SYNTHESIS OF 7H-THIOPYRANO[2,3-d]PYRIMIDINES BY HYDROBROMIC ACID-MEDIATED CYCLIZATION OF 1-[4-(1,1-DIMETHYLETHYLSULFANYL)PYRIMIDIN-5-YL]PROP-2-EN-1-OLS

Kazuhiro Kobayashi,*Teruhiko Suzuki, Ayumi Imaoka, Hidetaka Hiyoshi, and Kazuto Umezu

Abstract – 7-Aryl- or 5,7-diaryl-4-methoxy-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidines have been prepared in satisfactory overall yields starting from 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine by a facile three-step sequence. 4-Chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine was generated by the treatment of 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine with LDA and was allowed to react with 3-arylprop-2-enals (cinnamaldehyde and its derivatives) or 1,3-diarylprop-2-en-1-ones (chalcone and its derivatives) to give the corresponding 3-arylprop-2-en-1-ols (cinnamaldehyde and its derivatives) or 1,3-diarylprop-2-en-1-ones (chalcone and its derivatives) to give the corresponding 3-aryl- or 1,3-diaryl-1-(4-chloropyrimidin-5-yl)prop-2-en-1-ol derivatives, respectively. Substitution of the 4-chloro group with sodium 1,1-dimethylethylthiolate gave 3-aryl- or 1,3-diaryl-1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ol derivatives, of which treatment with an equivalent of hydrobromic acid provided the desired products.

Compounds having the 7H-thiopyrano[2,3-d]pyrimidine skeleton have received respective attention from a biologically point of view. However, there have been few works on their general preparation to date, while the reaction of 4-chloro-2-(methylsulfanyl)pyrimidine-5-carbonitrile with diethyl 2-sulfanylbutanedioate and the reaction of 1-(6-methyl-5-phenyl-4-sulfanylpyrimidin-5-yl)ethanone
with diethyl (Z)-but-2-enedioate\textsuperscript{3b} have been reported to give the corresponding 7H-thiopyrano[2,3-d]pyrimidines. Accordingly, we became interested in developing a general method for the preparation of 7H-thiopyrano[2,3-d]pyrimidine derivatives. In this report, we wish to demonstrate that 7-aryl- or 5,7-diaryl-4-methoxy-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidines (7) can be readily prepared utilizing hydrobromic acid-mediated cyclization of 3-aryl- or 1,3-diaryl-1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ol derivatives (4), derived from 4-chloro-6-methoxy-2-methylsulfanylpyrimidine (1) and 3-arylprop-2-enals (2a–e) (cinnamaldehyde and its derivatives) or 1,3-diarylprop-2-en-1-ones (2f–j) (chalcone and its derivatives), respectively.

Our three-step sequence for the preparation 7 from 1 was conducted as illustrated in Scheme 1. We first synthesized 3-aryl-1-(4-chloropyrimidin-5-yl)prop-2-en-1-ol derivatives (3a–e) by reacting 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine, generated by treating 1 with LDA under the conditions reported previously,\textsuperscript{3} with 2a–e. The yields of these products were fair to good as summarized Table 1 (Entries 1-5). The Michael adduct was not obtained in each case. Substitution of each of the 6-chloro group of 3a–e with 1,1-dimethylsulfanyl group could be performed with 1,1-dimethylethanethiol in the presence of sodium hydride as a base to afford the corresponding 3-aryl-1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]prop-2-en-1-ol derivatives (4a–e) in good yields. The final ring closure of these precursors forming the thiopyrano ring proved to be efficiently achieved on treatment with an equivalent of concentrated hydrobromic acid. The reaction proceeded smoothly and was complete within 20 min or less at 0 °C to give the desired 7-aryl-4-methoxy-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidines (7a–e) in good to excellent yields, as listed in Table 1 as well. The use of an equivalent of the acid was essential for complete conversion. When the reaction was carried out using a catalytic amount of the acid, a considerable amount of 4 was recovered in each reaction. The use of hydriodic acid or hydrochloric acid in place of hydrobromic both gave disappointing results; a complex mixture of products was produced in each case. It should be noted that the 2-methylsulfanyl group on the pyrimidine ring is necessary for successful cyclization of 4 to 7. For example, 1-[4-(1,1-dimethylethylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-ol could be similarly prepared from 4-chloro-6-methoxypyrimidine. However, an attempt of its cyclization to the corresponding 7H-thiopyrano[2,3-d]pyrimidine under the same conditions as described above resulted in the formation of an intractable mixture of products.

