid; mp 186–188 °C (hexane/CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3185, 3112, 1167 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 6.33 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 5.2 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 7.10 (td, *J* = 8.0, 1.1 Hz, 1H), 7.19–7.27 (m, 6H), 7.33 (d, *J* = d, *J* = 7.4 Hz, 1H), 8.02 (s, 1H), 8.13 (d, *J* = 5.2 Hz, 1H), 8.49 (s, 1H), 11.64 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 86.50, 121.50, 126.52, 126.92, 127.12, 127.57, 127.80, 128.08, 129.71, 130.62, 131.56, 132.46, 136.12, 140.60, 143.34, 143.53, 175.05. HR MS. Calcd for C<sub>19</sub>H<sub>16</sub>N<sub>3</sub>OS (M+H): 334.1014. Found: *m/z* 334.1009. Anal. Calcd for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>OS: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.32; H, 4.56; N, 12.40.

**4-(4-Chlorophenyl)-3-ethyl-4-hydroxy-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2e):** a pale-yellow solid; mp 140–141 °C (decomp) (hexane/THF); IR (KBr) 3183, 3125, 1109 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 1.07 (t, *J* = 7.3 Hz, 3H), 3.88–3.94 (m, 2H), 6.97 (d, *J* = 5.5 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 8.00 (s, 1H), 8.11 (d, *J* = 5.5 Hz, 1H), 8.36 (s, 1H), 11.28 (br s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 14.52, 42.86, 85.70, 120.97, 127.52, 128.61, 128.98, 130.93, 133.06, 135.87, 143.33, 143.51, 173.29. HR MS. Calcd for C<sub>15</sub>H<sub>15</sub>ClN<sub>3</sub>OS (M+H): 320.0624. Found: *m/z* 320.0609. Anal. Calcd for C<sub>15</sub>H<sub>14</sub>ClN<sub>3</sub>OS: C, 56.33; H, 4.41; N, 13.14. Found: C, 56.25; H, 4.48; N, 13.00.

**4-Hydroxy-4-(4-methoxyphenyl)-3-methyl-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2f):** a pale-yellow solid; mp 192–194 °C (decomp) (hexane/CHCl<sub>3</sub>); IR (KBr) 3196, 3127, 1613, 1171 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 3.02 (s, 3H), 3.72 (s, 3H), 6.92 (d, *J* = 5.2 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.84 (s, 1H), 8.08 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 1H), 11.31 (s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 35.19, 55.14, 85.52, 113.96, 121.35, 126.69, 129.02, 131.15, 135.81, 136.00, 143.39, 159.01, 173.86. HR MS. Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>S (M+H): 302.0963. Found: *m/z* 302.0953. Anal. Calcd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: C, 59.78; H, 5.02; N, 13.94; S, 10.64. Found: C, 59.48; H, 4.91; N, 13.96; S, 10.57.

**4-Hydroxy-4-(4-methoxyphenyl)-3-[(4-methoxyphenyl)methyl]-3,4-dihydropyrido[3,4-*d*]pyrimidine-2(1*H*)-thione (2g):** a pale-yellow solid; mp 232–234 °C (hexane/THF); IR (KBr) 3189, 3111, 1174 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 3.67 (s, 3H), 3.69 (s, 3H), 4.61 (d, *J* = 15.5 Hz, 1H), 5.10 (d, *J* = 15.5 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 5.2 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.89 (s, 1H), 8.13 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 11.36 (br s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 50.34, 54.96, 55.14, 86.73, 112.87, 113.79, 120.80, 126.83, 128.46, 129.02, 130.85, 131.98, 135.77, 135.94, 143.68, 157.59, 159.18, 175.41. HR MS. Calcd for C<sub>22</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S (M+H): 408.1382. Found: *m/z* 408.1370. Anal. Calcd for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S: C, 64.85; H, 5.19; N, 10.31. Found: C, 64.75; H, 5.21; N, 10.20.

