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SYNTHESIS OF 5-HYDROXYTHIENO[2,3-*d*]PYRIMIDIN-6(5*H*)-ONE DERIVATIVES BY THE REACTION OF 2-(4-CHLOROPYRIMIDIN-5-YL)-2-HYDROXYALKANOATE WITH SODIUM HYDROGENSULFIDE

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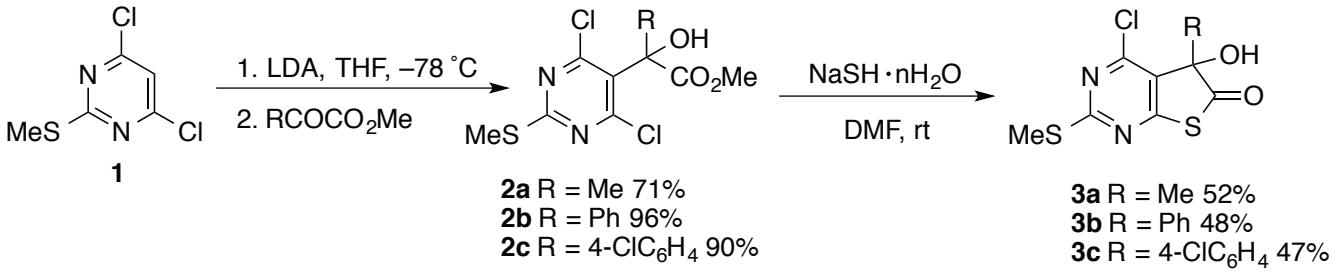
Abstract – A convenient sequence for the preparation of 5-hydroxythieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) has been developed. Thus, 4,6-dichloro-5-lithio-2-(methylsulfanyl)pyrimidine, generated by the reaction of DCSMP with lithium diisopropylamide (LDA), was allowed to react with α-keto esters to afford 2-(4,6-dichloropyrimidin-5-yl)-2-hydroxyalkanoate derivatives. These underwent cyclization on treatment with sodium hydrogensulfide to give the corresponding 4-chloro-5-hydroxythieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives. After displacement of one of the two chloro groups of 2-(4,6-dichloropyrimidin-5-yl)-2-hydroxyalkanoate derivatives with methoxy, dialkylamino, or ethyl(or phenyl)sulfanyl groups, the resulting 2-(4-chloropyrimidin-5-yl)-2-hydroxyalkanoates were similarly treated with sodium hydrogensulfide to afford the corresponding desired products.

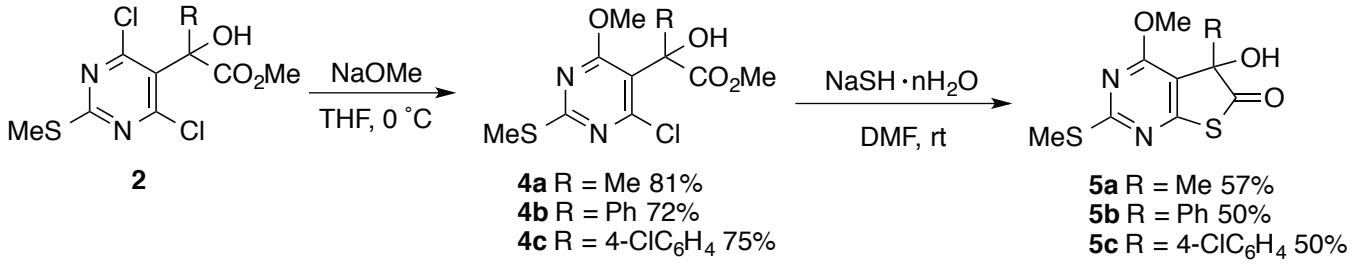
Thieno[2,3-*d*]pyrimidine derivatives are an important class of heterocycles, because large numbers of compounds with this heterocyclic unit have been reported to display interesting biological,[1] such as anticancer[1n] and menin and MLL (mixed lineage leukemia)-1 interaction inhibitory,[1o] activities and recently some reports on the general synthesis of these derivatives have been reported.[2a,3] However, there have been few reports on the synthesis of thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivative, though a compound having this structure have been reported to exhibit inhibitory activity against Fms-like tyrosine kinase 3.[4] In one of the early studies on the utilizations of 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) in the synthesis of pyrimidine-fused heterocycles,[2] we previously reported that 2-[4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxyalkanoates reacted with aliphatic primary amines to give the corresponding pyrrolo[2,3-*d*]pyrimidin-6(5*H*)-one derivatives.[2b] In this paper, we wish to report that 2-[4-chloro-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxyalkanoates carrying a substituent, such as chloro, methoxy, dialkylamino or ethyl(or phenyl)sulfanyl, at the 6-position of the pyrimidine ring, react with sodium hydrogensulfide to afford the corresponding 5-hydroxy-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives. To date, there have been no reports on the synthesis of this type of pyrrolo[2,3-*d*]pyrimidin-6(5*H*)-ones.