Next, we examined the usability of chalcone and its derivatives (2f–j) in the present reaction sequence. Fair yields of 1,3-diaryl-1-(4-chloropyrimidin-5-yl)prop-2-en-1-ol derivatives (3f–j) were obtained by the reaction of 4-chloro-5-lithio-6-methoxy-2-(methylsulfanyl)pyrimidine with 2f–j. Again, the Michael adduct was not obtained in each case. Transformation of 3f–j into the corresponding 1,1-dimethylsulfanyl derivatives (4f–j) was similarly achieved with sodium 1,1-dimethylethylthiolate in good yields. The
conversion to desired 5,7-diaryl-4-methoxy-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidines (7f-j) was carried out by treatment of 4f-j with concentrated hydrobromic acid under the same conditions as described for the preparation of 7a-e. The yields of these products listed in Table 1, Entries 6–10 are generally somewhat lower than those of 7a-e. This may be ascribed to the steric encumbrance between 4-methoxy and 5-aryl substituents of the products (7f-j).

Scheme 1

Table 1. Preparation of 7H-Thiopyrano[2,3-d]pyrimidines (7)

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
<th>3</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>7</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2a (Ar = Ph, R = H, R’ = H)</td>
<td>3a</td>
<td>71</td>
<td>4a</td>
<td>90</td>
<td>7a</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2b (Ar = Ph, R = Me, R’ = H)</td>
<td>3b</td>
<td>73</td>
<td>4b</td>
<td>85</td>
<td>7b</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>2c (Ar = 4-MeC₆H₄, R = H, R’ = H)</td>
<td>3c</td>
<td>73</td>
<td>4c</td>
<td>87</td>
<td>7c</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>2d (Ar = 4-ClC₆H₄, R = H, R’ = H)</td>
<td>3d</td>
<td>78</td>
<td>4d</td>
<td>84</td>
<td>7d</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>2e (Ar = 4-MeOC₆H₄, R = H, R’ = H)</td>
<td>3e</td>
<td>94</td>
<td>4e</td>
<td>88</td>
<td>7e</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>2f (Ar = Ph, R = H, R’ = Ph)</td>
<td>3f</td>
<td>72</td>
<td>4f</td>
<td>89</td>
<td>7f</td>
<td>61</td>
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<tr>
<td>7</td>
<td>2g [Ar = Ph, R = H, R’ = 3,4-(MeO)₂C₆H₃]</td>
<td>3g</td>
<td>62</td>
<td>4g</td>
<td>82</td>
<td>7g</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>2h [Ar = Ph, R = H, R’ = 3,4-(OCH₂O)C₆H₃]</td>
<td>3h</td>
<td>68</td>
<td>4h</td>
<td>92</td>
<td>7h</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>2i [Ar = 4-MeOC₆H₄, R = H, R’ = 4-ClC₆H₄]</td>
<td>3i</td>
<td>75</td>
<td>4i</td>
<td>78</td>
<td>7i</td>
<td>79</td>
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<tr>
<td>10</td>
<td>2j [Ar = 4-ClC₆H₄, R = H, R’ = 4-MeOC₆H₄]</td>
<td>3j</td>
<td>60</td>
<td>4j</td>
<td>97</td>
<td>7j</td>
<td>73</td>
</tr>
</tbody>
</table>

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

The need for an equivalent of hydrobromic acid may be explained as follows (Scheme 1). Treatment of 4 with concentrated hydrobromic acid generates the allylic carbenium ion intermediate (5), which is trapped
with the sulfur lone pair electrons to form the sulfonium ion intermediate (6). The subsequent removal of t-butyl bromide, via formation of t-butyl cation, from this intermediate gives 7.

In summary, we have presented a convenient synthesis of a new class of 7H-thiopyrano[2,3-d]-pyrimidines. This method may find some value in the synthesis of this type of fused heterocycles because of the ready availability of the starting materials and the ease of operations.

**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. 1H NMR spectra were recorded in CDCl3 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. 13C NMR spectra were recorded in CDCl3 using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz or a JEOL LA400FT NMR spectrometer operating at 100 MHz. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF254. 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.** 4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (1) was prepared from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) according to the reported procedure. Chalcone derivatives 2g, 2h, 2i, and 2j were prepared according to the appropriate reported procedures. Butyllithium was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

