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## Synthesis of Pyrimidines, Thienopyrimidines, and Pyrazolopyrimidines

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## SYNTHESIS OF PYRIMIDINES, THIENOPYRIMIDINES, AND PYRAZOLOPYRIMIDINES

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*5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6(1H)-thione (3), which was prepared from the reaction of ethyl  $\beta$ -aminocrotonate 1 with benzoyl isothiocyanate (2) in refluxing acetone, was reacted with a series of halogenated reagents to give S-alkyl derivatives 4a–g. Upon treatment of compounds 4a–c with sodium ethoxide were cyclized into thienopyrimidine 10a–c. Pyrimidinethione 3 was reacted with hydrazine hydrate to give hydroxypyrazolopyrimidine derivative 6. The later compound was obtained by heating compound 4a with hydrazine hydrate under neat conditions, but when the reaction was carried using hydrazine hydrate in ethanol, the corresponding carbohydrazide 5 was produced.*

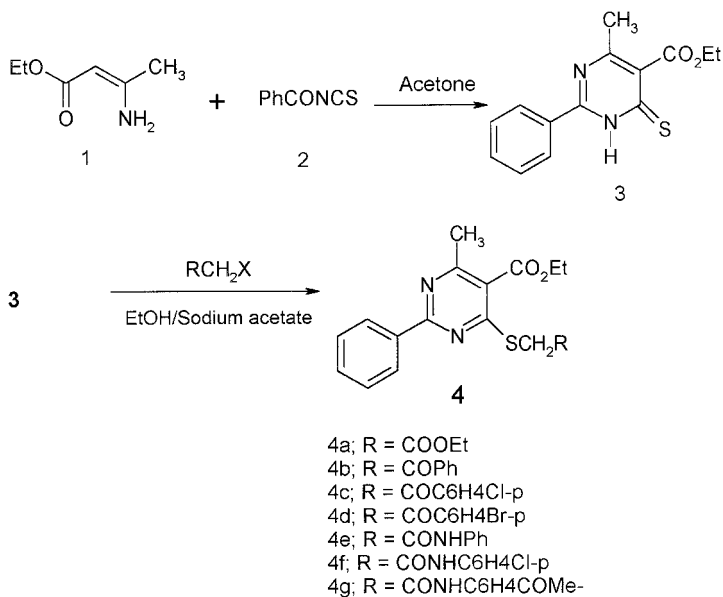
### INTRODUCTION

Thienopyrimidines still attract considerable attention of many research groups due to their wide applications in the medicinal chemistry. They were used as analgesics,<sup>1</sup> antipyretic,<sup>2</sup> and antiinflammatory agents.<sup>3,4</sup> In view of the pharmacological importance of thienopyrimidine and in continuation of our work,<sup>5,6</sup> herein we report on the synthesis of some thienopyrimidines in the hope that in the future they may prove to exhibit biological activity.

### RESULTS AND DISCUSSION

5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6(1H)-thione (3), which was prepared according to the method reported<sup>6</sup> previously, was allowed

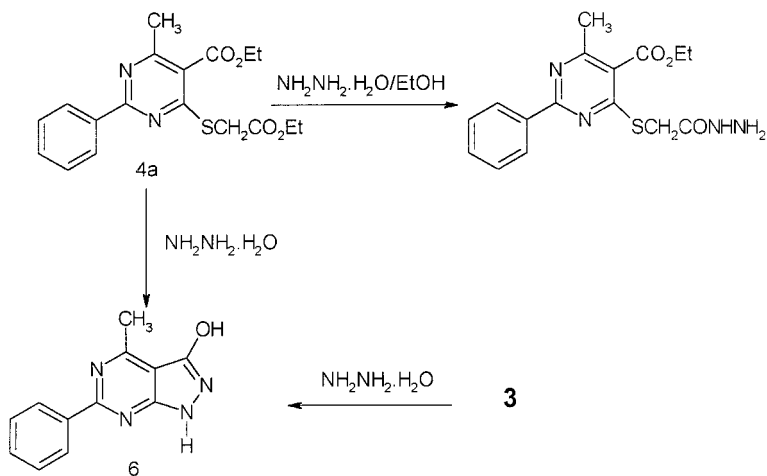
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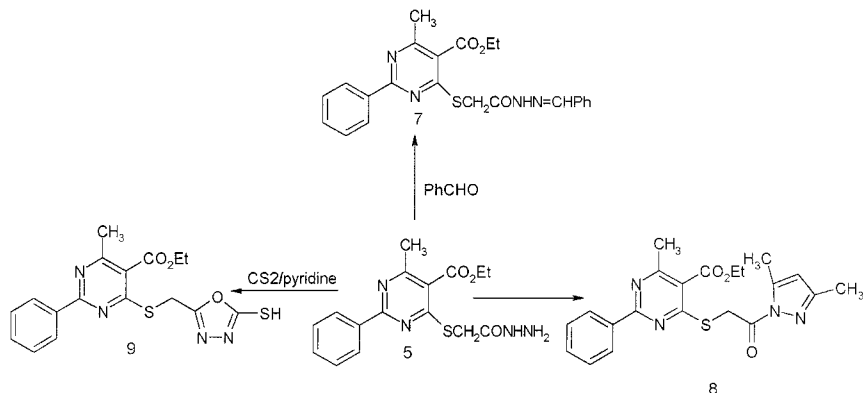
SCHEME 1