Scheme 1

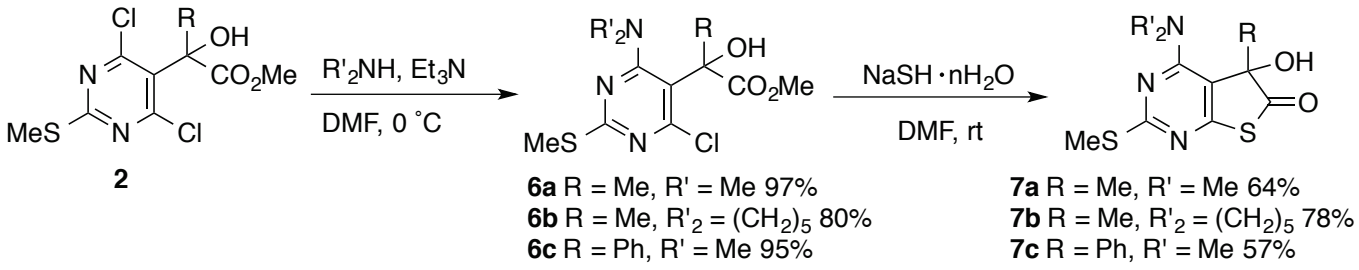
The synthesis of 4-chloro-5-hydroxy-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives **3** from commercially available 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP, **1**) was conducted according to the procedure illustrated in Scheme 1. 4,6-Dichloro-5-lithio-2-(methylsulfanyl)pyrimidine intermediate was generated *in situ* by treating **1** with lithium diisopropylamide (LDA) in THF at –78 ˚C as described previously,[2a] and was allowed to react with α-keto esters. After aqueous workup and subsequent recrystallization of the crude products, 2-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]alkanoates (**2**) were obtained in good yields. We found that these compounds (**2**) reacted relative smoothly with two equivalents of sodium hydrogensulfide in DMF at room temperature to give, after aqueous workup followed by purification with column chromatography on silica gel, the corresponding thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives (**3**) in moderate yields. The reaction at 0 ˚C did not improve the yields. It should be noted that the excess sodium hydrogensulfide did not react with the

4-position of the products and that the use of an equimolar amount of sodium hydrogensulfide could not complete the reaction and prolonged reaction times gave complex mixtures of products. The use of DMSO in place of DMF as a solvent resulted in the formation of rather complicated reaction mixtures, from which only about 20% yields of the products were obtained.



