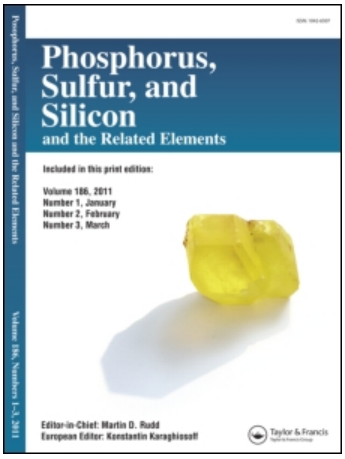

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A FACILE SYNTHESIS OF ISOXAZOLO [5',4':4,5]THIAZOLO[3,2-*a*]THIENO PYRIMIDINES A NEW RING SYSTEM

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To cite this Article Abdel-fattah, A. M. , Aly, As. , Gad, F. A. , Zaki, M. E. A. and El-gazzar, A. B. A.(1998) 'A FACILE SYNTHESIS OF ISOXAZOLO [5',4':4,5]THIAZOLO[3,2-*a*]THIENO PYRIMIDINES A NEW RING SYSTEM', Phosphorus, Sulfur, and Silicon and the Related Elements, 141: 1, 263 — 281
To link to this Article: DOI: 10.1080/10426509808033738
URL: http://dx.doi.org/10.1080/10426509808033738

Phosphorus, Sulfur and Silicon, 1998, Vol. 141, pp. 263-281
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A FACILE SYNTHESIS OF ISOXAZOLO [5′,4′:4,5]THIAZOLO[3,2-*a*]THIENO PYRIMIDINES A NEW RING SYSTEM

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(Received 26 February, 1998; In final form 02 July, 1998)

In a one-pot synthesis 6,7-dimethyl-2-arylidine-5-*H*-thieno[2,3-*d*]pyrimidine-3,5-diones **2** were prepared via the reaction of a ternary mixture of 5,6-dimethyl-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-4-one **(1),** chloroacetic acid, and a proper aldehyde. Compound **2** reacted with hydroxylamine to afford 2,3-dihydro-7,8-dimethyl-3-substituted-9*H*-isoxazolo[5′,4′:4,5]thiazolo [3,2-*a*] thieno[2,3-*d*]pyrimidin-9-ones **(4).**

Reaction of **1** with 3-chloropent-2,4-dione in ethanolic potassium hydroxide yielded the S-acetylacetone derivative **5**d. The latter compound reacted with hydrazines and thiourea affording the 2-pyrazolthio and the 2-pyrimidinylthio derivatives **11** and **12,** respectively. Compound **5**d also underwent cyclization on boiling with acetic anhydride/pyridine solution to yield 2-acetyl-3,6,7-trimethyl-5*H*-thieno[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one **(13).** The 2-methylthioderivative **5**a was converted into the corresponding 2-methyl sulphone derivative **9** on treatment with hydrogen peroxide.

Keywords: Pyrimidines; Ring system; NMR spectra; mass spectra

DISCUSSION

The biological[1–5], bactericidal[6], and medicinal[7,8] activities of pyrimidine and fused pyrimidine derivatives, prompted us to synthesize new derivatives of pyrimidine and fused pyrimidines.

We report convenient methods for the synthesis of thiazolothienopyrimidine, isoxazolothiazolothienopyrimidine, and pyrazolylthienopyrimidines derivatives. Upon heating under reflux a mixture of 5,6-dimethyl-2-thi-

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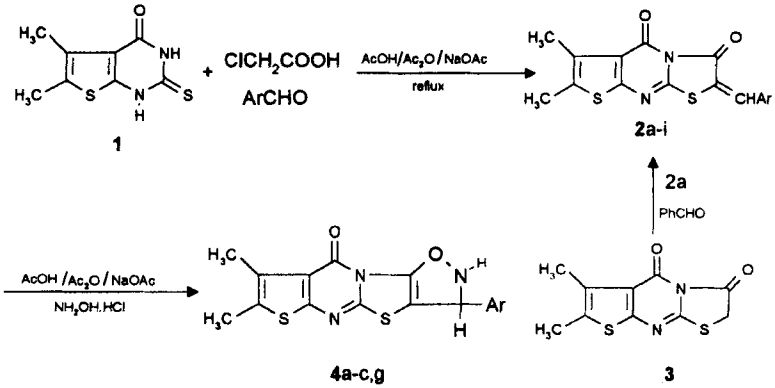
oxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-4-one (**1**), chloroacetic acid, and an aromatic aldehyde in acetic acid and acetic anhydride in the presence of anhydrous sodium acetate, heterocycles **2a-i** were obtained in good yields (Scheme 1).

The structure assignments are based inter alia on an independent preparation of **2a** by condensation of **3** with benzaldehyde in acetic acid in the presence of anhydrous sodium acetate. Compounds **2(a-c,g)** reacted with hydroxylamine hydrochloride in boiling acetic acid in the presence of anhydrous sodium acetate to give tetracyclic compounds **4a-d,** a new ring system.