to react with a series of  $\alpha$ -halocarbonyl compounds in ethanol and in the presence of anhydrous sodium acetate to produce the corresponding S-alkylated pyrimidine derivatives **4**.

Ethyl (5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6-yl)thioacetate **4a** was reacted with hydrazine hydrate in ethanol to afford the



SCHEME 2

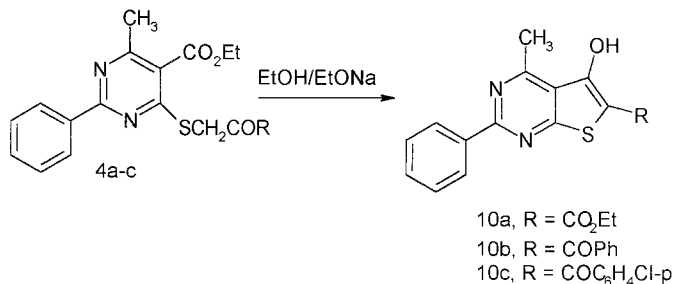


SCHEME 3

corresponding carbohydrazone **5**. But when the reaction was carried out without solvent, that is, under neat conditions, the mercaptoacetate group was replaced by the hydrazine group; under this reaction condition gave pyrazolopyrimidine **6**. The latter compound was obtained by refluxing pyrimidinethione **3** with hydrazine hydrate.

Carbohydrazone **5** was reacted with benzaldehydes, acetyl acetone, and carbon disulfide in pyridine to afford the corresponding carbohydrazone, pyrazolyl derivative, and oxadiazolyl derivatives (**7–9**) respectively.

When the alkylmercaptopyrimidine derivatives **4a–c** were refluxed in ethanol in the presence of sodium ethoxide, thienopyrimidines **10a–c** were obtained.



SCHEME 4

## EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The IR spectra were recorded using potassium

bromide disks on a Pye Unicam spectrophotometer using the KBr Wafer technique.  $^1\text{H}$  NMR spectra were obtained on Varian 390 90-MHz spectrometer in  $\text{CDCl}_3$ . Chemical shift were determined on the  $\delta$  scale by using tetramethylsilane as the internal standard. Elemental analyses were obtained on Perkin Elmer 240 C microanalyzer.

### 5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6(1H)-thione (3)

To a freshly prepared solution of benzoyl isothiocyanate (0.01 mmol) in dry acetone, a solution of ethyl- $\beta$ -aminocrotonate (0.01 mmol) in acetone was added. The mixture was stirred at room temperature for 1 h and then refluxed on a steam bath for additional 2 h. The solvent was removed and the product was collected and recrystallized from ethanol as yellow crystals, in 67% yield, m.p.  $138^\circ\text{C}$ .

IR:  $\nu = 3220\text{ cm}^{-1}$  (NH),  $1720\text{ cm}^{-1}$  (C=O), and  $1510\text{ cm}^{-1}$  (C=S).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.2\text{--}1.5$  (t, 3H,  $\text{CH}_3$  ester), 2.3 (s, 3H,  $\text{CH}_3$ ), 4.3–4.55 (q, 2H,  $\text{CH}_2$  ester), 7.35–7.7; 7.95–8.15 (2m, 5H, ArH). Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$  (274.34): C, 61.29; H, 5.14; N, 10.21; S, 11.69%. Found: C, 61.08; H, 4.92; N, 10.35; S, 11.42%.