**Typical Procedure for the Preparation of Compounds (3). Ethyl 2-(4-Hydroxy-4-phenyl-2-thioxo-1,4-dihydropyrido[3,4-*d*]pyrimidin-3(2*H*)-yl)acetate (3a).** To a stirred solution of **1a** (0.15 g, 0.62 mmol) and glycine ethyl ester hydrochloride (86 mg, 0.62 mmol) in THF (3 mL) at rt was added Et<sub>3</sub>N (63 mg, 0.62 mmol). After 20 min, the solvent was removed by evaporation and water (15 mL) was added in order to dissolve Et<sub>3</sub>N<sup>+</sup>HCl<sup>-</sup>. The precipitate was collected by filtration under reduced pressure and recrystallized from hexane/CH<sub>2</sub>Cl<sub>2</sub> to give **3a** (0.16 g, 74%); a pale-yellow solid; mp 170–172 °C; IR (KBr) 3189, 3121, 1737, 1205 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 1.08 (t, *J* = 6.9 Hz, 3H), 3.95–3.99 (m, 2H), 4.12 (d, *J* = 17.2 Hz, 1H), 4.42 (d, *J* = 17.2 Hz, 1H), 6.91 (d, *J* = 5.5 Hz, 1H), 7.31–7.48 (m, 5H), 8.11 (s, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 8.40 (s, 1H), 11.57 (br s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ

13.96, 48.98, 60.26, 86.18, 121.43, 125.96, 128.21, 128.44, 129.96, 130.96, 136.00, 143.24, 143.73, 167.58, 174.67. HR MS. Calcd for  $C_{17}H_{18}N_3O_3S$  (M+H): 344.1069. Found:  $m/z$  344.1054. Anal. Calcd for  $C_{17}H_{17}N_3O_3S$ : C, 59.46; H, 4.99; N, 12.24. Found: C, 59.29; H, 5.08; N, 12.06.

**Ethyl 2-[4-Hydroxy-4-(4-chlorophenyl)-2-thioxo-1,4-dihydropyrido[3,4-*d*]pyrimidin-3(2*H*)-yl]acetate (3b):** a pale-yellow solid; mp 254–255 °C (hexane/THF); IR (KBr) 3188, 3124, 1743, 1208  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.08 (t,  $J = 7.4$  Hz, 3H), 3.93–3.98 (m, 2H), 4.17 (d,  $J = 18.3$  Hz, 1H), 4.37 (d,  $J = 18.3$  Hz, 1H), 6.89 (d,  $J = 5.2$  Hz, 1H), 7.38 (d,  $J = 8.6$  Hz, 2H), 7.43 (d,  $J = 8.6$  Hz, 2H), 8.13 (d,  $J = 5.2$  Hz, 1H), 8.24 (s, 1H), 8.39 (s, 1H), 11.64 (s, 1H);  $^{13}C$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  13.98, 48.87, 60.39, 85.73, 121.46, 128.22, 128.44, 129.10, 130.56, 133.29, 136.13, 142.18, 143.89, 167.50, 174.55. HR MS. Calcd for  $C_{17}H_{17}ClN_3O_3S$  (M+H): 378.0679. Found:  $m/z$  378.0671. Anal. Calcd for  $C_{17}H_{16}ClN_3O_3S$ : C, 54.04; H, 4.27; N, 11.12. Found: C, 53.86; H, 4.31; N, 11.15.

**Ethyl 2-[4-Hydroxy-4-(4-methoxyphenyl)-2-thioxo-1,4-dihydropyrido[3,4-*d*]pyrimidin-3(2*H*)-yl]acetate (3c):** a pale-yellow solid; mp 214–215 °C (hexane/THF); IR (KBr) 3187, 3125, 1748, 1205  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  0.95 (t,  $J = 7.6$  Hz, 3H), 3.58 (s, 3H), 3.80–3.86 (m, 2H), 4.01 (d,  $J = 17.2$  Hz, 1H), 4.26 (d,  $J = 17.2$  Hz, 1H), 6.76 (d,  $J = 5.2$  Hz, 1H), 6.77 (d,  $J = 8.6$  Hz, 2H), 7.13 (d,  $J = 8.6$  Hz, 2H), 7.88 (s, 1H), 7.98 (d,  $J = 5.2$  Hz, 1H), 8.24 (s, 1H), 11.41 (s, 1H);  $^{13}C$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  13.99, 48.92, 55.16, 60.26, 86.06, 109.63, 113.72, 118.45, 121.41, 127.43, 130.98, 135.97, 1434.97, 159.68, 167.69, 174.59. HR MS. Calcd for  $C_{18}H_{20}N_3O_4S$  (M+H): 374.1174. Found:  $m/z$  374.1164. Anal. Calcd for  $C_{18}H_{19}N_3O_4S$ : C, 57.89; H, 5.13; N, 11.25. Found: C, 57.95; H, 5.27; N, 10.99.