2,4	Ar	2,4	Ar
a	ph	f	3,4-$CH_2O_2C_6H_3$
b	4-ClC_6H_4	g	2-thienyl
c	4-$MeOC_6H_4$	h	2-furyl
d	4-MeC_6H_4	i	2-pyridyl
e	4-$(Me)_2NC_6H_4$		

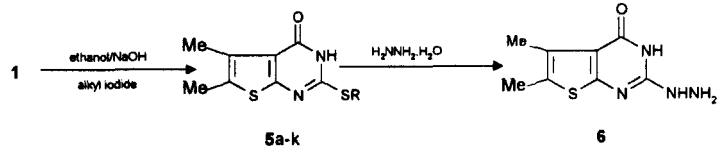
SCHEME 1

The ^{1}H-NMR spectrum (DMSO-d_6) of **4c,** as an example, showed signals for the methyl groups at δ 2.25, 2.33 and 3.97. The resonance of the isoxazoline ring proton appeared as a doublet (J = 18 Hz) at δ 6.38, and the AA'BB' coupling pattern was observed for the aromatic protons at δ 6.95

and 7.52. The NH signal at δ 12.22 was coupled to the signal at δ 6.38. The IR spectra of **4a-c** and **4g** displayed absorption bands around 3300 cm^{-1} (NH), 3080 (CH) and 1675 (C=O).

Heating **2** with hydrazine hydrate yielded the 2-hydrazino[9] derivative 6, which was synthesized by Shishoo[10] from the **5**a and hydrazine hydrate.

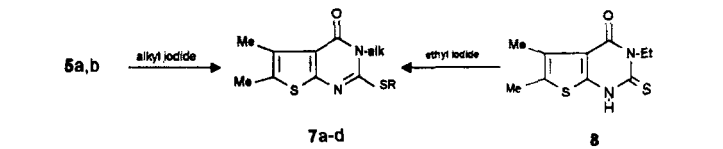
Alkylation of compound **1,** in ethanolic sodium hydroxide, with alkyl iodide or chloro-compounds yielded the alkylthio derivatives **5a-h** (Scheme 2). With hydrazine hydrate compounds **5a,b** gave the 2-hydrazino derivative **6** . This is conclusive for the structures of **5a,b.**



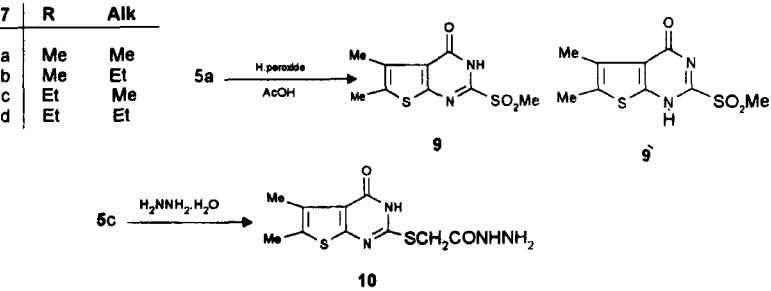
5	R
a	Me
b	Et
c	CH_2CO_2Et
d	$CH(Ac)_2$

5	R
e	$CH_2CONHph$
f	$CH_2CONHC_6H_4$-4-Cl
g	$CH_2CONHC_6H_4$-4-OMe
h	CH(Ac)N=Nph

5	R
i	$CH(Ac)N=NC_6H_4$-4-Cl
j	$CH(Ac)N=NC_6H_4$-4-NO_2
k	$CH(Ac)N=NC_6H_4$-4-OMe



7	R	Alk
a	Me	Me
b	Me	Et
c	Et	Me
d	Et	Et

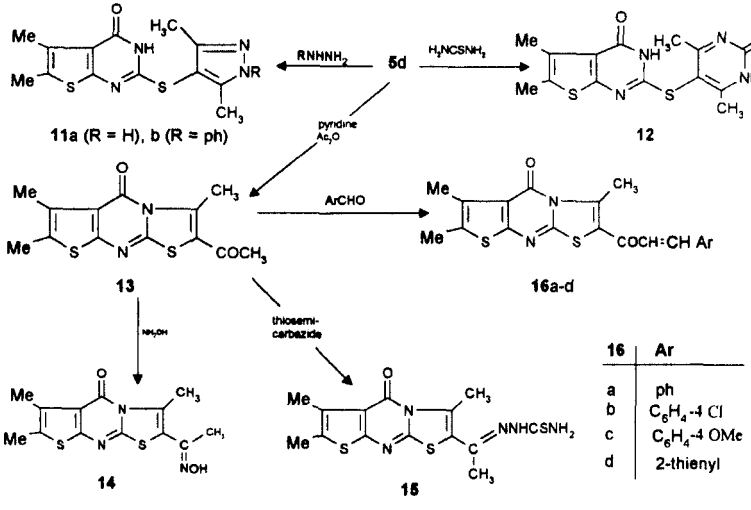


SCHEME 2

Treatment of **1** with 2-chloroacetanilide derivatives, and 1-arylazo-1-chloro- acetone yielded **5e-g** and **5h-k** respectively. IR and ^{1}H-NMR spectra of some examples of **5a-k** gave data which supports assigned structures, [Experimental].

The 2-alkylthio derivatives **5a,b** underwent further alkylation on treatment with alkyl iodide in aqueous ethanolic sodium ethoxide, the N-3 alkylated products **7a-d** (Scheme 2). Structural assignments of **7** are based on an independent preparation of **7d** by ethylation of compound **8** with ethyl iodide[11]. Oxidation of **5a** with hydrogen peroxide in acetic acid yielded the sulphone **9** or its tautomer **9** (Scheme 2).