### 5-Ethyl 6-Alkylmercapto-4-methyl-2-phenylpyrimidin-5-carboxylate (4a–g)

A mixture of compound 3 (2.75 g, 0.01 ml), sodium acetate (0.01 mmol) and appropriate halo compound (0.01 mmol) in ethanol (20 ml) was heated under reflux for 2 h, then allowed to cool. The solid product was collected, washed well with water, and recrystallized from ethanol. The physical constants and spectral data of compounds **4a–g** are listed in Tables I and II.

### 2-[5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6-yl]mercaptoacetichydrazide (5)

A mixture of compound 4 (3.6 g, 0.01 mmol) and hydrazine hydrate (99%, 0.05 mmol) in ethanol (30 ml) was heated under reflux for one hour, then allowed to cool. The solid product was collected and recrystallized from ethanol as white crystals in 82% yield, m.p.  $180^\circ\text{C}$ .

Anal. Calcd. for  $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$  (364.40): C, 55.48; H, 5.24; N, 16.17; S, 9.26%. Found: C, 55.64; H, 5.05; N, 15.98; S, 9.08%. IR:  $\nu = 3450, 3360, 3300\text{ cm}^{-1}$  ( $\text{NHNH}_2$ ) and,  $1700, 1670\text{ cm}^{-1}$  (2CO).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.3\text{--}1.5$  (t, 3H,  $\text{CH}_3$ ), 2.95 (s, 6H,  $2\text{CH}_3$ ), 3.9 (q, 2H,  $\text{CH}_2$ ), 4.1 (s, 2H,  $\text{CH}_2$ ) 4.3 (s, 2H,  $\text{NH}_2$ ) 7.2–7.5 (m, 5H, Ar–H), 9.5 (s, 1H, NH).

**TABLE I** Physical Constants of Compounds **4a–g**

No.	R	m.p. (°C)	Molecular formula	Analytical data (calcd/found)			
				C	H	N	S
<b>4a</b>	COOEt	85	C <sub>18</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S (360.43)	59.98 60.13	5.59 5.42	7.77 7.93	8.89 9.02
<b>4b</b>	COPh	114	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S (392.47)	67.33 67.52	5.14 4.93	7.14 6.95	8.17 8.33
<b>4c</b>	COC <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>	145	C <sub>22</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub> S (426.92)	61.90 62.09	4.49 4.67	6.56 6.38	7.51 7.71
<b>4d</b>	COC <sub>6</sub> H <sub>4</sub> Br- <i>p</i>	150	C <sub>22</sub> H <sub>19</sub> BrN <sub>2</sub> O <sub>3</sub> S (471.37)	56.06 55.89	4.06 4.13	5.94 6.14	6.80 6.66
<b>4e</b>	CONHPh	190	C <sub>22</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S (407.49)	64.85 65.03	5.19 5.00	10.31 10.37	7.87 8.02
<b>4f</b>	CONHC <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>	205	C <sub>22</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub> S (441.93)	59.79 59.92	4.56 4.34	9.51 9.22	7.25 7.42
<b>4g</b>	CONHC <sub>6</sub> H <sub>4</sub> COMe- <i>p</i>	190	C <sub>24</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub> S (449.52)	64.13 63.93	5.16 5.02	9.35 9.47	7.13 7.26
<b>10a</b>	CO <sub>2</sub> Et	180-2	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S (314.36)	61.13 60.89	4.49 4.66	8.91 9.18	10.20 10.00
<b>10b</b>	COPh	205	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S (346.40)	69.35 69.15	4.07 3.89	8.09 8.00	9.26 9.44
<b>10c<sup>a</sup></b>	COC <sub>6</sub> H <sub>4</sub> Cl	269	C <sub>20</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S (380.85)	63.07 62.90	3.44 3.34	7.36 7.30	8.42 8.18

<sup>a</sup>**10c**: Cl, Calcd = 9.31.

### 3-Hydroxy-4-methyl-1[H]-6-phenylpyrazolo[3,4-d]pyrimidin (**6**)

A mixture of compound **4a** (0.01 mmol) or **3** (0.01 mmol) and hydrazine hydrate (1 ml) was heated under reflux for 4 h, then ethanol (20 ml) was added and refluxing was continued for an additional 1 h. The solid product was collected and recrystallized from ethanol as orange crystals in 67% yield in the using **4a** as a starting material and 62% yield when **3** is used, m.p. 298°C, Lit.<sup>7</sup> m.p. 297°C.