Scheme 2

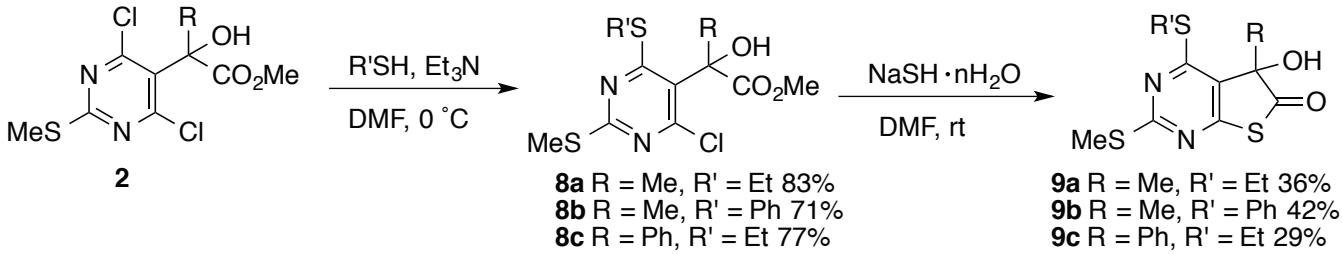
We subsequently found that one of the two chloro substituents of 2-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]alkanoates (**2**) could be easily displaced with a methoxy group on treatment with sodium methoxide in THF at 0 ˚C to give 2-[4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]alkanoates (**4**) in good yields. Subjection of these products to the treatment with sodium hydrogensulfide under the same conditions as described above for the preparation of **3** afforded the corresponding 4-methoxythieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives (**5**) in moderate yields, as illustrated in Scheme 2. Although *p*-tolyloxylation of **2a** could be similarly achieved to give a good yield of the corresponding 4-aryloxy derivative, the desired corresponding thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivative could not be obtained on treatment with sodium hydrogensulfide under the same conditions; the reaction gave an intractable mixture of products somehow.



Scheme 3

2-[4-Chloro-6-(dialkylamino)-2-(methylsulfanyl)pyrimidin-5-yl]alkanoates (**6**) were easily obtained by substitution of one of the two chloro substituents of **2** with secondary amines in DMF at 0 ˚C in the presence of triethylamine in good to excellent yields. Compounds (**6**) were subjected to the reaction with

sodium hydrogensulfide under the same conditions as described for the preparation of **3** and **5** to afford the corresponding 4-(dialkylamino)thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives (**7**) in moderate to fair yields, as shown in Scheme 3.

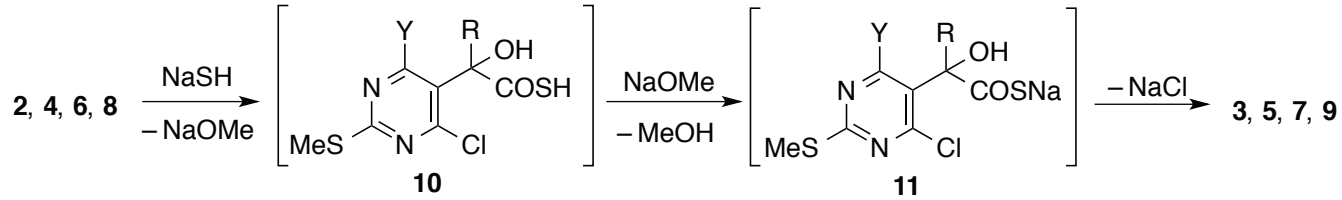


Scheme 4

Similarly, 4-(ethyl(or phenyl)sulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives (**9**) could be prepared by treating 2-[4-chloro-6-(ethyl(or phenyl)sulfanyl)-2-(methylsulfanyl)pyrimidin-5-yl]-alkanoates (**8**), derived by the reaction of **2** with thiols under the same conditions as described for the preparation of **6**, with sodium hydrogensulfide, as shown in Scheme 4.

The conversion of compounds (**3**) into compounds (**5**), (**7**), and (**9**) by replacement of the 4-chloro substituent with the nucleophiles may be possible. However, this must be required higher reaction temperatures than those for the formation of compounds (**4**), (**6**), and (**8**) due to the lowering of the reactivity of the 4-positions.