Ester **5c** was transformed into the hydrazide **10** upon treatment with hydrazine hydrate in ethanol. The IR spectrum of 10 displayed an absorption at 3310 cm^{-1} (br OH and NH). The ^{1}H-NMR spectrum (DMSO-d_6) showed signals at δ 2.34 and δ 2.40 for the methyl groups, and at δ 2.45 for NH_2. Further signals were observed at δ 4.27 (CH_2). δ 4.40 (NH), 6 4.81 (OH). On the other hand, compound **5d,** reacted as the 1,3-diketone with hydrazine hydrate, phenylhydrazine, and thiourea, respectivly, to afford the cyclized products **11a,b 12** (Scheme 3). The IR spectra of these compounds displayed absorption bands around 1670 cm^{-1}(C=O). The ^{1}H-NMR spectrum (DMSO-d_6) of **11a** showed signals for four methyl groups at δ 2.10-2.25, and NH resonances at δ 4.15 (1 H) and δ 5.25 (1 H).



SCHEME 3

Heating **5d** in a mixture of acetic anhydride/pyridine, led to formation of the cyclic product **13.** The IR spectrum of **13** displayed two carbonyl absorption bands at 1725 and 1650 cm^{-1}. The ^{1}H-NMR spectrum ($CDCl_3$) showed methyl signals at δ 2.37, 2.45, 2.56, 3.20. In the, ^{13}C-NMR spectrum, resonances for nine sp^2 and four sp^3 hybridized carbon atoms were observed. The mass-spectrum showed inter alia m/e 292 (100%) (M^+) and 277 ($M-CH_3$) (18%).

Ketone compound **13** formed an oxime **14** and a thiosemicarbazone **(15)**. Moreover, condensation of **13** with aromatic aldehydes furnished the derivatives **16a-d** (Scheme 3). The IR spectra of **16** displayed two carbonyl absorptions around 1703 and 1650 cm^{-1}. The ^{1}H-NMR spectrum (DMSO-d_6) of **(16b),** showed signals for three methyl groups at δ 2.55, δ 2.60, and δ 2.75, and the AA'BB' spectrum for the aromatic protons at δ 7.65 and 8.10 (J = 18 Hz). The vinyl protons appeared at δ 8.40 (J = 16 Hz) indicating the trans configuration of the double bond.

Experimental

The melting points are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker WM-250, a Bruker AC-250 spectrometers, and a Varian ^{1}H Gemini 200 spectrometer. Chemical shifts were expressed as δ values with TMS as internal standard. The IR spectra (cm^{-1}) were recorded as KBr pellets on a Perkin-Elmer 1430 and 1320 and 299 spectrometers. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu spectrometer.

2-Arylmethylene-2,3-dihydro-6, 7-dimethyl-5H-thiazolo[3,2-a] thieno[2,3- d]pyrimidine-3,5-dione (2a-i)

a) A mixture of **1** (2.13 g, 10 mmol), chloroacetic acid (0.95 g, 10 mmol), an aromatic aldehyde (10 mmol) and NaOAc (1.64 g, 20 mmol) was boiled under reflux for 3 h in AcOH (30 ml) and Ac_2O (15 ml). After cooling, the mixture was poured into H_2O (100 ml), and the precipitate was filtered off and crystallized.

b) A mixture of **3** (2.52 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol) and NaOAc (1.64 g, 20 mmol) was boiled under reflux for 2 h in AcOH (30 ml) and Ac_2O (15 ml). Workup as bdescribed afforded **2a.**

2,3-Dihydro-6,7-dimethyl-2-(phenylmethylene)-5H-thiazolo [3,2- a]thieno[2,3-d]pyrimidine-3,5-dione (2a)

According to a) from benzaldehyde (1.06 g, 10 mmol). Yield 2.79 g, (82%) of yellow crystals, after crystallization from dioxane, mp. 272–274 °C; IR 1770, 1700 (2C=O), 1580(C=N) ; ^{1}H-NMR (DMSO-d_6): δ 2.36, 2.47 (methyl protons), 7.25–7.59 (phenyl protons), 8.04 (CH);$C_{17}H_{12}N_2S_2O_2$ (340.4): **C**, 59.98; **H,** 3.55; **N,** 8.23; **Found: C,**60.06; **H,** 3.63; **N,** 7.99.

2-(4-Chlorophenylmethylene)-2,3-dihydro-6,7-dimethyl-5H-thiazolo [3,2 -a]thieno[2,3-d] pyrimidine-3,5-dione (2b).

According to a) from 4-chlorobenzaldehyde (1.41 g,10 mmol). Yield 3.00 g, (80%) of yellow crystals, after crystallization from dioxane; mp. 312–314 °C ; IR 1768, 1705 (2C=O),1604 (C=N); ^{1}H-NMR (CF_3CO_2H:$CDCl_3$(1:1) δ 2.45,2.48 (methyl protons), 7.59 (phenyl protons), 8.19 (CH); ^{13}C-NMR ppm 6:13.3,13.4 (CH_3), 117.8–159.8 (13 signals), 164.1, 165.0 (C=O); $C_{17}H_{11}N_2S_2O_2Cl$ (374.8): **C,** 54.47; **H,** 2.96; **N,** 7.47; **Found: C,** 54.38; **H,** 2.93; **N,** 7.39; mass spectrum m/e 374 (M^+).

2-(4-Methoxyphenylmethylene)-2,3-dihydro-6,7-dimethyl-5H-thizolo [3,2-a]thieno[2,3-d] pyrimidine-3,5-dione (2c)

According to a) from 4-methoxybenzaldehyde (1.36 g, 10 mmol). Yield 3.03g, (82%) of yellow crystals, after crystallization from dioxane; mp. 262–264 °C ; **IR** 1761, 1717 (2C=O), 1593 (C=N); **^{1}H-NMR** (DMSO-d_6): δ 2.32, 2.42, 4.15 (methyl protons), 7.10 (CH), 7.40, 7.80 (AA'BB' system for phenyl protons); $C_{18}H_{14}N_2S_2O_3$ (370.4): **C**, 58.36; **H**, 3.81; **N,** 7.56; **Found:** C, 58.32; **H**, 3.79; **N,** 7.53.