Anal. Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>4</sub>O (226.24): C, 63.71; H, 4.46; N, 24.76%. Found: C, 63.88; H, 4.34; N, 25.00%. IR:  $\nu$  = 3450, 3310, cm<sup>-1</sup> (NH, OH) and, 1580 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  = 3.00 (s, 3H, CH<sub>3</sub>), 4.5 (s, H, OH), 7.2–7.5 (m, 5H, Ar–H), 10.5 (s, 1H, NH).

### Benzyledine 2-[5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6-yl]mercaptoacetichydrazone (**7**)

A mixture of compound **5** (0.01 mmol) and benzaldehyde (0.01 mmol) in ethanol (20 ml) was heated under reflux for 3 h, then allowed to cool.

**TABLE II** Physical Constants of Compounds **4a–g**

No.	IR	<sup>1</sup> H NMR
<b>4a</b>	1730, 1700 cm <sup>-1</sup> (2C=O)	CDCl <sub>3</sub> : 1.2–1.7 (2t, 6H, 2CH <sub>3</sub> ), 3.0 (s, 3H, CH <sub>3</sub> ), 3.9–4.3 (m, 4H, 2CH <sub>2</sub> ), 4.4 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 5H, Ar–H)
<b>4b</b>	1720, 1690 cm <sup>-1</sup> (2C=O)	CDCl <sub>3</sub> : 1.3–1.5 (t, 3H, CH <sub>3</sub> ), 2.95 (s, 3H, CH <sub>3</sub> ), 3.9–4.1 (q, 2H, 2CH <sub>2</sub> ), 4.3 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 10H, Ar–H)
<b>4c</b>	1720, 1700 cm <sup>-1</sup> (2C=O)	CDCl <sub>3</sub> : 1.3–1.5 (t, 3H, CH <sub>3</sub> ), 2.90 (s, 3H, CH <sub>3</sub> ), 4.1 (q, 2H, 2CH <sub>2</sub> ), 4.3 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 9H, Ar–H)
<b>4d</b>	1720, 1700 cm <sup>-1</sup> (2C=O)	CDCl <sub>3</sub> : 1.3–1.5 (t, 3H, CH <sub>3</sub> ), 2.90 (s, 3H, CH <sub>3</sub> ), 4.0 (q, 2H, 2CH <sub>2</sub> ), 4.3 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 9H, Ar–H)
<b>4e</b>	3260 cm <sup>-1</sup> (NH), 1720, 1670 cm <sup>-1</sup> (2C=O)	CDCl <sub>3</sub> : 1.3–1.5 (t, 3H, CH <sub>3</sub> ), 2.95 (s, 3H, CH <sub>3</sub> ), 3.9–4.2 (q, 2H, 2CH <sub>2</sub> ), 4.3 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 9H, Ar–H), 11.3 (s, 1H, NH)
<b>4f</b>	3300 cm <sup>-1</sup> (NH), 1720, 1670 cm <sup>-1</sup> (2C=O)	CDCl <sub>3</sub> : 1.3–1.5 (t, 3H, CH <sub>3</sub> ), 2.95 (s, 3H, CH <sub>3</sub> ), 3.9–4.2 (q, 2H, 2CH <sub>2</sub> ), 4.3 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 9H, Ar–H), 11.3 (s, 1H, NH)
<b>4g</b>	3300 cm <sup>-1</sup> (NH), 1720, 1680, 1670 cm <sup>-1</sup> (3C=O)	CDCl <sub>3</sub> : 1.3–1.5 (t, 3H, CH <sub>3</sub> ), 2.95, 3.3 (2s, 6H, 2CH <sub>3</sub> ), 3.9–4.2 (q, 2H, 2CH <sub>2</sub> ), 4.3 (s, 2H, CH <sub>2</sub> ), 7.4–7.8 (m, 9H, Ar–H), 11.3 (s, 1H, NH)
<b>10a</b>	3420 cm <sup>-1</sup> (OH), 1720 cm <sup>-1</sup> (CO)	CDCl <sub>3</sub> : 1.5 (t, 3H, CH <sub>3</sub> ), 3.2 (s, 3H, CH <sub>3</sub> ), 3.9–4.2 (q, 2H, CH <sub>2</sub> ), 5.4 (s, 1H, OH), 7.4–7.8 (m, 5H, Ar–H)
<b>10b</b>	3400 cm <sup>-1</sup> (OH), 1690 cm <sup>-1</sup> (CO)	CDCl <sub>3</sub> : 3.2 (s, 3H, CH <sub>3</sub> ), 5.6 (s, 1H, OH), 7.4–7.8 (m, 10H, Ar–H)
<b>10c</b>	3420 cm <sup>-1</sup> (OH), 1690 cm <sup>-1</sup> (CO)	CDCl <sub>3</sub> : 3.3 (s, 3H, CH <sub>3</sub> ), 5.6 (s, 1H, OH), 7.4–7.8 (m, 9H, Ar–H)

