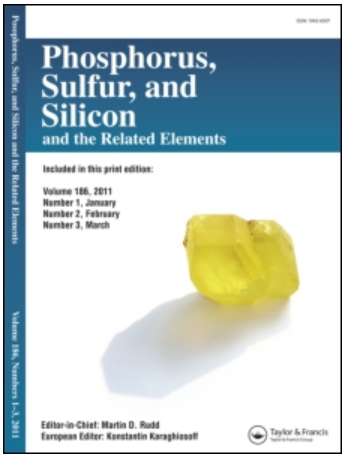

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SYNTHESIS OF SOME THIAZOLO[5,4-D] PYRIMIDINES

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SYNTHESIS OF SOME THIAZOLO[5,4-d] PYRIMIDINES

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4-Amino-3-phenyl-2-thioxothiazol-5-carboxamide (**1**) reacts with aromatic aldehydes to form thiazolopyrimidines ($\mathbf{2_{a,b}}$), and with acetic anhydride to thiazolopyrimidine ($\mathbf{2_c}$). Thiazolocarboxamides ($\mathbf{1_{a,b}}$) were converted to thiazolotriazines ($\mathbf{3_{a,b}}$) by reaction with nitrous acid. When thiazolopyrimidine ($\mathbf{2_c}$) was refluxed with $POCl_3$, the corresponding chlorothiazolopyrimidine (**4**) was isolated. The produced chloro compound (**4**) can be converted into the corresponding thiazolopyrimidindithiones (**5**) or substituted aminothiazolopyrimidines (**6,7**), when allowed to react either with thiourea, aromatic amine or hydrazine hydrate. S-alkylated thiazolopyrimidines ($\mathbf{8_{a-k}}$) were produced when compound (**5**) was reacted with halo compounds or acrylonitrile. Hydrazino compound (**7**) reacts with acetylacetone to produce the pyrazolylthiazolopyrimidine (**9**).

Key words: Thiazolopyrimidine; thiazolotriazine; thiazolopyrimidinedithione; pyrazolylthiazolopyrimidine

INTRODUCTION

According to our literature search most of the reported thiazolopyrimidines belong to the [3,2-a]-serie with a bridged nitrogen.[1–3] In contrast thiazolo[5,4-d]pyrimidines are little known. Thiazolopyrimidines have biologically interesting properties in medicinal chemistry for example as analgesics, fungicides, bactericides[3] or due to their interaction in the cerebral nervous system[4] or antipurine activity.[5]

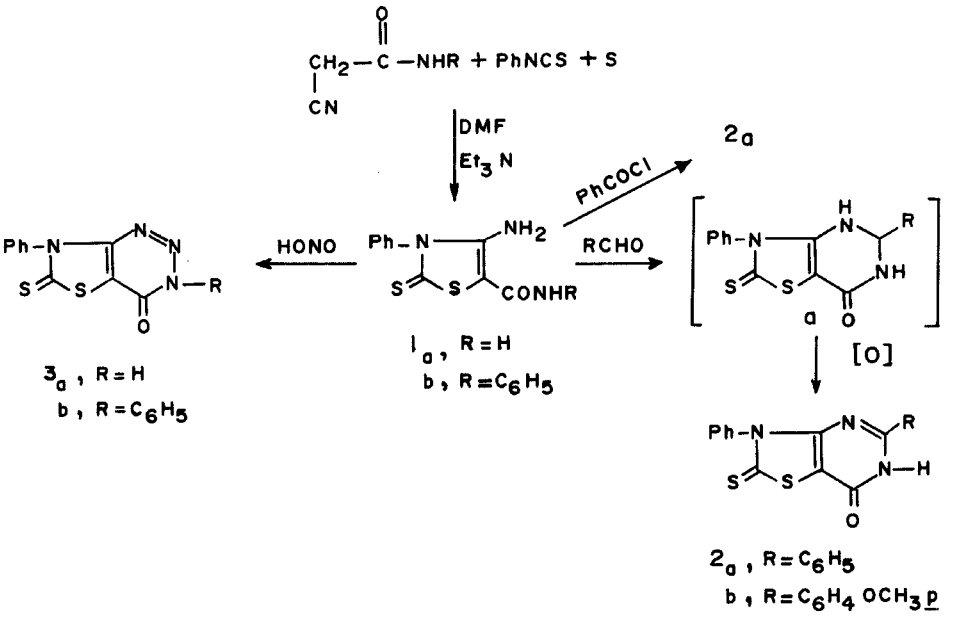
The synthesis of thiazolo[5,4-d]pyrimidines has already been reported in the literature. It can be achieved by cyclization of 5-acetamido- and benzamido-6-mercaptopyrimidines.[6] Earlier microbiological studies had indicated a greater potency for analogues unsubstituted in position 2.[7,8]