2-(4-Tolylmethylene)-2,3-dihydro-6, 7-dimethyl-5H-thiazolo[3,2-a] thieno[2,3-d]pyrimidine-3,5-dione (2d)

According to a) from 4-methylbenzaldehyde (1.20 g, 10 mmol). Yield 2.90g, (82%) of yellow crystals, after crystallization from dimethylformamide, mp.258–260 °C ; IR 1766,1703 (2C=O); $C_{18}H_{14}N_2S_2O_2$ (354.4): **C,** 60.99; **H,** 3.98; **N,** 7.90; **Found: C,** 60.83; **H,** 3.89; **N,** 7.78.

2-(4-Dimethylaminophenylmethylene)-2,3-dihydro-6,7-dimethyl-5H-thiazolo[3, 2-a]thieno [2,3-d]pyrimidine-3,5-dione (2e)

According to a) from 4-dimethylaminobenzaldehyde (1.49 g, 10 mmol). Yield 2.22 g, (58%) of brown crystals, after crystallization from dioxane, mp 270–272 °C; **IR** 1748, 1705 (2C=O), 1615 (C=N); $C_{19}H_{17}N_3S_2O_2$ (383.5): **C,** 59.51 ; **H,** 4.47; N, 10.96; **Found: C,** 59.54; **H,** 4.50; **N,** 11.01.

2-(3,4-Pipreonylmethylene)-2,3-dihydro-6,7-dimethyl-5H-thiazolo [3,2- a]thieno[2,3-d/pyrimidine (2f)

According to a) from 3,4-(methylendioxy)benzaldehyde (1.50 g, 10 mmol). Yield 2.88g, (75%) of brown crystals, after crystallization from dioxane, mp. 286–288 °C ; IR 1664, 1601 (2C=O) 1557 (C=N); $C_{18}H_{12}N_2S_2O_4$ (384.4): **C,** 56.24; **H,** 3.15; **N,** 7.29; **Found: C,** 55.97; **H,** 3.21; **N,** 7.37.

2-(2-Thienylmethylene)-2,3-dihydro-6,7-dimethyl-5H-thiazolo [3,2- a]thieno[2,3-d]pyrimidine-3,5-dione (2g)

According to a) from thiophene-2-carboxaldehyde (0.96 g, 10 mmol). Yield 2.08 g, (60%) of green crystals after crystallization from ethanol, mp.240–242 °C ; IR 1699, 1647 (2C=O), 1557 (C=N); **^{1}H-NMR** (DMSO-d_6): δ 2.24, 2.37 (methyl protons), 7.22, 7.43 , 7.65 (ABM-system for theinyl proton), 8.21 (CH); $C_{15}H_{10}N_2S_3O_2$ (346.4): **C,** 52.00; **H,** 2.91; **N,** 8.09; **Found: C,** 51.89; **H,** 2.93; **N,** 8.13.

2-(2-Furfurylmethylene)-2,3-dihydro-6,7-dimethyl-5H-thiazolo [3,2- a]thieno[2,3-d]pyrimidine-3,5-dione (2h)

According to a) from furan-2-carboxaldehyde (0.96 g, 10 mmol). Yield 2.24 g,(68%) of red crystals, after crystallization from dioxane, mp. 284–286 °C; IR 1759, 1711 (2C=O), 1675 (C=N); ^{1}H-NMR (CF_3CO_2H:$CDCl_3$(1:1)): δ 2.52, 2.55 (methyl proton), 6.87, 7.45, 8.00 (ABM-system for furyl protons), 8.30 (CH);^{13}C-NMR ppm: 12.6, 13.0 (CH_3), 117.8-157.3 (11 1 signals), 160.3, 161.9 (2C=O); $C_{15}H_{10}N_2S_2O_3$ (330.4): **C,** 54.53; **H,** 3.05; **N,** 8.48; **Found: C,** 54.48; **H,** 3.11 ; **N,** 8.39,

2-(2-Pyridylmethylene)-2,3-dihydro-6, 7-dimethyl-5H-thiazolo [3,2- a]thieno[2,3-d]pyrimidine (2i)

According to a) from pyridine-2-carboxaldehyde (1.10 g, 10 mmol). Yield 1.77 g, (52%) of brown crystala, after crystallization from dioxane, mp 244–246 °C; IR 1686, 1646 (2C=O), 1635 (C=N); $C_{16}H_{11}N_3S_2O_2$ (341.4): **C,** 56.29; **H,** 3.25; **N,** 12.13; **Found: C,** 56.31; **H,** 3.28; **N,** 12.21.

1,2-Dihydro-6,7-dimethyl-5H-thiazolo[3,2-a]thieno[2,3-d] pyrimidine (3)

A mixture of **1** (2.13 g,10 mmol), chloroacetic acid (0.95 g,10 mmol) and (1.64 g, 20 mmol) anhydrous sodium acetate was heated gently with stirring on a waterbath (60°C) for 2 hours. The reaction mixture was allowed to cool, poured into water (100 ml). The precipitate was filtered off, yield 1.71 g, (68%) of white powder, after crystallization from dioxane, mp. 260–262 °C; IR 1700, 1650 (2C=O), 1550 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.12, 2.23 (methyl protons), 2.50 (CH2); $C_{10}H_8N_2S_2O_2$ (252.3): **C,** 47.60; **H,** 3.19; **N,** 11.11; **Found: C, 47.52; H,** 3.28; **N,** 10.89.