The following pathway to the products (**3**), (**5**), (**7**), and (**9**) may be proposed (Scheme 5). Thus, the thiocarboxylic acid intermediate (**10**) generates by the attack of hydrogensulfide anion to the ester moiety of **2**, **4**, **6**, and **8**, which is deprotonated with the resulting sodium methoxide to give the sodium thiocarboxylate intermediate (**11**). Finally, intramolecular nucleophilic substitution of this intermediate is assumed to take place quickly to provide the products.



Scheme 5

In conclusion, we have developed an efficient method for the preparation of 5-hydroxythieno[2,3-*d*]pyrimidin-6(5*H*)-one derivatives from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) and α-keto esters. The products carrying chloro, methoxy, dialkylamino, or ethyl(or phenyl)sulfanyl groups at the

4-position are accessible by the present synthetic sequences. As the starting materials are readily available and the manipulations are very simple, the present method may be valuable in organic synthesis.

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 Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (ESI or DART, positive). Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. 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. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 2-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxyalkanoates (2). Methyl 2-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (2a). To a stirred solution of LDA (6.0 mmol), generated from *n*-BuLi (1.6 M in hexane; 6.0 mmol) and *i*-Pr_2NH (0.61 g, 6.0 mmol) by the standard method, in THF (20 mL) at –78 °C was added a solution of **1** (0.98 g, 5.0 mmol) in THF (10 mL) dropwise. After 30 min, $MeCOCO_2Me$ (0.61 g, 6.0 mmol) was added dropwise, and stirring was continued for an additional 10 min at the same temperature. Saturated aqueous NH_4Cl (50 mL) was added and temperature was raised to rt, and the resulting mixture was extracted with AcOEt (3 × 25 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to give **2a** (1.1 g, 71%); a white solid; mp 61–63 °C; IR (KBr) 3428, 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.57 (s, 3H), 3.54 (br s, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.3, 26.5, 53.6, 75.9, 126.4, 160.2, 171.2, 174.0. Anal. Calcd for $C_9H_{10}Cl_2N_2O_3S$: C, 36.38; H, 3.39; N, 9.43. Found: C, 36.32; H, 3.65; N, 9.34.

Methyl 2-[4,6-Dichloro-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxy-2-phenylacetate (2b): a pale-yellow solid; mp 143–145 °C (hexane/CH_2Cl_2); IR (KBr) 3451, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 3.80 (s, 3H), 4.60 (s, 1H), 7.35–7.38 (m, 3H), 7.53 (dd, J = 8.0, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 54.4, 78.57, 126.1, 126.9, 128.46, 128.50, 139.7, 161.7, 171.5, 173.8. Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_3S$: C, 46.81; H, 3.37; N, 7.80. Found: C, 46.99; H, 3.51; N, 7.80.

Methyl 2-(4-Chlorophenyl)-2-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxyacetate (2c): a white solid; mp 88–90 °C (hexane/CH_2Cl_2); IR (KBr) 3463, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.57 (s,

3H), 3.81 (s, 3H), 4.60 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 54.5, 78.3, 126.2, 127.6, 128.7, 134.6, 138.4, 161.0, 171.8, 173.5. HR-MS (ESI). Calcd for $C_{14}H_{12}Cl_3N_2O_3S$: (M+H): 392.9634. Found: *m/z* 392.9619.

General Procedure for the Preparation of Thieno[2,3-*d*]pyrimidin-6(5*H*)-ones (3), (5), (7), and (9). A solution of **2**, **4**, **6**, or **8** (0.25 g, 0.70 mmol) and NaSH•nH_2O (70% as NaSH; 0.11 g, 1.4 mmol) in DMF (5 mL) was stirred at rt until TLC analyses on SiO_2 (AcOEt/hexane or Et_2O/hexane) had revealed disappearance of the starting material. Water (20 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give the desired product.

4-Chloro-5-hydroxy-5-methyl-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (3a): a white solid; mp 126–128 °C (hexane/CH_2Cl_2); IR (KBr) 3284, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H), 2.55 (s, 3H), 3.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.8, 82.3, 122.8, 155.3, 169.3, 174.2, 201.2. HR-MS (ESI). Calcd for $C_8H_8ClN_2O_2S_2$: (M+H): 262.9716. Found: *m/z* 262.9711. Anal. Calcd for $C_8H_7ClN_2O_2S_2$: C, 36.57; H, 2.69; N, 10.66. Found: C, 36.73; H, 3.02; N, 10.60.