**Typical Procedure for the Preparation of Pyrimydinylalkenols (3).** (E)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-ol (3a). To a stirred solution of LDA (2.0 mmol) in THF (3 mL), generated by the standard method from n-BuLi and i-Pr2NH, at −78 °C was added dropwise a solution of 1 (0.38 g, 2.0 mmol) in THF (3 mL). After 1.5 h, (E)-3-phenylprop-2-enal (0.26 g, 2.0 mmol) was added and stirring was continued for additional 30 min at the same temperature before saturated aqueous NH4Cl and water (5 mL each) were added. The mixture was warmed to rt and extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na2SO4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give 3a (0.46 g, 71%); a pale-yellow oil; Rf 0.14 (AcOEt–hexane 1:10); IR (neat) 3403, 1562, 1523, 1360, 1036 cm⁻¹; 1H NMR (400 MHz) δ 2.56 (s, 3H), 3.18 (d, J = 10.7 Hz, 1H), 4.09 (s, 3H), 5.70 (dd, J = 10.7, 5.9 Hz, 1H), 6.42 (dd, J = 15.6, 5.9 Hz, 1H), 6.60 (d, J = 15.6 Hz, 1H), 7.26 (t, J = 6.8 Hz, 1H), 7.32 (dd, J = 7.8, 6.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H). Anal. Calcd for C15H15ClN2O2S: C, 55.81; H, 4.68; N, 8.68.
Found: C, 55.73; H, 4.54; N, 8.53.

\((E)-1-[4\text{-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl}]-2\text{-methyl-3-phenylprop-2-en-1-ol (3b)}\): a colorless oil; \(R_f\) 0.06 (THF–hexane 1:15); IR (neat) 3429, 1563, 1522, 1369, 1038 cm\(^{-1}\); \(^1\)H NMR (500 MHz) \(\delta\) 1.83 (s, 3H), 2.57 (s, 3H), 3.21 (d, \(J = 10.9\) Hz, 1H), 4.05 (s, 3H), 5.58 (d, \(J = 10.9\) Hz, 1H), 6.53 (s, 1H), 7.21–7.24 (m, 3H), 7.33 (dd, \(J = 8.0, 7.4\) Hz, 2H). Anal. Calcd for \(C_{16}H_{17}ClN_2O_2S\): C, 57.05; H, 5.09; N, 8.32. Found: C, 56.77; H, 5.24; N, 8.04.

\((E)-1-[4\text{-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl}]-3-(4\text{-methylphenyl})\text{prop-2-en-1-ol (3c)}\): a pale-yellow oil; \(R_f\) 0.16 (AcOEt–hexane 1:5); IR (neat) 3413, 1564, 1523, 1369, 2036 cm\(^{-1}\); \(^1\)H NMR (500 MHz) \(\delta\) 2.33 (s, 3H), 2.56 (s, 3H), 3.13 (d, \(J = 10.9\) Hz, 1H), 4.08 (s, 3H), 5.68 (dd, \(J = 10.9, 6.3\) Hz, 1H), 6.37 (dd, \(J = 16.0, 6.3\) Hz, 1H), 6.56 (d, \(J = 16.0\) Hz, 1H), 7.12 (d, \(J = 8.0\) Hz, 2H), 7.26 (d, \(J = 8.0\) Hz, 2H). Anal. Calcd for \(C_{16}H_{17}ClN_2O_2S\): C, 57.05; H, 5.09; N, 8.32.

\((E)-1-[4\text{-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl}]-3-(4\text{-chlorophenyl})\text{prop-2-en-1-ol (3d)}\): a pale-yellow oil; \(R_f\) 0.17 (AcOEt–hexane 1:5); IR (neat) 3406, 1563, 1523, 1369, 1036 cm\(^{-1}\); \(^1\)H NMR (500 MHz) \(\delta\) 2.56 (s, 3H), 3.16 (d, \(J = 10.9\) Hz, 1H), 4.08 (s, 3H), 5.67 (ddd, \(J = 10.9, 6.3, 1.7\) Hz, 1H), 6.39 (dd, \(J = 16.0, 6.3\) Hz, 1H), 6.56 (d, \(J = 16.0\) Hz, 1H), 7.28 (d, \(J = 9.1\) Hz, 2H), 7.29 (d, \(J = 9.1\) Hz, 2H). Anal. Calcd for \(C_{15}H_{14}Cl_2N_2O_2S\): C, 50.43; H, 3.95; N, 7.84. Found: C, 50.24; H, 3.95; N, 7.74.

\((E)-1-[4\text{-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl}]-1,3\text{-diphenylprop-2-en-1-ol (3f)}\): a white solid; mp 47–49 °C (hexane); IR (KBr) 3531, 1550, 1337, 1033 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\) 2.56 (s, 3H), 3.95 (s, 3H), 4.71 (s, 1H), 6.55 (d, \(J = 15.6\) Hz, 1H), 6.81 (d, \(J = 15.6\) Hz, 1H), 7.22–7.42 (m, 10H). Anal. Calcd for \(C_{21}H_{19}ClN_2O_2S\): C, 63.23; H, 4.80; N, 7.02. Found: C, 63.12; H, 5.03; N, 6.74.