**Typical Procedure for the Preparation of Tricyclic Heterocycles (4). 5-Phenyl-2,3-dihydro-5*H*-pyrido[3,4-*d*]thiazolo[3,2-*a*]pyrimidin-5-ol (4a).** To a stirred mixture of **1a** (0.15 g, 0.62 mmol) and  $Br(CH_2)_2NH_3^+Br^-$  (0.13 g, 0.62 mmol) in THF (6 mL) at rt was added  $Et_3N$  (0.13 g, 1.2 mmol) dropwise. After stirring for 3.5 h, the solvent was evaporated. Water (15 mL) was added and the precipitate was collected by filtration under reduced pressure. Recrystallization of the crude product from hexane/THF afforded pure **4a** (0.16 g, 88%); a pale-yellow solid; mp 216–218 °C (hexane/THF); IR (KBr) 3241, 1574, 1547  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  3.20–3.38 (m, 3H), 3.81–3.86 (m, 1H), 6.74 (d,  $J = 5.2$  Hz, 1H), 7.33 (t,  $J = 7.4$  Hz, 1H), 7.39–7.44 (m, 4H), 7.61 (s, 1H), 8.06 (d,  $J = 5.2$  Hz, 1H), 8.27 (s, 1H);  $^{13}C$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  25.59, 48.26, 83.99, 121.34, 126.22, 128.23, 128.49, 132.90, 137.69, 143.50, 144.00, 144.97, 162.31. HR MS. Calcd for  $C_{15}H_{14}N_3OS$  (M+H): 284.0857. Found:  $m/z$  284.0849. Anal. Calcd for  $C_{15}H_{13}N_3OS$ : C, 63.58; H, 4.62; N, 14.83. Found: C, 63.40; H, 4.81; N, 14.53.

**6-(4-Chlorophenyl)-3,4-dihydro-2*H*,6*H*-pyrido[3',4':4,5]pyrimido[2,1-*b*][1,3]thiazin-6-ol (4b):** a white solid; mp 235–237 °C ( $CH_2Cl_2$ /THF); IR (KBr) 3264, 1569, 1525  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.88–1.93 (m, 2H), 2.89–2.93 (m, 1H), 3.04–3.07 (m, 2H), 3.32–3.35 (m, 1H), 6.71 (d,  $J = 4.6$  Hz, 1H), 7.42 (d,  $J = 8.6$  Hz, 2H), 7.45 (d,  $J = 8.6$  Hz, 2H), 7.82 (br s, 1H), 7.98 (d,  $J = 4.6$  Hz, 1H),

8.18 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  23.79, 27.65, 43.00, 85.26, 121.17, 128.04, 128.54, 132.84, 132.98, 136.60, 143.08, 143.48, 144.48, 155.70. HR MS. Calcd for  $\text{C}_{16}\text{H}_{15}\text{ClN}_3\text{OS}$  (M+H): 332.0624. Found:  $m/z$  332.0616. Anal. Calcd for  $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{OS}$ : C, 57.91; H, 4.25; N, 12.66. Found: C, 58.02; H, 4.42; N, 12.52.

**6-(4-Methoxyphenyl)-3,4-dihydro-2H,6H-pyrido[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-6-ol (4c):** a white solid; mp 209–210 °C (hexane/THF); IR (KBr) 3177, 1610, 1573, 1524  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.84–1.94 (m, 2H), 2.92–2.97 (m, 1H), 3.04 (t,  $J = 6.8$  Hz, 1H), 3.19–3.35 (m, 2H), 3.73 (s, 3H), 6.71 (d,  $J = 5.2$  Hz, 1H), 6.93 (d,  $J = 9.2$  Hz, 2H), 7.31 (d,  $J = 9.2$  Hz, 2H), 7.59 (br s, 1H), 7.96 (d,  $J = 5.2$  Hz, 1H), 8.15 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  23.84, 27.65, 42.79, 55.13, 85.41, 113.69, 121.23, 127.31, 133.69, 136.65, 136.78, 142.84, 144.29, 155.53, 158.82. HR MS. Calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_2\text{S}$  (M+H): 328.1119. Found:  $m/z$  328.1108. Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ : C, 62.36; H, 5.23; N, 12.83. Found: C, 62.28; H, 5.30; N, 12.70.