4-Chloro-5-hydroxy-2-(methylsulfanyl)-5-phenylthieno[2,3-*d*]pyrimidin-6(5*H*)-one (3b): a viscous oil; R_f 0.30 (AcOEt/$CHCl_3$ 1:30); IR (neat) 3418, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.73 (br s, 1H), 7.40 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.5, 85.7, 99.9, 123.8, 125.0, 129.1, 129.5, 136.0, 156.0, 174.8, 198.5. HR-MS (ESI). Calcd for $C_{13}H_{10}ClN_2O_2S_2$: (M+H): 324.9872. Found: *m/z* 324.9856.

4-Chloro-(4-chlorophenyl)-5-hydroxy-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (3c): a white solid; mp 177–179 °C (hexane/CH_2Cl_2); IR (KBr) 3537, 1748 cm^{-1}; ^{1}H NMR (THF-d_8) δ 2.52 (s, 3H), 6.85 (s, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (THF-d_8) δ 13.5, 85.3, 124.8, 127.3, 128.6, 134.6, 136.0, 156.1, 170.6, 174.4, 197.9. Anal. Calcd for $C_{13}H_8Cl_2N_2O_2S_2$: C, 43.46; H, 2.24; N, 7.80. Found: C, 43.52; H, 2.46; N, 7.73.

Typical Procedure for the Preparation of 2-[4-Chloro-6-methoxy-2-(methylsulfanyl)-pyrimidin-5-yl]-2-hydroxyalkanoates (4). Methyl 2-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (4a). To a stirred suspension of NaH (60% in mineral oil; 23 mg, 0.58 mmol) in THF (5 mL) at 0 °C was added dropwise MeOH (0.19 g, 0.58 mmol). After 5 min, a solution of **2a** (0.17 g, 0.58 mmol) in THF (3 mL) was added and stirring was continued for an additional 15 min. The mixture was worked up as described for the preparation of **2a** and the residual solid was purified by recrystallization to give **4a** (0.14 g, 80%); a white solid; mp 58–60 °C (hexane/CH_2Cl_2) (lit.,[2f] 59–62 °C). The spectral (IR and ^{1}H NMR) data for this product were identical to those reported previously.[2f]

Methyl 2-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxy-2-phenylacetate (4b): a white solid; mp 118–120 °C (hexane/CH_2Cl_2) (lit.,[2b] 116–118 °C). The spectral (IR and ^{1}H NMR) data for

this product were identical to those reported previously.[2b]

Methyl 2-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-(4-chlorophenyl)-2-hydroxy-acetate (4c): a pale-yellow solid; mp 118–120 ˚C (hexane/CH_2Cl_2); IR (KBr) 3469, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.76 (s, 3H), 3.92 (s, 3H), 4.52 (br s, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 54.2, 55.4, 76.7, 115.1, 128.0, 128.5, 134.2, 139.2, 160.4, 167.4, 171.5, 174.3. HR-MS (DART). Calcd for $C_{15}H_{15}Cl_2N_2O_4S$: (M+H): 389.0130. Found: *m/z* 389.0114.

5-Hydroxy-4-methoxy-5-methyl-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (5a): a white solid; mp 128–130 ˚C (hexane/CH_2Cl_2); IR (KBr) 3400, 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H), 2.57 (s, 3H), 2.80 (br, 1H), 4.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.3, 23.6, 54.4, 81.9, 110.9, 163.3, 166.8, 173.4, 202.6. HR-MS (ESI). Calcd for $C_9H_{11}N_2O_3S_2$: (M+H): 259.0211. Found: *m/z* 259.0204. Anal. Calcd for $C_9H_{10}N_2O_3S_2$: C, 41.85; H, 3.90; N, 10.84. Found: C, 41.87; H, 3.77; N, 10.60.