\((E)-1-[4\text{-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl}]-3-(3,4\text{-dimethoxyphenyl})\text{prop-2-en-1-ol (3g)}\): a yellow oil; \(R_f\) 0.17 (AcOEt–hexane 1:4); IR (neat) 3502, 1548, 1510, 1365, 1029 cm\(^{-1}\); \(^1\)H NMR (500 MHz) \(\delta\) 2.56 (s, 3H), 3.95 (s, 3H), 4.71 (s, 1H), 6.55 (d, \(J = 15.6\) Hz, 1H), 6.81 (d, \(J = 15.6\) Hz, 1H), 7.22–7.42 (m, 10H). Anal. Calcd for \(C_{23}H_{23}ClN_2O_4S\): C, 60.19; H, 5.05; N, 6.10. Found: C, 60.08; H, 5.28; N, 6.04.
prop-2-en-1-ol (3h): a yellow solid; mp 169–171 °C (hexane–CH₂Cl₂); IR (KBr) 3537, 1550, 1504, 1336, 1036 cm⁻¹; ¹H NMR (500 MHz) δ 2.56 (s, 3H), 3.94 (s, 3H), 4.68 (s, 1H), 5.95 (s, 2H), 6.43 (d, J = 15.5 Hz, 1H), 6.63 (d, J = 15.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.83 (dd, J = 8.0, 1.7 Hz, 1H), 6.96 (d, J = 1.7 Hz, 1H), 7.27–7.36 (m, 5H). Anal. Calcd for C₂₂H₁₉ClN₂O₄S: C, 59.66; H, 4.32; N, 6.32. Found: C, 59.69; H, 4.30; N, 6.14.

(E)-1-[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-ol (3i): a pale-yellow solid; mp 43–45 °C (hexane); IR (KBr) 3527, 1551, 1511, 1337, 1034 cm⁻¹; ¹H NMR (400 MHz) δ 2.56 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.73 (s, 1H), 6.44 (d, J = 15.6 Hz, 1H), 6.62 (d, J = 15.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.30 (s, 4H), 7.34 (d, J = 8.8 Hz, 2H). Anal. Calcd for C₂₂H₂₀Cl₂N₂O₃S: C, 57.02; H, 4.35; N, 6.05. Found: C, 56.82; H, 4.51; N, 6.07.

Typical Procedure for the Preparation of [(1,1-Dimethylethylsulfanyl)pyrimidinyl]alkenols (4).

(E)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-phenylprop-2-en-1-ol (4a). To a stirred suspension of NaH (60% in mineral oil; 37 mg, 0.93 mmol) in DMF (1 mL) at −20 °C was added 2-methylpropan-2-thiol (84 mg, 0.93 mmol). After evolution of H₂ had ceased, a solution of 3a (0.30 g, 0.93 mmol) in DMF (3 mL) was added slowly. The temperature was warmed to −10 °C and stirring was continued for 30 min before saturated aqueous NH₄Cl and water (5 mL each) were added. The mixture was warmed to rt and extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water twice and brine once (10 mL each), dried (Na₂SO₄), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:3) to give 4a (0.32 g, 90%); a white solid; mp 82–84 °C (hexane–Et₂O); IR (KBr) 3553, 1548, 1518, 1360, 1036 cm⁻¹; ¹H NMR (400 MHz) δ 1.63 (s, 9H), 2.56 (s, 3H), 3.49 (d, J = 10.7 Hz, 1H), 4.01 (s, 3H), 5.61 (dd, J = 10.7, 5.9 Hz, 1H), 6.39 (dd, J = 16.6, 5.9 Hz, 1H), 6.56 (d, J = 16.6 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.3 Hz, 2H), 7.37 (d, J = 7.3 Hz, 2H). Anal. Calcd for C₁₉H₂₄N₂O₂S₂: C, 60.61; H, 6.42; N, 7.44. Found: C, 60.50; H, 6.72; N, 7.32.

(E)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-2-methyl-3-phenylprop-2-en-1-ol (4b): a colorless oil; Rf 0.19 (AcOEt–hexane 1:5); IR (neat) 3449, 1545, 1519, 1361, 1041 cm⁻¹; ¹H NMR (500 MHz) δ 1.62 (s, 9H), 1.82 (s, 3H), 2.57 (s, 3H), 3.53 (d, J = 11.5 Hz, 1H), 3.98 (s, 3H), 5.51 (d, J = 11.5 Hz, 1H), 6.48 (s, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.32
(dd, J = 8.0, 7.4 Hz, 2H). Anal. Calcd for C₂₀H₂₆N₂O₂S₂: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.30; H, 6.72; N, 7.08.