In this paper we describe the synthesis of several 2-thioxo-3-phenyl thiazolo[5,4-d]pyrimidine derivatives starting from thiazoles $\mathbf{1_{a,b}}$ which might have biologically interesting properties.

RESULTS AND DISCUSSION

4-Amino-3-phenyl-2-thioxothiazolo-5-carboxamides $\mathbf{1_{a,b}}$, prepared according to Gewald's method[9] were used as starting materials to synthesise many of the thiazolopyrimidine derivatives.

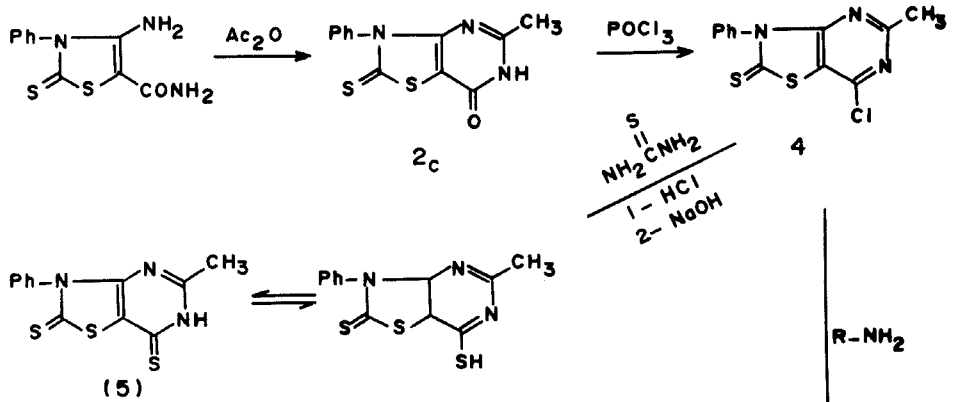
Amide $\mathbf{I_a}$ when refluxed with aromatic aldehydes in the presence of a catalytic amount of piperidine underwent condensation followed by cycloaddition of the amidic NH- group at the so formed azomethine group to give intermediate (**a**) which suffered spontaneous oxidation leading to thiazolopyrimidines ($\mathbf{2_{a,b}}$). In addition to spectral data and elemental analysis, further structural confirmation for compound $\mathbf{2_a}$ was given by its synthesis using an alternative route by cyclization of



1a, R = H
b, R = C6H5

3a, R = H
b, R = C6H5

2a, R = C6H5
b, R = C6H4 OCH3 p



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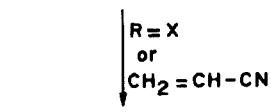
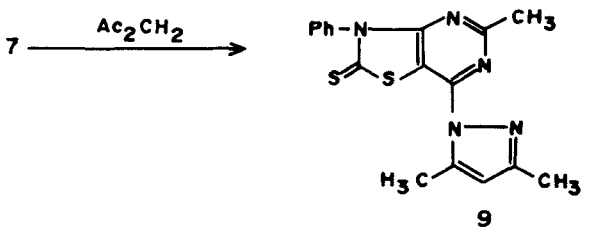


8a, R = CH3 b, R = C2H5 c, R = CH2 CN
d, R = CH2COC6H5 e, R = CH2C6H5 f, R = CH2CONH2
g, R = CH2CONHC6H5 h, R = CH2COCH3 i, R = CH2COOC2H5
j, R = CH(CH3)—COOC2H5 k, R = CH2CH2CN

6a, R = C6H5
b, R = C6H4CH3 p
7, R = NH2



9

$\mathbf{1}_a$ with benzoyl chloride. The products of the two routes were identicals in all respects (m.p., m.m.p. and T.L.C.).