5-Hydroxy-4-methoxy-2-(methylsulfanyl)-5-phenylthieno[2,3-*d*]pyrimidin-6(5*H*)-one (5b): a white solid; mp 154–156 ˚C (hexane/CH_2Cl_2); IR (KBr) 3274, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.39 (s, 1H), 3.91 (s, 3H), 7.36–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 54.4, 85.4, 111.4, 125.1, 128.8, 129.1, 137.4, 163.1, 168.0, 174.0, 200.0. HR-MS (ESI). Calcd for $C_{14}H_{13}N_2O_3S_2$: (M+H): 321.0367. Found: *m/z* 321.0360. Anal. Calcd for $C_{14}H_{12}N_2O_3S_2$: C, 52.49; H, 3.78; N, 8.74. Found: C, 52.60; H, 4.13; N, 8.71.

5-(4-Chlorophenyl)-5-hydroxy-4-methoxy-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (5c): a white solid; mp 133–135 ˚C (hexane/CH_2Cl_2); IR (KBr) 3368, 1745cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.55 (s, 3H), 3.79 (s, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.44 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.8, 54.3, 84.5, 112.1, 127.2, 128.5, 133.2, 136.6, 162.8, 167.2, 172.3, 200.7. Anal. Calcd for $C_{14}H_{11}ClN_2O_3S_2$: C, 47.39; H, 3.12; N, 7.90. Found: C, 47.04; H, 3.34; N, 7.78.

Typical Procedure for the Preparation of 2-[6-(Dialkylamino)pyrimidin-5-yl]-2-hydroxyalkanoates (6). Methyl 2-[4-Chloro-6-(dimethylamino)-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (6a). To a stirred solution of **2a** (0.30 g, 1.0 mmol) in DMF (4 mL) containing Et_3N (0.10 g, 1.0 mmol) at 0 ˚C was added Me_2NH (50% in water; 90 mg, 1.0 mmol) dropwise. After 25 min, saturated aqueous NH_4Cl (50 mL) was added, and the resulting mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with H_2O (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized to give **6a** (0.22 g, 74%); a pale-yellow solid; mp 99–101 ˚C (hexane/CH_2Cl_2); IR (KBr) 3480, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 3H), 2.54 (s, 3H), 2.95 (s, 6H), 3.76 (s, 3H), 6.02 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 26.0, 43.2, 53.3, 75.3, 115.8, 159.5, 167.5, 169.0, 175.1. HR-MS (DART). Calcd for $C_{11}H_{17}ClN_3O_3S$: (M+H): 306.0679. Found: *m/z* 306.0664.

Methyl 2-[4-Chloro-2-(methylsulfanyl)-6-(piperidin-1-yl)pyrimidin-5-yl]-2-hydroxypropanoate (6b): a white solid; mp 84–86 ˚C (hexane/CH_2Cl_2); IR (KBr) 3470, 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (br s, 2H), 1.72–1.74 (m, 4H), 1.84 (s, 3H), 2.55 (s, 3H), 3.17–3.20 (m, 4H), 3.74 (s, 3H), 8.31 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.5, 25.4, 25.9, 52.9, 53.0, 76.2, 119.6, 159.7, 168.2, 169.9, 173.4. Anal. Calcd for $C_{14}H_{20}ClN_3O_3S$: C, 48.62; H, 5.83; N, 12.15. Found: C, 48.55; H, 5.90; N, 12.04.

Methyl 2-[4-Chloro-6-(dimethylamino)-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxy-2-phenylacetate (6c): a white solid; mp 113–115 ˚C (hexane/CH_2Cl_2); IR (KBr) 3471, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 2.58 (s, 6H), 3.66 (s, 3H), 4.86 (s, 1H), 7.27–7.30 (m, 3H), 7.48 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 40.7, 54.3, 76.7, 108.4, 126.7, 127.5, 128.1, 139.6, 160.9, 164.4, 167.8, 175.4. Anal. Calcd for $C_{16}H_{18}ClN_3O_3S$: C, 52.24; H, 4.93; N, 11.42. Found: C, 52.27; H, 5.08; N, 11.23.