3-Aryl-7,8 -dimethyl-2,3-dihydroisoxazolo[4′,5′:4,5]thiazolo [3,2-a]thieno [2,3-d]pyrimidine-9(9H)-one (4a-d)

General procedure

A mixture of **2(a-c,g)** (10 mmol), hydroxylamine hydrochloride (0.70 g, 10 mmol) and (1.64 g, 10 mmol) anhydrous sodium acetate was stirred under reflux in AcOH (30 ml) for 5 h. The reaction mixture was allowed to cool, poured into cold watre (100 ml), the precipitate was filtered off, dried and crystallized.

3-(Phenyl)-7,8-dimethyl-2,3-dihydroisoxazolo[5′,4′:4,5]thiazolo[3,2-a] thieno[2,3-d] pyrimidin-9(9H)-one (4a)

From **(2a)** (3.40 g, 10 mmol). Yield 1.81 g, (51%) of colorless crystals, after crystallization from benzene, mp. 172–174 °C; IR : 3551 (br, NH), 1672 (C=O). 1599 (C=N); $C_{17}H_{13}N_3S_2O_2$ (355.4): **C,** 57.45; **H,** 3.69; **N,** 11.82; **Found: C,** 57.43, **H,** 3.71 ; **N,** 11.93.

3-(4-Chlorophenyl)-7,8-dimethyl-2,3-dihydroisoxazolo[4′,5′-:5,4] thiazolo[3,2 -d]thieno[2,3- d]pyrimidin-9(9H)-one (4b)

From **(2b)** (3.75 g, 10mmol). Yield 2.54 g, (65%) of yellow crystals, after crystallization from ethanol, mp. 248–250 °C; IR : 3450 (br, NH),1680 (C=O), 1640 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.15, 2.25 (methyl protons), 6.40 (CH), 7.25–7.55 (AA'BB'system for phenyl protons), 12.15 (br, NH); $C_{17}H_{12}N_3S_2O_2Cl$ (389.8): **C,** 52.37; **H,** 3.10; **N,** 10.78; **Found: C,** 52.42; **H,** 3.18; **N,** 10.59.

3-(Methoxyphenyl)-7,8-dimethyl,2,3-dihydroisoxazolo[5′,4′:4,5] thiazolo[3,2-a]thieno[2,3-d] pyrimidin-9(9H)-one (4c)

From **(2c)** (3.70 g, 10 mmol). Yield 2.31 g,(60%) of yellow crystals, after crystallization from dioxane/ethanol (2:1). mp. 212–214 °C; IR: 3300 (br, NH), 1675 (C=O), 1600 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.21, 2.32, δ 4.00 (methyl protons), 6.30 (CH), 12.17 (br,NH); $C_{18}H_{15}N_3S_2O_3$ (385.4): **C,** 56.09; **H,** 3.92; **N,** 10.90; **Found: C,** 55.93; **H,** 3.78; **N,** 10.81.

3-(2-Thienyl)-7,8-dimethyl-2,3-dihydroisoxazolo[5′,4′: 4,5]thiazolo [3,2-a]thieno[2,3-d] pyrimidin-9(9H)-one (4d)

From **(2g)** (3.46 g, 10 mmol) Yield 1.99 g, (55%) of brown crystals, after crystallized from ethanol, mp. 232–234 °C ; **IR:** 3250 (br, NH), 1700 (C=O), 1600 (C=N); $C_{15}H_{11}N_3S_3O_2$ (361.4): **C,** 49.84; **H,** 3.07; **N,** 11.63; **Found: C,** 50.03; **H,** 3.11; **N,** 11.52.

2-Hydrazino-5,6-dimethyl-3H, 4H-thieno[2,3-d]pyrimidin-4-one (6)

a. A suspention of dry compound **5**a (2.26 g,10 mmol) in hydrazine hydrate (99%) (25ml) was stirred under gently reflux. The insoluble solid went into solution within 10 minutes with copious evalution of methylmercaptan to form a clear solution. After 30 minutes when the solid product started separating out, heating was continued for 8 h, The reaction mixture was allowed to cool, the solid which separated was filtered, washed with ethanol and dried and crystallized from dioxane in 1.79 g, (85%) yield, m.p. 271–273 °C.

b. A suspention of **2** (10 mmol) and hydrazine hydrate (99%) (25 ml) was stirred under reflux for 12 h. The reaction mixture was allowed to cool, poured into cold water. The deposited precipitate was filtered off, washed with water, ethanol, dried and crystallized from dioxane in 1.51 g, (72%) yield, mp.272–274 °C; IR; 3360 (br, NH), 1680 (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.24, 2.29 (methyl proton), 4.41 (br, NH), 8.06 (br,NH); ^{13}C-NMR ppm: 12.2, 12.8 (CH_3), 113.8–157.9 (5C signals), 163.2(C=O); $C_8H_{10}N_4SO$ (210.3): **C,** 45.70: **H,** 4.79; **N,** 26.65; **Found: C,** 45.63; **H,**4.75; **N,** 26.78.