When compounds $\mathbf{1}_{a,b}$ were treated with sodium nitrite in acetic acid, the thiazolo[5,4-d]triazines ($\mathbf{3}_{a,b}$) were produced.

5-Methyl-3-phenyl-2-thioxothiazolo[5,4-d]pyrimidin-7-one ($\mathbf{2}_c$) was produced when compound ($\mathbf{1}_a$) was refluxed with acetic anhydride. By further reaction of $\mathbf{2}_c$ with $POCl_3$, the corresponding chlorothiazolopyrimidine (**4**) was obtained.

7-Chloro-5-methyl-3-phenylthiazolo[5,4-d]pyrimidin-2-thione (**4**) was converted into 5-methyl-3-phenylthiazolo[5,4-d]pyrimidin-2,7-dithione (**5**) by refluxing compound (**4**) in ethanolic solution with thiourea followed by subsequent treatment with NaOH and HCl solution.

Chloro compound (**4**) was further converted to 5-methyl-3-phenyl-7-substituted amino-thiazolo[5,4-d]pyrimidin-2-thiones ($\mathbf{6}_{a,b}$,**7**) by treating with amines or hydrazine hydrate.

S-Alkylation at position **7** to thiazolopyrimidindithione (**5**) producing compounds ($\mathbf{8}_{a-j}$), was easily performed by refluxing compound (**5**) with halocompounds (R-Hal) in ethanol in the presence of sodium acetate.

S-Cyanoethylation of compound (**5**) leading to $\mathbf{8}_k$ was performed by refluxing it with acrylonitrile in ethanol in the presence of sodium acetate.

The hydrazino compound **7** easily reacted with acetylacetone to form pyrazolylthiazolopyrimidine (**9**).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using KBr Wafer technique. The ^1H NMR spectra were obtained on a Varian EM-390 MHz NMR spectrometer. Elemental analysis were determined using Perkin-Elmer 240 C Microanalyser.

3-Amino-4-phenyl-5-thioxo-thiazolo-2-carboxamide ($\mathbf{1}_{a,b}$). $\mathbf{1}_a$ was prepared according to Gewald method, m.p. 248–50° C lit.,[9] 248° C. $\mathbf{1}_b$ was obtained according to the previously reported method in 65% yield, m.p. 242–5° C, crystallized from ethanol.

Anal. Calcd. for $C_{16}H_{13}N_3OS_2$: C, 58.71; H, 3.97; N, 12.84; S, 19.57%.
Found: C, 58.82; H, 4.14; N, 12.60; S, 19.32%.
IR, 3450-3180 cm^{-1} (NH, NH_2), 1680-1640 cm^{-1} (C=O).

3-Phenyl-5-aryl-2-thioxo-thiazolo[5,4-d]pyrimidin-7-one ($\mathbf{2}_{a,b}$). A mixture of $\mathbf{1}_a$ (0.005 mol) and aromatic aldehyde was fused in the presence of a catalytic amount of piperidine for ½ hr. Then ethanol (30 ml) was added and the mixture was refluxed for an additional 3 hrs. The reaction mixture was allowed to cool, the solid product isolated and recrystallized from ethanol. The physical constants and spectral data of compounds $\mathbf{2}_{a,b}$ are listed in Table I.

Synthesis of $\mathbf{2}_a$ *using benzoyl chloride.* A sample of compound $\mathbf{1}_a$ (0.5 gm) and benzoyl chloride (3 ml) was refluxed for ½ hr. Then benzene (30 ml) was added, the mixture refluxed for one additional hour and then allowed to cool. The solid product was isolated and recrystallized from ethanol.

TABLE I

Physical contants and spectral data of compounds **2,3** and **6–8**.