The solid product was collected and recrystallized from ethanol as white crystals in 77% yield, m.p. 177°C.

Anal. Calcd. for C<sub>23</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>S (434.51): C, 63.58; H, 5.10; N, 12.89; S, 7.38%. Found: C, 63.73; H, 4.95; N, 13.04; S, 7.22%. IR:  $\nu$  = 3340 cm<sup>-1</sup> (NH) and, 1710–1680 cm<sup>-1</sup> (2CO). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.5 (t, 3H, CH<sub>3</sub>), 3.00 (s, 3H, CH<sub>3</sub>), 4.0 (q, 2H, CH<sub>2</sub>), 4.1 (s, 2H, CH<sub>2</sub>), 7.1–7.7 (m, 10H, Ar–H), 8.1 (s, 1H, CH), 11.2 (s, 1H, NH).

### Ethyl 4-Methyl-2-phenyl-6-[3,5-dimethylpyrazol-1-oxomethylenethio-1-yl]pyrimidin-5-carboxylate (**8**)

A mixture of compound **5** (0.01 mmol) and acetylacetone (0.01 mmol) in ethanol (20 ml) was heated under reflux for 5 h, then allowed to cool. The solid product was collected and recrystallized from ethanol as white crystals in 72% yield, m.p. 176°C.

Anal. Calcd. for  $C_{21}H_{22}N_4O_3S$  (410.49): C, 61.45; H, 5.40; N, 13.65; S, 7.81%. Found: C, 61.32; H, 5.25; N, 13.84; S, 8.00%. IR:  $\nu = 2950\text{ cm}^{-1}$  (CH aliphatic) and,  $1710\text{--}1680\text{ cm}^{-1}$  (2CO).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.5$  (t, 3H,  $\text{CH}_3$ ), 2.95, 3.1, 3.2, (3s, 9H,  $3\text{CH}_3$ ), 3.9 (q, 2H,  $\text{CH}_2$ ), 4.0 (s, 2H,  $\text{CH}_2$ ), 6.1 (s, 1H, CH), 7.2–7.6 (m, 5H, Ar–H).

### Ethyl 4-Methyl-2-phenyl-6-[2-mercaptooxadiazol-5-methylenethio-5-yl]pyrimidin-5-carboxylate (9)

A sample of compound **5** (0.01 mmol) and carbon disulfide (1 ml) in pyridine (10 ml) was heated on a water bath for 12 h, then the solvent was evaporated under reduced pressure. The solid product was collected and recrystallized from ethanol as white crystals in 65% yield, m.p.  $120^\circ\text{C}$ .

Anal. Calcd. for  $C_{17}H_{16}N_4O_3S_2$  (388.46): C, 52.56; H, 4.15; N, 14.42; S, 16.51%. Found: C, 52.67; H, 3.98; N, 14.35; S, 16.71%. IR:  $\nu = 2900\text{--}2750\text{ cm}^{-1}$  (SH) and,  $1700\text{ cm}^{-1}$  (CO).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.5$  (t, 3H,  $\text{CH}_3$ ), 2.95 (s, 3H,  $\text{CH}_3$ ), 3.9 (q, 2H,  $\text{CH}_2$ ), 4.0 (s, 2H,  $\text{CH}_2$ ), 7.2–7.6 (m, 5H, Ar–H).

### 3-Hydroxy-4-methyl-6-phenylthieno[2,3-d]-2-substitutedpyrimidin (10a–c)

A sample of compound **4a–c** (0.005 mmol) in ethanol (20 ml) containing sodium ethoxide (0.01 mmol) was heated under reflux for 1 h, allowed to cool, diluted with water (50 ml), and acidified with HCl (0.1 N) to just acidic. The solid product was collected. The physical properties and spectral data of compounds **10a–c** are listed in Tables I and II.

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