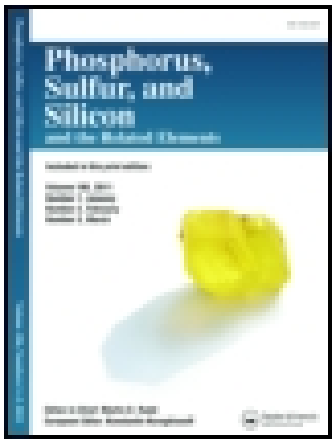

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Synthesis of Pyrimidines, Thienopyrimidines, and Pyrazolopyrimidines

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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 β-aminocrotonate **1** with benzoyl isothiocyanate (**2**) in refluxing acetone, was reacted with a series of halopgenated 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 analgecics,[1] antipyretic,[2] and antiinflammatory agents.[3,4] In view of the pharmacological importance of thienopyrimidine and in continuation of our work,[5,6] 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[6] previously, was allowed

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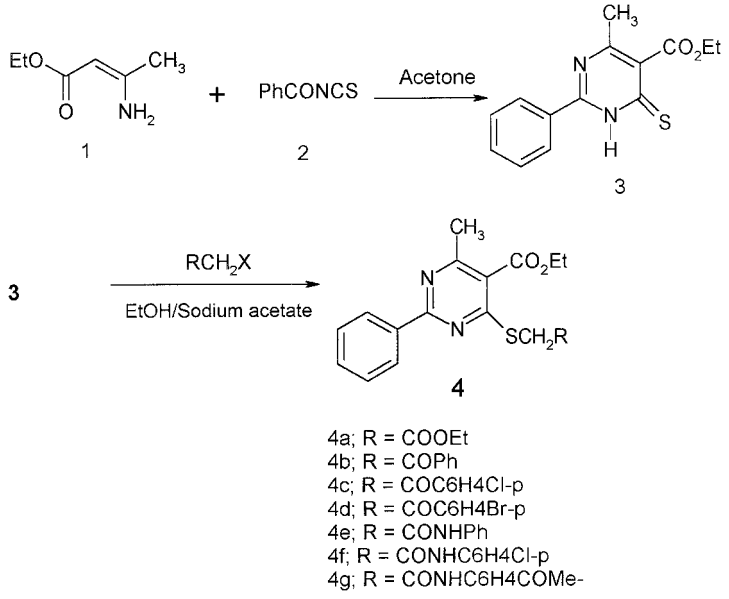
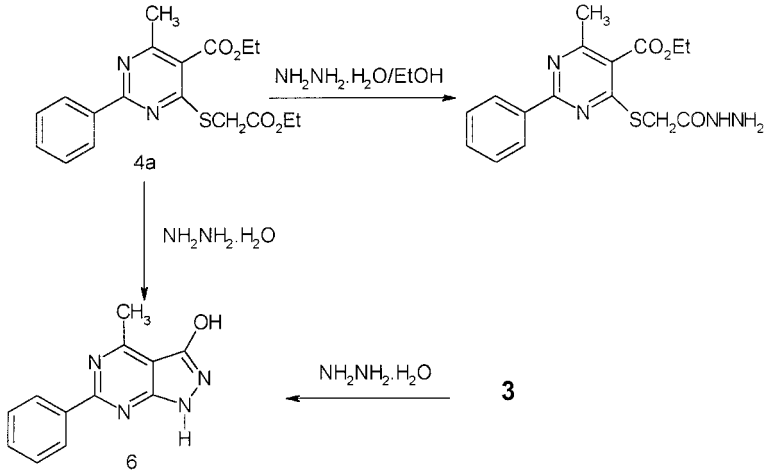