**5-Methoxy-5-phenyl-2,3-dihydro-5H-pyrido[3,4-d]thiazolo[3,2-a]pyrimidine (5).** A mixture of **1a** (0.15 g, 0.62 mmol) and 2-bromoethanamine hydrobromide (0.13 g, 0.62 mmol) in MeOH (5 mL) containing  $\text{Et}_3\text{N}$  (0.13 g, 1.2 mmol) was stirred overnight at rt. After evaporation of the solvent, water (15 mL) was added, and the precipitate was collected by filtration under reduced pressure. Purification of the crude product by recrystallization from hexane/ $\text{CH}_2\text{Cl}_2$  gave **5** (0.13 g, 73%); a white solid; mp 178–180 °C; IR (KBr) 1575, 1541  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.07 (s, 3H), 3.16–3.25 (m, 2H), 3.39–3.44 (m, 1H), 3.71–3.76 (m, 1H), 6.72 (d,  $J = 5.2$  Hz, 1H), 7.33 (t,  $J = 7.4$  Hz, 1H), 7.38 (t,  $J = 7.4$  Hz, 2H), 7.48 (d,  $J = 7.4$  Hz, 2H), 8.18 (d,  $J = 5.2$  Hz, 1H), 8.55 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  26.01, 48.39, 50.18, 89.47, 121.32, 126.65, 128.14, 128.41, 128.57, 139.63, 142.45, 144.89, 146.19, 163.26. HR MS. Calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_3\text{OS}$  (M+H): 298.1014. Found:  $m/z$  298.1001. Anal. Calcd for  $\text{C}_{16}\text{H}_{15}\text{N}_3\text{OS}$ : C, 64.62; H, 5.08; N, 14.13. Found: C, 64.49; H, 5.06; N, 14.07.

## ACKNOWLEDGEMENTS

This work was supported in part by JSPS KAKENHI Grant Number 22550035. Assistance in recording mass spectra and performing combustion analyses by Mrs. Miyuki Tanmatsu of our university is gratefully acknowledged.

## REFERENCES

- (a) C. D. Cox, I. T. Raheem, B. A. Flores, and D. B. Whitman, *US Patent* 2011, 20110319409 (*Chem. Abstr.*, 2011, **156**, 92460); (b) M. Redondo, J. G. Zarruk, P. Ceballos, D. I. Pérez, C. Pérez, A. Perez-Castillo, M. A. Moro, J. Brea, C. Val. M. I. Cadavid, M. I. Loza, N. E. Campillo, A. Martínez, and C. Gil, *Eur. J. Med. Chem.*, 2012, **47**, 175; (c) H. J. Breslin, B. D. Dorsey, B. J. Dugan,



- K. M. Fowler, R. L. Hudkins, E. F. Mesaros, N. J. T. Monk, E. L. Morris, I. Olowoye, G. R. Ott, G. A. Pave, J. R. A. Roffey, C. N. Soudy, M. Tao, C. A. Zificsak, and A. L. Zulli, *PCT Int. Appl.*, 2014, WO 2014052699 (*Chem. Abstr.*, 2014, **160**, 544688).
2. I. V. Dyachenko, R. I. Vas'kevich, and M. V. Vovk, *Russ. J. Org. Chem.*, 2014, **50**, 263.
  3. (a) K. Kobayashi, T. Kozuki, S. Fukamachi, and H. Konishi, *Helv. Chim. Acta*, 2010, **93**, 2086; (b) K. Kobayashi, T. Kozuki, M. Konishi, T. Suzuki, M. Tanmatsu, and H. Konishi, *Helv. Chim. Acta*, 2011, **94**, 1234.
  4. The preparation of 4-hydroxy-2,3-dihydroquinazoline-2(1*H*)-thiones by the reaction of 2-isothiocyanatophenyl ketones with primary amines has already been reported: (a) P. Richter and O. Morgenstern, *Pharmazie*, 1982, **37**, 379; (b) O. Morgenstern, P. H. Richter, and P. Vainiotalo, *Pharmazie*, 1992, **47**, 297.
  5. S. Fujiwara, T. Shin-Ike, N. Sonoda, M. Aoki, K. Okada, N. Miyoshi, and N. Kambe, *Tetrahedron Lett.*, 1991, **32**, 3503.