Compd. No.	R	M.P. °C	Yield %	Molecular Formula	Analytical Data Calcd./Found C	H	N	S	Spectral Data
2_a	C_6H_5	344-5	75	$C_{17}H_{11}N_3OS_2$	60.53 60.62	3.26 3.00	12.46 12.58	18.99 19.12	IR: 3120 cm^{-1} (NH), 1660 cm^{-1} (C=O), 1600 cm^{-1} (C=N), ^1H NMR in DMSO-d_6: δ2.7(s,3H,CH_3), δ7.0-7.8(m,10H,Ar-H); and δ13.5(s,1H,NH).
2_b	$C_6H_4OCH_3$-p	260	78	$C_{18}H_{13}N_3O_2S_2$	5 .85 59.05	3.54 3.68	11.44 11.30	17.43 17.23	IR: 3100 cm^{-1} (NH), 1660 cm^{-1} (C=O), 1600 cm^{-1} (C=N).
3_a	H	230 dec.	85	$C_{10}H_6N_4OS_2$	45.80 45.96	2.29 2.05	21.37 21.30	24.42 24.56	IR: 3160 cm^{-1} (NH); 1680 cm^{-1} (C=O), 1600 cm^{-1} (N=N).
3_b	C_6H_5	180 dec.	82	$C_{16}H_{10}N_4OS_2$	56.80 56.72	2.95 3.08	16.56 16.68	18.93 19.12	IR: 1685 cm^{-1} (C=O), 1600 cm^{-1} (N=N), ^1H NMR in DMSO-d_6: δ7.0-7.8(m,10H,Ar-H).
6_a	C_6H_5	274-5	65	$C_{18}H_{14}N_4S_2$	61.71 62.00	4.00 3.82	16.00 15.90	18.28 18.44	IR: 3180 cm^{-1} (NH), 1600 cm^{-1} (C=N); ^1H NMR in DMSO-d_6: δ2.8(s,3H,CH_3), δ7.0-7.8(m,10H,Ar-H), δ10.5(s,1H,NH).
6_b	$C_6H_4CH_3$-p	283-5	70	$C_{19}H_{16}N_4S_2$	62.63 62.80	4.39 4.52	15.38 15.22	17.58 17.70	IR: 3180 cm^{-1} (NH), 1600 cm^{-1} (C=N).
7	NH_2	330	58	$C_{12}H_{11}N_5S_2$	49.82 50.00	3.80 4.08	24.22 24.38	22.14 22.28	IR: 3350-3150 cm^{-1} (NH_2,NH).
8_a	CH_3	220-23	80	$C_{13}H_{11}N_3S_3$	51.14 50.98	3.60 3.76	13.77 14.00	31.47 31.56	IR: 1600 cm^{-1} (C=N); no absorption characteristic for (NH).
8_b	C_2H_5	190	82	$C_{14}H_{13}N_3S_3$	52.66 52.78	4.07 4.00	13.16 12.98	30.09 30.22	IR: 1600 cm^{-1} (C=N); ^1H NMR in $CDCl_3$; δ1.4 (t,3H,CH_3), δ2.5(s,3H,CH_3), δ3.4(q,2H,CH_2) and δ7.1-7.7(m,5H,Ar-H).
8_c	CH_2CN	175-6	85	$C_{14}H_{10}N_4S_3$	50.90 51.08	3.03 3.18	16.96 17.12	29.09 28.86	IR: 2230 cm^{-1} (C≡N), 1600 (C=N); ^1H NMR in $CDCl_3$: δ2.6 (s,3H,CH_3), δ4.1(s,2H,CH_2), and δ7.00-7.60(m,5H,Ar-H).

TABLE I (*continued*)