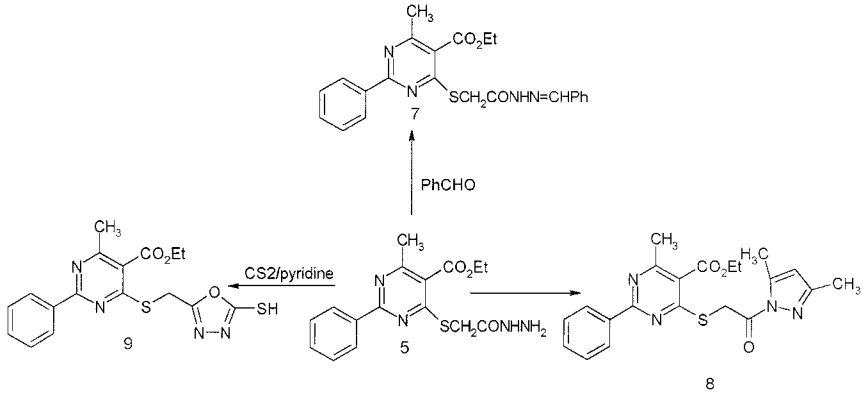
SCHEME 1

to react with a series of α-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

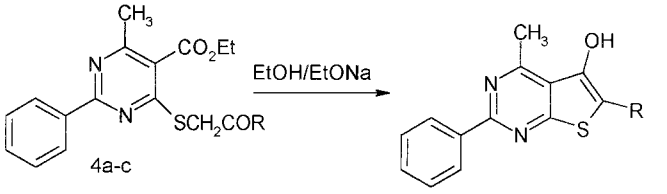


SCHEME 3

corresponding carbohydrazide **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.

Carbohydrazide **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.



10a, R = CO_2Et
10b, R = COPh
10c, R = COC_6H_4Cl-p

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}H NMR spectra were obtained on Varian 390 90-MHz spectrometer in $CDCl_3$. Chemical shift were determined on the δ scale by using tetramethylsilan 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-β-aminocrotonate (0.01 mmol) in acetone was added. The mixture was stirred at room tempereature 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°C.

IR: $\nu = 3220$ cm^{-1} (NH), 1720 cm^{-1} (C=O), and 1510 cm^{-1} (C=S). ^{1}H NMR ($CDCl_3$): $\delta = 1.2$–1.5 (t, 3H, CH_3 ester), 2.3 (s, 3H, CH_3), 4.3–4.55 (q, 2H, CH_2 ester), 7.35–7.7; 7.95–8.15 (2m, 5H, ArH). Anal. Calcd. for $C_{14}H_{14}N_2O_2S$ (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°C.

Anal. Calcd. for $C_{16}H_{18}N_4O_3S$ (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 cm^{-1} ($NHNH_2$) and, 1700, 1670 cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$): $\delta =$ 1.3–1.5 (t, 3H, CH_3), 2.95 (s, 6H, $2CH_3$), 3.9 (q, 2H, CH_2), 4.1 (s, 2H, CH_2) 4.3 (s, 2H, 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
4a	COOEt	85	$C_{18}H_{20}N_2O_4S$	59.98	5.59	7.77	8.89
			(360.43)	60.13	5.42	7.93	9.02
4b	COPh	114	$C_{22}H_{20}N_2O_3S$	67.33	5.14	7.14	8.17
			(392.47)	67.52	4.93	6.95	8.33
4c	COC_6H_4Cl-*p*	145	$C_{22}H_{19}ClN_2O_3S$	61.90	4.49	6.56	7.51
			(426.92)	62.09	4.67	6.38	7.71
4d	COC_6H_4Br-*p*	150	$C_{22}H_{19}BrN_2O_3S$	56.06	4.06	5.94	6.80
			(471.37)	55.89	4.13	6.14	6.66
4e	CONHPh	190	$C_{22}H_{21}N_3O_3S$	64.85	5.19	10.31	7.87
			(407.49)	65.03	5.00	10.37	8.02
4f	$CONHC_6H_4Cl$-*p*	205	$C_{22}H_{20}ClN_3O_3S$	59.79	4.56	9.51	7.25
			(441.93)	59.92	4.34	9.22	7.42
4g	$CONHC_6H_4COMe$-*p*	190	$C_{24}H_{23}N_3O_4S$	64.13	5.16	9.35	7.13
			(449.52)	63.93	5.02	9.47	7.26
10a	CO_2Et	180-2	$C_{16}H_{14}N_2O_3S$	61.13	4.49	8.91	10.20
			(314.36)	60.89	4.66	9.18	10.00
10b	COPh	205	$C_{20}H_{14}N_2O_2S$	69.35	4.07	8.09	9.26
			(346.40)	69.15	3.89	8.00	9.44
10c[a]	COC_6H_4Cl	269	$C_{20}H_{13}ClN_2O_2S$	63.07	3.44	7.36	8.42
			(380.85)	62.90	3.34	7.30	8.18

[a]**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.[7] m.p. 297°C.

