Synthesis of Pyrimidines, Thienopyrimidines and Pyrazolopyrimidine

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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 halo compounds to give S-alkyl derivatives **4a-h**. Treatment of compounds **4a-c** with sod. ethoxide cyclized into thienopyrimidine **10a-c**. Hydrazinolysis of compound **3** gave hydroxypyrazolopyrimidine derivative **6**. Also the latter compound was obtained upon heating compound **4a** with hydrazine hydrate under neat conditions, but when compound **4a** refluxed with hydrazine hydrate in ethanol the corresponding carbohydrazide **5** was produced.

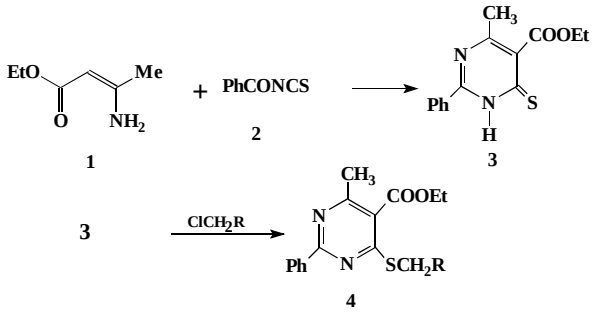
INTRODUCTION

Thienopyrimidines still attract considerable attention of many research groups due to their wide applications in medicinal chemistry. They are used as analgecics,[1] antipyretics,[2] and antiinflammatory agents.[3,4]

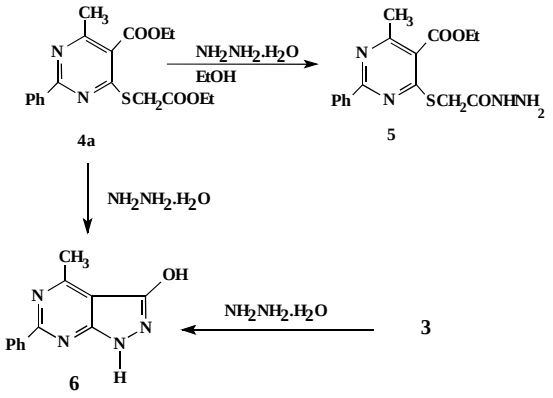
In view of the pharmacological importance of thienopyrimidine and in continuation of our work[5-6] herein we report the synthesis of some thienopyrimidines hoping that they may be biologically active.

RESULTS AND DISCUSSION

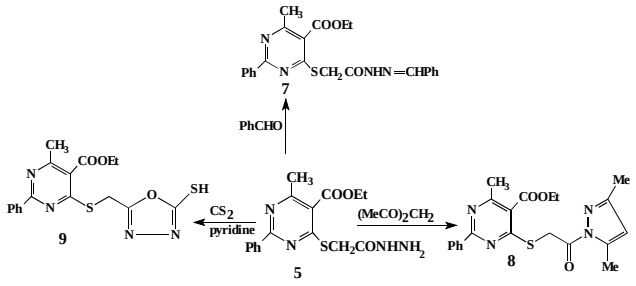
5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6(1H)-thione (**3**), which was prepared according to the method reported[6] previously was allowed to react with α-halocarbonyl compounds in ethanol and in the presence of anhydrous sodium acetate to produce the corresponding S-alkylated pyrimidine derivatives **4**.



Ethyl (5-Ethoxycarbonyl-4-methyl-2-phenylpyrimidin-6-yl)thioacetate **4a** was reacted with hydrazine hydrate in ethanol to afford the corresponding carbohydrazide **5**. But when the reaction was carried out without solvent, i.e. under neat conditions, the mercaptoacetate group was replaced by the hydrazine group which under the reaction conditions gave pyrazolopyrimidine **6**. The latter compound was obtained by refluxing pyrimidinethion **3** with hydrazine hydrate.



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



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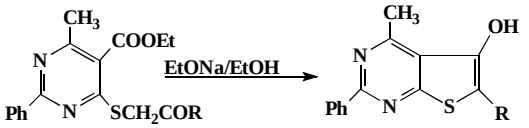
When alkylmercaptopyrimidine derivatives **4a-c** refluxed in ethanol in the presence of sodium ethoxide, thienopyrimidines **10a-c** were obtained.