(E)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methylphenyl)prop-2-en-1-ol (4c): a colorless oil; Rf 0.26 (AcOEt–hexane 1:5); IR (neat) 3430, 1547, 1519, 1361, 1039 cm⁻¹; ¹H NMR (500 MHz) δ 1.63 (s, 9H), 2.32 (s, 3H), 2.56 (s, 3H), 3.44 (d, J = 10.9 Hz, 1H), 4.00 (s, 3H), 5.60 (dd, J = 10.9, 6.3 Hz, 1H), 6.34 (dd, J = 16.0, 6.3 Hz, 1H), 6.52 (d, J = 16.0 Hz, 1H), 7.10 (d, J = 7.4 Hz, 2H), 7.26 (d, J = 7.4 Hz, 2H). Anal. Calcd for C₂₀H₂₆N₂O₂S₂: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.43; H, 6.72; N, 7.08.

(E)-3-(4-Chlorophenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-prop-2-en-1-ol (4d): a colorless oil; Rf 0.26 (AcOEt–hexane 1:5); IR (neat) 3436, 1547, 1520, 1361, 1039 cm⁻¹; ¹H NMR (400 MHz) δ 1.63 (s, 9H), 2.56 (s, 3H), 3.48 (d, J = 10.7 Hz, 1H), 4.01 (s, 3H), 5.60 (dd, J = 10.7, 5.9 Hz, 1H), 6.36 (dd, J = 15.6, 5.9 Hz, 1H), 6.51 (d, J = 15.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H). Anal. Calcd for C₁₉H₂₃ClN₂O₂S₂: C, 55.53; H, 5.64; N, 6.82. Found: C, 55.41; H, 5.68; N, 6.75.

(E)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-3-(4-methoxyphenyl)prop-2-en-1-ol (4e): a colorless oil; Rf 0.36 (AcOEt–hexane 1:3); IR (neat) 3455, 1607, 1547, 1513, 1362, 1038 cm⁻¹; ¹H NMR (500 MHz) δ 1.63 (s, 9H), 2.56 (s, 3H), 3.42 (d, J = 10.3 Hz, 1H), 3.80 (s, 3H), 4.00 (s, 3H), 5.59 (dd, J = 10.3, 6.3 Hz, 1H), 6.27 (dd, J = 15.5, 6.3 Hz, 1H), 6.49 (d, J = 15.5 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H). Anal. Calcd for C₂₀H₂₆N₂O₃S₂: C, 59.08; H, 6.45; N, 6.89. Found: C, 59.04; H, 6.54; N, 6.84.

(E)-1-[4-(1,1-Dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1,3-diphenylprop-2-en-1-ol (4f): a colorless oil; Rf 0.33 (THF–hexane 1:7); IR (neat) 3528, 1534, 1505, 1328, 1038 cm⁻¹; ¹H NMR (400 MHz) δ 1.53 (s, 9H), 2.56 (s, 3H), 3.80 (s, 3H), 4.95 (s, 1H), 6.53 (d, J = 15.6 Hz, 1H), 6.81 (d, J = 15.6 Hz, 1H), 7.20–7.36 (m, 8H), 7.41 (d, J = 7.3 Hz, 2H). Anal. Calcd for C₂₅H₂₈N₂O₂S₂: C, 66.34; H, 6.24; N, 6.19. Found: C, 66.27; H, 6.20; N, 6.16.

(E)-3-(3,4-Dimethoxyphenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4g): a pale-yellow oil; Rf 0.29 (AcOEt–hexane 1:3); IR (neat) 3517, 1601, 1535, 1506, 1329, 1036 cm⁻¹; ¹H NMR (500 MHz) δ 1.53 (s, 9H), 2.56 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.96 (s, 1H), 6.41 (d, J = 16.0 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.97 (s, 1H), 7.25 (tt, J = 7.4, 1.7 Hz, 1H), 7.31 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 7.4, 1.7 Hz, 2H). Anal. Calcd for C₂₇H₃₂N₂O₄S₂: C, 63.25; H, 6.29; N, 5.46. Found: C, 63.28; H, 6.56; N, 5.16.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4h): a yellow oil; Rf 0.18 (AcOEt–hexane 1:7); IR (neat) 3527,
1536, 1504, 1353, 1039 cm⁻¹; ¹H NMR (500 MHz) δ 1.54 (s, 9H), 2.56 (s, 3H), 3.79 (s, 3H), 4.91 (s, 1H), 5.94 (s, 2H), 6.41 (d, J = 15.5 Hz, 1H), 6.62 (d, J = 15.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 7.25 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H). Anal. Calcd for C₂₆H₂₈N₂O₄S₂: C, 62.88; H, 5.68; N, 5.64. Found: C, 62.82; H, 5.72; N, 5.53.