Anal. Calcd. for $C_{12}H_{10}N_4O$ (226.24): C, 63.71; H, 4.46; N, 24.76%. Found: C, 63.88; H, 4.34; N, 25.00%. IR: $\nu = 3450, 3310, cm^{-1}$ (NH, OH) and, 1580 cm^{-1} (C=N). ^1H NMR (DMSO-d_6): $\delta = 3.00$ (s, 3H, CH_3), 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	^{1}H NMR
4a	1730, 1700 cm^{-1} (2C═O)	$CDCl_3$: 1.2–1.7 (2t, 6H, $2CH_3$), 3.0 (s, 3H, CH_3), 3.9–4.3 (m, 4H, $2CH_2$), 4.4 (s, 2H, CH_2), 7.4–7.8 (m, 5H, Ar—H)
4b	1720, 1690 cm^{-1} (2C═O)	$CDCl_3$: 1.3–1.5 (t, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.9–4.1 (q, 2H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.4–7.8 (m, 10H, Ar—H)
4c	1720, 1700 cm^{-1} (2C═O)	$CDCl_3$: 1.3–1.5 (t, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.1 (q, 2H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.4–7.8 (m, 9H, Ar—H)
4d	1720, 1700 cm^{-1} (2C═O)	$CDCl_3$: 1.3–1.5 (t, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.0 (q, 2H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.4–7.8 (m, 9H, Ar—H)
4e	3260 cm^{-1} (NH), 1720, 1670 cm^{-1} (2C═O)	$CDCl_3$: 1.3–1.5 (t, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.9–4.2 (q, 2H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.4–7.8 (m, 9H, Ar—H), 11.3 (s, 1H, NH)
4f	3300 cm^{-1} (NH), 1720, 1670 cm^{-1} (2C═O)	$CDCl_3$: 1.3–1.5 (t, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.9–4.2 (q, 2H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.4–7.8 (m, 9H, Ar—H), 11.3 (s, 1H, NH)
4g	3300 cm^{-1} (NH), 1720, 1680, 1670 cm^{-1} (3C═O)	$CDCl_3$: 1.3–1.5 (t, 3H, CH_3), 2.95, 3.3 (2s, 6H, $2CH_3$), 3.9–4.2 (q, 2H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.4–7.8 (m, 9H, Ar—H), 11.3 (s, 1H, NH)
10a	3420 cm^{-1} (OH), 1720 cm^{-1} (CO)	$CDCl_3$: 1.5 (t, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.9–4.2 (q, 2H, CH_2), 5.4 (s, 1H, OH), 7.4–7.8 (m, 5H, Ar—H)
10b	3400 cm^{-1} (OH), 1690 cm^{-1} (CO)	$CDCl_3$: 3.2 (s, 3H, CH_3), 5.6 (s, 1H, OH), 7.4–7.8 (m, 10H, Ar—H)
10c	3420 cm^{-1} (OH), 1690 cm^{-1} (CO)	$CDCl_3$: 3.3 (s, 3H, CH_3), 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 $C_{23}H_{22}N_4O_3S$ (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^{-1} (NH) and, 1710–1680 cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$): $\delta = 1.5$ (t, 3H, CH_3), 3.00 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 4.1 (s, 2H, CH_2), 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: $\nu = 2950\ cm^{-1}$ (CH aliphatic) and, 1710–1680 cm^{-1} (2CO). ^1H NMR ($CDCl_3$): $\delta = 1.5$ (t, 3H, CH_3), 2.95, 3.1, 3.2, (3s, 9H, $3CH_3$), 3.9 (q, 2H, CH_2), 4.0 (s, 2H, 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°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: $\nu = 2900$–$2750\ cm^{-1}$ (SH) and, 1700 cm^{-1} (CO). ^1H NMR ($CDCl_3$): $\delta = 1.5$ (t, 3H, CH_3), 2.95 3 (s, 3H, CH_3), 3.9 (q, 2H, CH_2), 4.0 (s, 2H, 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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