2-(S-Alkyl)-5,6-dimethyl-3H, 4H-thieno[2,3-d]pyrimidin-4-one (5a-d)

General procedure

To a warmed ethanolic potassium hydroxide solution (prepared by dissolving (0.56 g,10 mmol) of potassium hydroxide in ethanol (50 ml) was added each of compound **(1)** (2.13 g, 10 mmol), the heating was continued for 30 minutes and the mixture was allowed to cooled to room temperature, and the proper halo-compound (12 mmol) was added. The mixture was stirred under reflux for 5 h, then cool to room temperature, poured into cold water (100 ml). The solid product was filtered off, washed with 100 ml water, dried and crystallized.

2-(Methylthio)-5,6-dimethyl-3H.4H-thieno[2,3-d]pyrimidin-4-one (5a)

From methyliodide (1.71 g, 12 mmol). Yield 1.97 g, (87%) white crystals, after crystallization from ethanol, mp. 291–293 °C; IR: 3400 (br, NH), 1640 (C=O), 1520 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.31, 2.34, 2.51 (methyl proton), 12.52 (br, NH) ; ^{13}C-NMR ppm: 12.3, 12.7 (CH_3), 12.8 (SCH_3), 119.6–158.2 (5 signals),161.9 (C=O) $C_9H_{10}N_2S_2O$ (226.3): **C,** 47.76; **H,** 4.45; **N,** 12.38; **Found: C,** 47.81; **H,** 4.53; **N,** 12.20.

2-(Ethylthio)-5,6-dimethyl-3H.4H-thieno[2,3-d]pyrimidine-4 -one (5b)

From ethyl iodide (1.86 g, 12 mmol). Yield 1.73 g, (72%) of white crystals, after crystallization from ethanol, mp. 272–273 °C; IR: 3300 (br, NH), 1650 (C=O), 1550 (C=N). $C_{10}H_{12}N_2S_2O$ (240.3): **C,** 49.97; **H,** 5.03; **N,** 11.66; **Found: C,** 50.07; **H,** 5.14; **N,** 11.73.

2-(Ethylacetatethio)-5,6-dimethyl-3H,4H-thieno[2,3-d]pyrimidin-4-one (5c)

From ethylbromoacetate (2.00 g, 12 mmol). Yield 2.24 g, (75%) of white crystals, after crystallization from ethanol, mp. 180–182 °C; IR: 3230 (br, NH), 1720, 1680 (2C=O), 1580 (C=N); ^{1}H-NMR (DMSO-d_6) ppm: δ 1.20, 2.25, 2.30 (methyl protons), 4.05 (CH_2), 4.10 (CH_2) and 5.80 (br, NH); $C_{12}H_{14}N_2S_2O_3$ (298.3): **C,** 48.30; **H,** 4.73; **N,** 9.39; **Found: C,** 48.28; **H,** 4.70; **N,** 9.41.

2-(Acetylacetonethio)-5,6-dimethyl-3H,4H-thieno[2,3-d]pyrimidin-4-one (5d)

From chloroacetylacetone (1.61 g, 12 mmol). Yield 2.64 g, (88%)of white powders, after crystallization from dioxane, mp. 263–265 °C; IR: 3307 (br, NH), 1743, 1665 (2C=O), 1654 (C=N); $C_{13}H_{14}N_2S_2O_3$ (310.4): **C,** 50.30; **H,** 4.55; **N,** 9.03; **Found: C,** 50.41; **H,** 4.63; **N,** 9.12.

2-(S-Arylacetamido)-5,6-dimethyl-3H,4H-thieno[2,3-d]pyrimidin-4-one (5e-g)

General procedure

To a warmed ethanolic sodium hydroxide solution (prepared by dissolving (0.40 g, 10 mmol) of sodium hydroxide in (40 ml, ethanol) was added each of **(1)** (2.13 g, 10 mmol), the heating was continued for 30 minutes and the mixture was allowed to cool to room temperature, and the proper 2-chloro-acetanilide derivatives (10 mmol) was added. The mixture was stirred under reflux for 3 h., then cool, poured into cold water (100 ml). The solid product was filtered off, washed with water, ethanol, dried and crystallized.

2-[S-(N-Phenylacetamido)]-5,6-dimethyl-3H,4H-thieno [2,3 -d]pyrimidin-4-one (5e)

From 2-chloroacetanilide (1.69 g, 10 mmol). Yield 3.17 g, (92%) of white crystals, crystallization from dioxane, mp. 274–276 °C; IR: 3250 (br, NH), 1670, 1640 (2C=O), 1550 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.15, 2.30 (methyl protons), 2.54 (CH_2), 7.30–8.00 (phenyl protons), 12.00 (br, NH); $C_{16}H_{15}N_3S_2O_2$ (345.4): **C,** 55.63: **H,** 4.38; **N,** 12.16; **Found: C,** 55.72; **H,** 4.41; **N,** 12.21.

2-[S-(N-Chlorophenyl(4)-acetamido)]-5,6-dimethyl-3H,4H-thieno [2,3-d]pyrimidin-4-one (5f)

Form 4-chloroacetanilide-2-chloride (2.04 g, 10 mmol). Yield 3.53 g, (93%) of yellow crystals, after crystallization from dioxane, mp. 290–292 °C; IR: 3350 (br, NH), 1680, 1600 (2C=O), 1580 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.30, 2.34 (methyl protons), 4.14 (CH_2), 7.32–7.36, 7.57–7.61 (AA'BB' system for phenyl protons), 12.23 (br, NH); ^{13}C.NMR ppm: 12.3, 12.6 (CH_3), 35.3 (CH_2), 120.0–158.2 (11 signals), 161.6, 165.8 (C=O); $C_{16}H_{14}N_3S_2O_2Cl$ (379.8): **C,** 50.59; **H,** 3.71; **N,** 11.06; **Found: C,** 50.48; **H,** 3.86; **N,** 10.91.