(E)-1-(4-Chlorophenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-3-(4-methoxyphenyl)-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4i): a white solid; mp 126–128 ºC (hexane); IR (KBr) 3525, 1607, 1536, 1505, 1357, 1037 cm⁻¹; ¹H NMR (500 MHz) δ 1.53 (s, 9H), 2.55 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.96 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H). Anal. Calcd for C₂₆H₂₉ClN₂O₃S₂: C, 60.39; H, 5.65; N, 5.42. Found: C, 60.30; H, 5.68; N, 5.34.

(E)-3-(4-Chlorophenyl)-1-[4-(1,1-dimethylethylsulfanyl)-6-methoxy-1-(4-methoxyphenyl)-2-(methylsulfanyl)pyrimidin-5-yl]-1-phenylprop-2-en-1-ol (4j): a white solid; mp 45–47 ºC (hexane); IR (KBr) 3532, 1607, 1534, 1505, 1357 cm⁻¹; ¹H NMR (500 MHz) δ 1.53 (s, 9H), 2.55 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.95 (s, 1H), 6.44 (d, J = 15.5 Hz, 1H), 6.77 (d, J = 15.5 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H). Anal. Calcd for C₂₆H₂₉ClN₂O₃S₂: C, 60.39; H, 5.65; N, 5.42. Found: C, 60.09; H, 5.67; N, 5.46.

Typical Procedure for the Preparation of 7H-Thiopyrano[2,3-d]pyrimidines (7). 4-Methoxy-2-methylsulfanyl-7-phenyl-7H-thiopyrano[2,3-d]pyrimidine (7a). To a stirred solution of 4a (0.11 g, 0.29 mmol) in MeCN (3 mL) at 0 ºC was added dropwise concd. HBr (50 mg, 0.29 mmol). After the consumption of 4a had been confirmed by TLC (SiO₂) analyses (ca. 20 min), saturated aqueous NaHCO₃ (10 mL) was added. The mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give 7a (65 mg, 74%); a pale-yellow oil; Rₜ 0.65 (AcOEt–hexane 1:5); IR (neat) 1632, 1550, 1515, 1361, 1052 cm⁻¹; ¹H NMR (500 MHz) δ 2.52 (s, 3H), 4.01 (s, 3H), 5.05 (d, J = 4.9 Hz, 1H), 5.83 (dd, J = 9.8, 4.9 Hz, 1H), 6.78 (d, J = 9.8 Hz, 1H), 7.28–7.34 (m, 5H); ¹³C NMR (125 MHz) δ 14.15, 44.81, 54.10, 107.15, 120.28, 122.00, 127.64, 128.04, 128.87, 141.43, 163.21, 164.16, 169.66. HR MS. Calcd for C₁₅H₁₅N₂O₂S₂ (M+H): 303.0627. Found: m/z 303.0619. Anal. Calcd for C₁₅H₁₄N₂O₂S₂: C, 59.57; H, 4.67; N, 9.26. Found: C, 59.36; H, 4.72; N, 9.26.

4-Methoxy-2-methylsulfanyl-7-phenyl-7H-thiopyrano[2,3-d]pyrimidine (7b): a pale-yellow solid; mp 105–108 ºC (hexane–Et₂O); IR (KBr) 1545, 1527, 1368, 1054 cm⁻¹; ¹H NMR (500 MHz) δ 1.92 (s, 3H), 2.50 (s, 3H), 4.01 (s, 3H), 4.60 (s, 1H), 6.62 (s, 1H), 7.23–7.29 (m, 5H); ¹³C NMR (125 MHz) δ 14.10, 23.30, 48.55, 54.03, 107.76, 116.45, 127.11, 127.95, 128.86, 130.86, 141.32, 161.95, 162.79, 168.55. HR MS. Calcd for C₁₆H₁₇N₂O₂S (M+H): 317.0783. Found: m/z 317.0755. Anal. Calcd for C₁₆H₁₆N₂O₂S₂: C, 60.73; H, 5.10; N, 8.85. Found: C, 61.03; H, 5.12; N, 8.59.
4-Methoxy-7-(4-methylphenyl)-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidine (7c): a yellow oil; 
$R_f$ 0.40 (AcOEt–hexane 1:7); IR (neat) 1550, 1515, 1360, 1052 cm$^{-1}$; $^1$H NMR (500 MHz) $\delta$ 2.32 (s, 3H), 2.51 (s, 3H), 4.00 (s, 3H), 5.03 (d, $J = 5.2$ Hz, 1H), 5.81 (dd, $J = 10.3, 5.2$ Hz, 1H), 6.73 (dd, $J = 10.3, 1.7$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H); $^{13}$C NMR (125 MHz) $\delta$ 14.13, 21.09, 44.62, 54.06, 107.18, 120.12, 122.26, 127.55, 129.54, 137.88, 138.49, 163.21, 164.31, 169.58. HR MS. Calcd for C$_{16}$H$_{17}$N$_2$O$_2$ (M+H): 317.0783. Found: m/z 317.0765. Anal. Calcd for C$_{16}$H$_{16}$N$_2$O$_2$: C, 60.73; H, 5.10; N, 8.85. Found: C, 60.62; H, 5.12; N, 8.87.