4-(Dimethylamino)-5-hydroxy-5-methyl-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (7a): a white solid; mp 133–135 ˚C (hexane/CH_2Cl_2); IR (KBr) 3210, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3H), 2.50 (s, 3H), 3.35 (s, 6H), 3.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 25.2, 40.6, 83.1, 107.4, 158.1, 166.0, 170.3, 203.9. HR-MS (DART). Calcd for $C_{10}H_{14}N_3O_2S_2$: (M+H): 272.0527. Found: *m/z* 272.0514. Anal. Calcd for $C_{10}H_{13}N_3O_2S_2$: C, 44.26; H, 4.83; N, 15.49; S, 23.63. Found: C, 44.00; H, 4.77; N, 15.60; S, 23.98.

5-Hydroxy-5-methyl-2-(methylsulfanyl)-6-(piperidin-1-yl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (7b): a white solid; mp 135–137 ˚C (hexane/CH_2Cl_2); IR (KBr) 3467, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (br s, 5H), 1.70–1.72 (m, 4H), 2.49 (s, 3H), 3.23 (s, 1H), 3.83–3.88 (m, 2H), 3.92–3.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.2, 24.6, 26.0, 49.1, 83.2, 108.4, 157.9, 166.4, 170.7, 203.5. Calcd for $C_{13}H_{18}N_3O_2S_2$: (M+H): 312.0840. Found: *m/z* 312.0831. Anal. Calcd for $C_{13}H_{17}N_3O_2S_2$: C, 50.14; H, 5.50; N, 13.49. Found: C, 50.04; H, 5.56; N, 13.48.

4-(Dimethylamino)-5-hydroxy-2-(methylsulfanyl)-5-phenylthieno[2,3-*d*]pyrimidin-6(5*H*)-one (7c): a white solid; mp 183–185 ˚C (hexane/CH_2Cl_2); IR (KBr) 3434, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 2.95 (s, 6H), 4.26 (br, 1H), 7.37 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 40.1, 86.9, 106.4, 125.3, 128.9, 129.1, 138.8, 157.0, 168.0, 171.0, 201.1. HR-MS (DART). Calcd for $C_{15}H_{16}N_3O_2S_2$: (M+H): 334.0684. Found: *m/z* 334.0670. Anal. Calcd for $C_{15}H_{15}N_3O_2S_2$: C, 54.03; H, 4.53; N, 12.60; S, 19.23. Found: C, 53.78; H, 4.64; N, 12.59; S, 19.32.

Typical Procedure for the Preparation of 2-[6-(Alkyl(or aryl)sulfanyl)pyrimidin-5-yl]-2-hydroxyalkanoates (8). Methyl 2-[4-Chloro-6-(ethylsulfanyl)-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (8a). To a stirred solution of **2a** (0.44 g, 1.5 mmol) in DMF (5 mL) containing Et_3N (0.15 g, 1.5 mmol) at 0 ˚C was added EtSH (93 mg, 1.5 mmol) dropwise. After 1.5 h, the mixture was worked up as described for the preparation of **6a**. The residual solid was recrystallized to give **8a** (0.40 g,

83%); a pale-yellow solid; mp 88–90 °C (hexane/CH_2Cl_2); IR (KBr) 3448, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (t, *J* = 7.4 Hz, 3H), 1.82 (s, 3H), 2.55 (s, 3H), 2.97 (s, 1H), 3.10–3.18 (m, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 22.7, 25.8, 53.2, 77.1, 125.6, 158.2, 169.3, 171.1, 172.9. HR-MS (positive). Calcd for $C_{11}H_{16}ClN_2O_3S_2$: (M+H): 323.0291. Found: *m/z* 323.0277.