Compd. No.	R	M.P. °C	Yield %	Molecular Formula	Analytical Data Calcd./Found C	H	N	S	Spectral Data
8d	$CH_2COC_6H_5$	160	87	$C_{20}H_{15}N_3OS_3$	58.67 58.68	3.66 3.88	10.26 10.00	23.49 0 23.42	IR: 1720 cm^{-1} (C=O) and 1600 cm^{-1} (C=N); ^1H NMR in DMSO-d_6: δ2.6(s,3H,CH_3), δ4.1(s,2H,CH_2) and δ7.0-7.8 (m,10H,Ar-H).
8e	$CH_2C_6H_5$	195-7	82	$C_{19}H_{15}N_3S_3$	59.84 60.10	3.93 4.12	11.02 10.92	25.19 24.98	IR: 1600 cm^{-1} (C=N), ^1H NMR in DMSO-d_6: δ2.6(s,3H,CH_3) δ3.7(s,2H,CH_2) and δ7.0-7.7(m,10H,Ar-H).
8f	CH_2CONH_2	260	62	$C_{14}H_{12}N_4OS_3$	48.27 48.40	3.44 3.50	16.09 15.88	27.58 27.70	IR: 3400-3200 cm^{-1} (NH_2), and 1680 cm^{-1} (C=O); ^1H NMR in DMSO-d_6: δ2.7(s,3H,CH_3), δ3.6(s,2H,CH_2) δ7.1-7.7 (m,5H,Ar-H) and δ6.5(s,2H,NH_2).
8g	$CH_2CONHC_6H_5$	245-7	68	$C_{20}H_{16}N_4OS_3$	56.60 56.88	3.77 3.90	13.20 13.00	22.64 22.50	IR: 3200 cm^{-1} (NH), 1670 cm^{-1} (C=O); ^1H NMR in DMSO-d_6 δ2.5(s,3H,CH_3), δ4.4(s,2H,CH_2), δ7.0-7.6(m,10H,Ar-H), δ14.5(s,1H,NH).
8h	CH_2COCH_3	152-54	80	$C_{15}H_{13}N_3OS_3$	51.87 52.00	3.74 3.80	12.10 11.95	27.66 27.80	IR: 1720 cm^{-1} (C=O), 1600 cm^{-1} (C=N); ^1H NMR in DMSO-d_6: δ2.5, 2.7(2s,6H,2CH_3), δ4.2(s,2H,CH_2) δ7.0-7.7(m,5H,Ar-H).
8i	$CH_2COOC_2H_5$	155	78	$C_{16}H_{15}N_3O_2S_2$	50.92 51.12	3.97 4.18	11.14 10.92	25.46 25.32	IR: 1750 cm^{-1} (C=O); ^1H NMR in $CDCl_3$: δ1.3(t,3H,CH_3), δ2.5(s,3H,CH_3); δ3.9(q,2H,CH_2), δ4.1(s,2H,CH_2), δ7.0-7.6(m,5H,Ar-H).
8j	$CH(CH_3)COOC_2H_5$	120	82	$C_{17}H_{17}N_3O_2S_3$	52.17 51.98	4.34 4.50	10.74 10.50	24.55 24.68	IR: 1740 cm^{-1} (C=O).
8k	CH_2CH_2CN	178-80	65	$C_{15}H_{12}N_4S_3$	52.32 52.44	3.48 3.62	16.27 16.05	27.90 28.08	IR: 2230 cm^{-1} (C≡N).

3-Phenyl-5-methyl-2-thioxo thiazolo[5,4-d]pyrimidin-7-one (**2$_c$**). A sample of compound **1$_a$** (2 gm) was refluxed in acetic anhydride (10 ml) for 4 hrs then allowed to cool. The solid was separated and recrystallized from acetic acid. Yellow needles, 65% yield, m.p. 345° C.

Anal. Calcd. for $C_{12}H_9N_3OS_2$: C, 52.36; H, 3.27; N, 11.20; S, 17.06%.
Found: C, 52.30; H, 3.50; N, 11.36; S, 16.92%.
IR 3180 cm^{-1} (NH), 1700-1650 cm^{-1} (C=O), 1590 cm^{-1} (C=N); ^1H NMR in DMSO-d_6: δ2.6 (s, 3H, CH_3), δ7.0-7.6 (m, 5H, Ar-H), δ13.3 (s, 1H, NH).

3-Phenyl-2-thioxo thiazolo[5,4-d][1,2,3]triazin-7-one (**3$_{a,b}$**). To a solution of compound **1$_a$** or **1$_b$** (1 gm) in acetic acid (30 ml), sodium nitrite solution (1 gm in 5 ml H_2O) was added dropwise under stirring. The reaction mixture was allowed to stand for 5 hrs. The solid product was collected and crystallized from acetic acid as red crystals. Physical constants and spectral data of compound **3$_{a,b}$** are listed in Table I.