4

10a; R = CO_2Et
10b; R = COPh
10c; R = C_6H_4Cl-*p*

EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The IR spectra were recorded on potassium bromide disks on a Pye Unicam spectrophotometer using the KBr Wafer technique. ^{1}H NMR spectra were obtained on a Varian 390 90-MHz spectrometer in a suitable deuterated solvent. Chemical shifts were determined on the δ scale by using tetramethylsilan as the internal standard. Elemental analyses were obtained on a 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 mol) in dry acetone, a solution of ethyl-β-aminocrotonate (0.01 mol) in acetone was added. The mixture was stirred at room temperature for 1 h and then refluxed on a steam bath for an 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: ν = 3220 cm^{-1} (NH), 1720 cm^{-1} (C=O), and 1510 cm^{-1} (C=S). ^{1}H NMR ($CDCl_3$): δ = 1.2-15 (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-h)

A mixture of compound **3** (2.75 g, 0.01 mL), sod. acetate (0.01 mol) and an appropriate halo compound (0.01 mol) 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-h** are listed in Tables 1 and 2.

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

A mixture of compound **4** (3.6 g, 0.01 mL) and hydrazine hydrate (99%, 0.05 mol) 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 $C_{16}H_{18}N_4O_3S$ (346.40): 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: ν = 3450, 3360, 3300 cm^{-1} ($NHNH_2$) and, 1700, 1670 cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$): δ = 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).

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

A mixture of compound **4a** (0.01 mol) or **3** (0.01 mol) and hyrdrazine hydrate (1 mL) was heated under reflux for 4 h, then ethanol (20 mL) was added and refluxing was continued for an additional one hour. The solid product was collected and recrystallized from ethanol as orange crystals in 67% yield in using **4a** as a starting material and 62% yield when **3** was 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: ν = 3450, 3310 cm^{-1} (NH, OH) and, 1580 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6): δ = 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]mercaptoacetic-hydrazone (7)

A mixture of compound **5** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (20 mL) was heated under reflux for 3 h, then allowed to cool. 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: ν = 3340 cm^{-1} (NH) and, 1710-1680 cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$): δ = 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 mol) and acetylacetone (0.01 mol) 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,

Table 1. Physical Constants of Compounds **4a-h**

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	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

10c: Cl, Calcd = 9.31

Table 2. Spectral Data of Compounds **4a-h**

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), !720 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), !690 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), !690 cm^{-1} (CO)	$CDCl_3$: 3.3 (s, 3H, CH_3), 5.6 (s, 1H, OH), 7.4-7.8 (m, 9H, Ar-H).

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: ν = 2950 cm^{-1} (CH aliphatic) and, 1710-1680 cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$): δ = 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 mol) 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 pres-

sure. 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: ν = 2900-2750 cm^{-1} (SH) and, 1700 cm^{-1} (CO). ^1H NMR ($CDCl_3$): δ = 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-substituted-pyrimidin (10a-c)

A sample of compound **4a-c** (0.005) in ethanol (20 mL) containing sod. ethoxide (0.01 mol) was heated under reflux for 1 h, then 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 1 and 2.

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Key Words

Synthesis; Pyrimidines; Thienopyrimidines and pyrazolopyrimidines.

REFERENCES

1. Dave, C. G.; Shah, P. R.; Dave, K. C.; Patel V. J. *J. Indian Chemical Soc.* **1989**, *66*, 48.
2. Bousquet, E.; Romero, G.; Guerrera, F.; Caruso, A.; Roxas, M. A. *Farmaco Ed. Sci.* **1985**, *40*, 869.
3. Vieweg, H.; Leistner, S.; Wagner, G.; Boehm, N.; Krasset, U. G.; Lohmann, R. D.; Loban, G. *East Ger. Patent*; 1988, pp 257,830; C. A. 110, 1989, p95262.
4. Leistner, S.; Wagner, G.; Guetscharo, M.; Glusa, E. *Pharmazie* **1989**, *41*, 54.
5. Kamal El-Dean, A. M. *J. Chem., Res.* **1996**, *M*, 1401.
6. Kamal El-Dean, A. M. *Monatsche. fur Chemie* **1998**, *129*, 523.
7. Goerdeler, J.; Wieland, D. *Chem. Ber.* **1967**, *100*, 47.