2-[S-(N-Methoxyphenyl(4)-acetamido)]-5,6-dimethyl-3H,4H-thieno [2,3-d]pyrimidin-4-one (5g)

From 4-methoxyacetanilide-2-chloride (1.99 g, 10 mmol). Yield 3.30 g, (88%) of white crystals, after crystallization from dioxane, mp. 268–270 °C; IR: 3380 (br, NH), 1700, 1675 (2C=O), 1600 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.19, 2.21, 2.32 (methyl protons), 4.12 (CH_2), 7.08–7.11, 7.42–7.45 (AA′BB′ system for phenyl protons), 10.03 (br, NH), 12.48 (br, NH); ^{13}C.NMR ppm: 12.3, 12.6, 20.3 (CH_3), 35.3 (CH_2). 119.5–158.2(11 signals), 161.6, 165.4 (C=O); $C_{17}H_{17}N_3S_2O_3$ (375.4): **C,** 54.38; **H,** 4. 56; **N,** 11.19; **Found: C,** 54.42; **H,** 4.61 ; **N,** 11.23.

2-[S-(Acetonyl-1-arylazo)]-5,6-dimethyl-3H,4H-thieno[2,3-d] pyrimidin (5h-k)

General procedure

A suspention of **1** (2.13 g, 10 mmol) and 1-arylazo-1-chloroacetone (10 mmol) in dry chloroform (30 ml) was stirred under reflux for 20 h. The deposited was filtered off, washed with chloroform (30 ml), dried and crystallized.

2-[S-(Acetonyl-1-phenylazo)]-5,6-dimethyl-3H,4H-thieno[2,3-d] pyrimidin -4-one (5h)

From 1-phenylazo-1-chloroacetone (1.97 g, 10 mmol). Yield 2.64 g, (71%) of brown crystals, after crystallization from dioxane, mp. 206–208 °C; IR: 3426 (br, NH), 1730, 1700 (2C=O), 1590 (C=N); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.19, 2.30, 2.34 (methyl protons), 3.58 (CH), 7.43–

7.60 (phenyl protons), 12.62 (br, NH); $C_{17}H_{16}N_4S_2O_2$ (372.49): **C,** 54.82; **H,** 4.33; **N,** 15.04; **Found: C,** 54.73; **H,** 4.41 ; **N,** 15.11.

2-[S-(Acetonyl-1-chlorophenylazo(4)]-5,6-dimethyl-3H,4H-thieno [2,3- d]pyrimidin-4-one (5i)

From 1-chlorophenyl-(4) azo-1-chloroacetone (2.31 g, 10 mmol) Yield 2.99 g, (73%) of yellow crystals, after crystallization from dioxane, mp. 230–232 °C: IR: 3400 (br, NH), 1700, 1670 (2C=O), 1550 (C=N); $C_{17}H_{15}N_4S_2O_2Cl$ (409.9): **C.** 50.18; **H,** 3.72; **N,** 13.77; **Found: C,**49.98; **H,** 3.72; **N,**14.08,

2-[S-(Acetonyl-1-nitrophenylazo(4)]-5,6-dimethyl-3H,4H-thieno [2,3 -d]pyrimidin-4-one (5j)

From 1-nitrophenyl-(4) azo-1-chloroacetone (2.42 g, 10 mmol). Yield 2.84 g, (68%) of yellow crystals, after crystallization from dioxane, mp. 215–17 °C; IR: 3256 (br. NH), 1710, 1680 (2C=O) 1550 (C=N) $C_{17}H_{15}N_5S_2O_4$(417.4) **C,** 48.91 **H,** 3.62; **N** 16.78; **Found: C,** 48.83 ; **H,** 3.71 ; **N,** 17.01.

2-[S-(Acetonyl-1-methoxyphenylazo(4)]-5,6-dimethyl-3H,4H -thieno [2,3-d]pyrimidin-4-one (5k)

From 1-methoxyphenyl-(4) azo-1-chloroacetone (2.11 g, 10 mmol). Yield 3.14 g, (78%) of white crystals, after crystallization from dioxane, mp. 218–220 °C; IR: 3400 (br, NH), 1660, 1640 (2C=O), 1560 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.29, 2.32, 2.37 (methyl protons), 3.70 (CH), 4.71 (OCH_3), 7.51–7.54, 8.00–8.03 (AA′BB′ system for phenyl protons), 12.35 (br, NH); ^{13}C-NMR ppm: 12.6, 12.8 (CH_3), 37.9 ($COCH_3$), 39.0 (OCH_3), 78.3 (CH), 120.3158.9 (1 1 signals), 162.0, 193.3 (C=O); $C_{18}H_{18}N_4S_2O_3$ (402.5): **C,** 53.71; **H,** 4.51; **N,** 13.92; **Found: C,** 53.78; **H,** 4.60; **N,** 13.77

2-Alkylthio-3-alkyl-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidin-4-one i(7a-d)

General procedure

To a warmed ethanolic sodium ethoxide solution prepared by dissolving (0.23 g, 10 mmol) of sodium metal in ethanol (30 ml) was added each of compound (**5**a) or (**5**b) (10 mmol), the heating was continued for 30 minutes and the mixture was allowed to cool and the proper alkyl iodide (12

mmol) was added. The mixture was stirred under reflux for 3 h, then cool to room temperature, poured into cold water (100 ml). The precipitated was filtered off, washed with water, dried and crystallized.