7-Chloro-5-methyl-3-phenyl thiazolo[5,4-d]pyrimidin-2-thione (**4**). A sample of compound **2$_c$** (2 gm) in $POCl_3$ (5 ml) was refluxed for 4 hrs then allowed to cool. The reaction mixture was poured under stirring into cold water/ice mixture, the solid product was collected and recrystallized from ethanol. Yellow needles, 88% yield, m.p. 170° C.

Anal. Calcd. for $C_{12}H_8ClN_3S_2$: C, 49.06; H, 2.72; Cl, 12.09; N, 14.31; S, 21.80%.
Found: C, 48.90; H, 3.00; Cl, 11.95; N, 14.52; S, 22.00%.
IR: the IR showed no absorptions characteristic for NH- and CO- groups in **2$_c$**. H^1NMR in $CDCl_3$: δ2.7 (s, 3H, CH_3); δ7.00-7.6 (m, 5H, Ar-H).

5-Methyl-3-phenyl thiazolo[5,4-d]pyrimidin-2,7-dithione (**5**). A mixture of compound 4 (2.9 gm, 0.01 mol) and thiourea (3.7 gm, 0.05 mol) in ethanol (30 ml) was refluxed for 2 hrs or until the thiourenium salt was precipitated. Then the reaction mixture was allowed to cool, sodium hydroxide solution (30 ml 10%) was added, and the mixture was warmed for 5 minutes, then acidified with HCl. The solid product was collected and recrystallized from ethanol giving yellow crystals, 90% yield, m.p. 340° C.

Anal. Calcd. for $C_{12}H_9N_3S_3$: C, 49.48; H, 3.09; N, 14.43; S, 32.98%.
Found: C, 49.62; H, 2.86; N, 14.65; S, 33.22%.
IR: 3180 cm^{-1} (NH), 1450 cm^{-1} (C=S); 1580 cm^{-1} (C=N); ^1H NMR in DMSO-d_6: δ2.8 (s, 3H, CH_3), δ7.0-7.6 (m, 5H, Ar-H); δ13.5 (s, 1H, NH).

7-Substituted amino-5-methyl-3-phenyl thiazolo[5,4-d]pyrimidin-2-thione (**6,7**).

General procedure. An equimolar ratio of compound **4** (0.001 mol) and aromatic amine or hydrazine hydrate (0.001 mol) was warmed for 10 minutes, then ethanol (20 ml) was added, and the mixture was warmed for additional 10 minutes, then allowed to cool, and the solid product collected and recrystallized from ethanol to give compounds (**6,7**). The physical constants and spectral data for compounds **6,7** are listed in Table I.

5-Methyl-3-phenyl-7-thio-substituted thiazolo[5,4-d]pyrimidin-2-thione (**8$_{a-k}$**).

General procedure. A mixture of compound (**5**) (0.005 mol), halocompound or acrylonitrile (0.005 mol) and sodium acetate (0.01 mol) in ethanol (30 ml) was refluxed for 1 hr, then allowed to cool. The solid product was collected, washed with water and recrystallized from ethanol to give compounds (**8$_{a-k}$**). THe physical constants and spectral data for compounds (**8$_{a-k}$**) are listed in Table I.

3-Phenyl-5-methyl-7[3,5-dimethylpyrazol-1-yl]thiazolo[5,4-d]pyrimidin-2-thione (**9**). A mixture of hydrazinocompound (**7**) (0.5 gm) and acetylacetone (2 ml) was refluxed for ½ hr, then ethanol was added and the mixture was refluxed for additional 1 hr then allowed to cool and recrystallized from ethanol, 68% yield m.p. 273–5° C decom.

Anal. Calcd. for $C_{17}H_{15}N_5S_2$: C, 57.79; H, 4.24; N, 19.83; S, 18.13%.
Found: C, 58.00; H, 4.05; N, 20.05; S, 17.95%.
IR showed the disappearance of bands characteristic for $NHNH_2$. ^1H NMR in DMSO-d_6: δ2.5, 2.7 (2s, 9H, $3CH_3$), δ6.2 (s, 1H, CH), δ7.1-7.6 (m, 5H, Ar-H).

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