Methyl 2-[4-Chloro-2-(methylsulfanyl)-6-(phenylsulfanyl)pyrimidin-5-yl]-2-hydroxypropanoate (8b): a white solid; mp 145–147 °C (hexane/CH_2Cl_2); IR (KBr) 3400, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (s, 3H), 1.92 (s, 3H), 3.08 (s, 1H), 3.82 (s, 3H), 7.40–7.43 (m, 3H), 7.49 (dd, *J* = 8.0, 2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.3, 22.8, 53.2, 77.1, 125.2, 129.0, 129.5, 129.8, 136.5, 156.3, 169.4, 171.3, 172.7. Anal. Calcd for $C_{15}H_{15}ClN_2O_3S_2$: C, 48.58; H, 4.08; N, 7.55. Found: C, 48.59; H, 4.08; N, 7.47.

Methyl 2-[4-Chloro-6-(ethylsulfanyl)-2-(methylsulfanyl)pyrimidin-5-yl]-2-hydroxy-2-phenylacetate (8c): a white solid; 112–114 °C (hexane/CH_2Cl_2); IR (KBr) 3412, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, *J* = 7.4 Hz, 3H), 2.53 (s, 3H), 2.89–2.33 (m, 1H), 2.97–3.01 (m, 1H), 3.77 (s, 3H), 4.38 (s, 1H), 7.33–7.54 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 26.5, 54.1, 78.8, 125.1, 127.3, 128.3, 128.8, 138.9, 158.7, 169.3, 173.1, 174.2. HR-MS (DART). Calcd for $C_{16}H_{18}ClN_2O_3S_2$ (M+H): 385.0447. Found: *m/z* 385.0433. Anal. Calcd for $C_{16}H_{17}ClN_2O_3S_2$: C, 49.93; H, 4.45; N, 7.28; S, 16.66. Found: C, 50.09; H, 4.47; N, 7.28; S, 17.01.

4-(Ethylsulfanyl)-5-hydroxy-5-methyl-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (9a): a colorless oil; R_f 0.26 (AcOEt/hexane 1:8); IR (neat) 3396, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.4 Hz, 3H), 1.75 (s, 3H), 2.54 (s, 3H), 3.03 (s, 1H), 3.24 (q, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 22.7, 23.9, 82.7, 121.4, 164.6, 164.7, 171.9, 202.7. HR-MS (DART). Calcd for $C_{10}H_{13}N_2O_2S_3$: (M+H): 289.0139. Found: *m/z* 289.0125.

5-Hydroxy-5-methyl-2-(methylsulfanyl)-4-(phenylsulfanyl)thieno[2,3-*d*]pyrimidin-6(5*H*)-one (9b): a colorless viscous oil; R_f 0.35 (AcOEt/hexane 1:4); IR (neat) 3445, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (s, 3H), 1.97 (s, 3H), 3.12 (s, 1H), 7.42–7.46 (m, 3H), 7.56 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 23.1, 82.6, 120.8, 126.7, 129.1, 129.8, 136.4, 164.6, 165.2, 172.1, 202.6. HR-MS (DART). Calcd for $C_{14}H_{13}N_2O_2S_3$: (M+H): 337.0139. Found: *m/z* 337.0130.

4-(Ethylsulfanyl)-5-hydroxy-2-(methylsulfanyl)-5-phenylthieno[2,3-*d*]pyrimidin-6(5*H*)-one (9c): a colorless viscous oil; R_f 0.23 (AcOEt/hexane 1:10); IR (neat) 3452, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.4 Hz, 3H), 2.59 (s, 3H), 3.04–3.08 (m, 1H), 3.17–3.21 (m, 1H), 3.63 (br s, 1H), 7.38–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 24.1, 85.8, 122.0, 125.3, 127.3, 128.9, 135.7, 165.5, 166.3, 172.5, 199.9. HR-MS (DART). Calcd for $C_{15}H_{15}N_2O_2S_3$: (M+H): 351.0296. Found: *m/z* 351.0284.

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