7-(4-Chlorophenyl)-4-methoxy-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidine (7d): a pale-yellow solid; mp 96–98 $^\circ$C (hexane); IR (KBr) 1550, 1515, 1361, 1052 cm$^{-1}$; $^1$H NMR (500 MHz) $\delta$ 2.51 (s, 3H), 4.01 (s, 3H), 4.99 (d, $J = 5.9$ Hz, 1H), 5.80 (dd, $J = 8.8, 5.9$ Hz, 1H), 6.77 (d, $J = 8.8$ Hz, 1H), 7.24 (d, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H); $^{13}$C NMR (125 MHz) $\delta$ 14.15, 44.01, 54.14, 107.06, 120.66, 121.35, 128.96, 129.00, 133.87, 139.97, 163.25, 163.76, 169.92. HR MS. Calcd for C$_{16}$H$_{14}$ClN$_2$O$_2$ (M+H): 337.0237. Found: m/z 337.0236. Anal. Calcd for C$_{15}$H$_{13}$ClN$_2$O$_2$: C, 53.48; H, 3.89; N, 8.32. Found: C, 53.47; H, 3.98; N, 8.58.

4-Methoxy-7-(4-methoxyphenyl)-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidine (7e): a pale-yellow oil; $R_f$ 0.44 (AcOEt–hexane 1:5); IR (neat) 1609, 1550, 1511, 1361, 1051 cm$^{-1}$; $^1$H NMR (500 MHz) $\delta$ 2.51 (s, 3H), 3.78 (s, 3H), 4.00 (s, 3H), 5.02 (dd, $J = 5.2, 1.1$ Hz, 1H), 5.80 (dd, $J = 10.3, 5.2$ Hz, 1H), 6.73 (dd, $J = 10.3, 1.1$ Hz, 1H), 6.84 (d, $J = 8.6$ Hz, 2H), 7.24 (d, $J = 8.6$ Hz, 2H); $^{13}$C NMR (125 MHz) $\delta$ 14.12, 44.35, 54.05, 55.29, 107.17, 114.22, 120.10, 122.38, 128.84, 133.59, 159.37, 163.23, 163.60, 169.60. HR MS. Calcd for C$_{16}$H$_{17}$ClN$_2$O$_2$ (M+H): 333.0732. Found: m/z 333.0717. Anal. Calcd for C$_{16}$H$_{16}$ClN$_2$O$_2$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.74; H, 5.06; N, 8.22.

4-Methoxy-2-methylsulfanyl-5,7-diphenyl-7H-thiopyrano[2,3-d]pyrimidine (7f): a white solid; mp 179–181 $^\circ$C (hexane–Et$_2$O); IR (KBr) 1604, 1538, 1503, 1358, 1048 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 2.55 (s, 3H), 3.63 (s, 3H), 5.03 (d, $J = 5.4$ Hz, 1H), 6.02 (d, $J = 5.4$ Hz, 1H), 7.18 (dd, $J = 7.3, 1.9$ Hz, 2H), 7.29–7.36 (m, 6H), 7.43 (d, $J = 6.9$ Hz, 2H); $^{13}$C NMR (100 MHz) $\delta$ 14.14, 44.54, 58.59, 109.78, 124.76, 126.81, 127.34, 128.07, 128.14, 128.84, 137.68, 139.04, 140.29, 163.96, 168.62, 169.60. HR MS. Calcd for C$_{21}$H$_{19}$N$_2$OS$_2$ (M+H): 379.0940. Found: m/z 379.0939. Anal. Calcd for C$_{21}$H$_{18}$N$_2$O$_2$: C, 66.64; H, 4.79; N, 7.40. Found: C, 66.79; H, 4.90; N, 7.10.

7-(3,4-Dimethoxyphenyl)-4-methoxy-2-methylsulfanyl-5-phenyl-7H-thiopyrano[2,3-d]pyrimidine (7g): a pale-yellow solid; mp 135–137 $^\circ$C (hexane–Et$_2$O); IR (KBr) 1603, 1538, 1503, 1357, 1046 cm$^{-1}$; $^1$H NMR (500 MHz) $\delta$ 2.56 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.00 (d, $J = 5.7$ Hz, 1H), 6.82 (d, $J = 9.2$ Hz, 1H), 6.95–6.96 (m, 2H), 7.18–7.20 (m, 2H), 7.30–7.31 (m, 4H); $^{13}$C NMR (125 MHz) $\delta$ 14.15, 44.61, 53.60, 55.84, 109.79, 110.92, 111.03, 120.44, 125.04, 126.80 (2C), 127.37, 127.86, 131.08, 137.60, 140.26, 148.87, 149.02, 163.96, 168.78, 169.61. HR MS. Calcd for C$_{23}$H$_{23}$N$_2$O$_3$S$_2$ (M+H):
7-(Benza[d][1,3]-dioxol-5-yl)-4-methoxy-2-methylsulfonyl-5-phenyl-7H-thiopyrano[2,3-d]pyrimidine (7h): a white solid; mp 154–156 °C (hexane–CH2Cl2); IR (KBr) 1607, 1539, 1502, 1358, 1041 cm−1; 1H NMR (400 MHz) δ 2.55 (s, 3H), 3.63 (s, 3H), 4.95 (d, J = 5.9 Hz, 1H), 5.95 (s, 2H), 5.98 (d, J = 5.9 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.87 (dd, J = 7.8, 2.0 Hz, 1H), 6.92 (s, 1H), 7.15–7.20 (m, 3H), 7.30 (dd, J = 7.8, 2.9 Hz, 2H); 13C NMR (125 MHz) δ 14.14, 44.44, 53.58, 101.25, 108.36, 108.44, 109.65, 121.54, 124.80, 126.80, 127.35, 127.83, 132.80, 137.64, 140.29, 147.49, 147.92, 163.96, 168.47, 169.63. HR MS. Calcd for C22H19N2O3S2 (M+H): 423.0838. Found: m/z 423.0825. Anal. Calcd for C22H18N2O3S2: C, 62.75; H, 5.30; N, 6.36.

5-(4-Chlorophenyl)-4-methoxy-7-(4-methoxyphenyl)-2-methylsulfanyl-7H-thiopyrano[2,3-d]pyrimidine (7i): a white solid; mp 126–128 °C (hexane); IR (KBr) 1614, 1540, 1503, 1361, 1051 cm−1; 1H NMR (500 MHz) δ 2.55 (s, 3H), 3.66 (s, 3H), 3.80 (s, 3H), 4.98 (d, J = 5.2 Hz, 1H), 5.98 (d, J = 5.2 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H); 13C NMR (125 MHz) δ 14.14, 44.44, 53.58, 109.35, 114.23, 125.54, 127.97, 128.16, 129.19, 130.70, 133.05, 136.43, 138.88, 159.47, 163.80, 168.77, 169.83. HR MS. Calcd for C22H19N2O3S2 (M+H): 443.0655. Found: m/z 443.0646. Anal. Calcd for C22H18N2O3S2: C, 59.65; H, 4.32; N, 6.32. Found: C, 59.94; H, 4.47; N, 6.25.

7-(4-Chlorophenyl)-4-methoxy-5-(4-methoxyphenyl)-2-methylsulfonyl-7H-thiopyrano[2,3-d]pyrimidine (7j): a white solid; mp 48–50 °C (hexane); IR (KBr) 1607, 1539, 1510, 1359, 1046 cm−1; 1H NMR (500 MHz) δ 2.55 (s, 3H), 3.67 (s, 3H), 3.83 (s, 3H), 4.95 (d, J = 6.3 Hz, 1H), 5.93 (d, J = 6.3 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H); 13C NMR (125 MHz) δ 14.12, 43.65, 53.74, 55.27, 109.72, 113.23, 122.82, 128.96, 129.38, 130.37, 132.58, 133.93, 137.53, 137.70, 159.11, 164.05, 168.11, 169.66. HR MS. Calcd for C22H19ClN2O3S2 (M+H): 443.0655. Found: m/z 443.0647. Anal. Calcd for C22H18ClN2O3S2: C, 59.65; H, 4.32; N, 6.32. Found: C, 59.60; H, 4.29; N, 6.17.

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