2-Methylthio-3,5,6-trimethyl-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (7a)

From **5**a (2.26 g, 10 mmol) and methyliodode (1.72 g, 12 mmol). Yield 1.44 g, (60%) of white powder, after crystallization from ethanol, mp. 268–269 °C; IR: 1700 (C=O). 1600 (C=N); ^{1}H-NMR ($CDCl_3$): δ 2.34, 2.35, 2.44, 3.54 (methyl protons); ^{13}C-NMR ppm: 12.9, 13.1 1 (CH_3), 15.1 (SCH_3), 29.8 (NCH_3), 119.2–158.9 (5 signals), 161.5 (C=O); $C_{10}H_{12}N2S_2O$ (240.3): **C,** 49.97; **H,** 5.03; **N,** 11.66; **Found: C,** 50.08; **H,** 5.14; **N,** 11.49.

2-Ethylthio-3,5,6-trimethyl-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (7b)

From **5**b (2.40 g, 10 mmol) and methyliodide (1.72 g, 12 mmol). Yield 2.06g, (81%) of white powder, after crystallization from ethanol, mp. 110–112 °C; IR: 1700 (C=O), 1650 (C=N); $C_{11}H_{14}N_2S_2O$ (254.3): **C,** 51.94; **H,** 5.55; **N,** 11.01 ; **Found: C**, 52.01: **H,** 5.62; **N,** 10.97.

2-Methylthio-3-ethyl-5,6-dimethyl-3,4-dihydrothieno[2,3- d] pyrimidin-4-one (7c)

From **5**a (2.26 g, 10 mmol) and ethyliodide (1.86 $_g$,12 mmol). Yield 2.11 $_g$,(83%) white crystals, after crystallization from ethanol, mp. 106–108 °C; IR: 1700 (C=O), 1650 (C=N); ^{1}H-NMR ($CDCl_3$): δ 1.43, 2.32, 2.42, 3.44 (methyl protons), 4.46 (CH_2);^{13}C-NMR ppm: 12.7, 12.9 (CH_3), 14.3 (SCH_3), 27.6 (N-C-CH_3), 64.9 (N-CH_2). 118.0–159.4 (5 signals), 161.2 (C=O); $C_{11}H_{14}N_2S_2O$ (254.3): **C,** 51.94; **H,** 5.55; **N,** 11.01 ; **Found: C,** 51.89; **H,** 5.58; **N,** 11.12.

2-Ethylthio-3-ethyl-5,6-dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-4-one (7d)

From **5**b (2.40 g, 10 mmol) and ethyliodide (1.86 g, 12 mmol). Yield 1.82 g, (68%) of white powder, after crystallization from ethanol, mp. 98–

100 °C; IR: 1700 (C=O), 1600 (C=N); $C_{12}H_{16}N_2S_2O$ (268.4): **C,** 53.70; **H,** 6.01; **N,** 10.44; **Found: C,** 53.83; **H,** 6.13; **N,** 10.35.

2-Methyl-(5, 6-dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-2-yl)-sulphone (9)

A mixture of **5a** (2.26 g, 10 mmol) and excess amount of hydrogen peroxide (5 ml) in acetic acid (30 ml) was heated gently with stirring for 10 h, the reaction mixture was allowed to cool to 0°C. The precipitate was filtered off, and crystallized from dioxane in 1.32 g, (51%) yield, mp.246–248 °C; IR: 3200 (br, NH), 1680 (C=O), 1560 (C=N), 1165, 1340 (SO_2); ^{1}H-NMR (DMSO-d_6): δ 2.40, 2.41, 3.43 (methyl protons), 13.67 (br,NH); ^{13}C-NMR: 12.7, 13.0 (CH_3), 39.7 (SCH_3), 122.5–160.9 (5 signals), 160.4 (C=O); $C_9H_{10}N_2S_2O_3$(258.3): **C,** 41.85; **H,** 3.90; **N,** 10.84; **Found: C,** 42.13; **H,** 3.97; **N,** 10.86.

2-(5,6-Dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-2-yl) acetylhydrazone (10)

A mixture of **6c** (2.98 g, 10 mmol) and hydrazine hydrate (99%. 6ml) in ethanol (30 ml) was stirred under reflux for 5 h. The reaction mixture was allowed to cool to 0°C, the 1.48 g, (52%) yield, mp. 188-190 °C; IR: 3310 (br, NH), 1730, 1680 (2C=O), 1550 (C=N); ^{1}H-NMR ($CDCl_3$:DMSO-d_6(4:1)): δ 2.34, 2.40 (methyl protons), 4.28 (br, NH), 4.42 (CH_2), 4.81 (br, NH); ^{13}C-NMR ppm: 12.6, 14.0 (CH_3), 66.9 (CH_2), 113.3–158.3 (5 signals), 165.1, 167.0 (C=O); $C_{10}H_{12}N_4S_2O_2$ (284.3): **C,** 42.24; **H,** 4.25; **N,** 19.70; **Found: C,** 42.31; **H,** 4.32; **N,** 20.0.

2-(3,5-Dimethyl-1H-or(1-phenyl)pyrazol-4-ylthio)-5,6-dimethyl -3,4-dihydrothieno-[2,3-d] pyrimidin-4-one (11a,b)

General procedure

A mixture of **5d** (3.10 g, 10 mmol) and hydrazine hydrate (99%) or phenyl hydrazine (10 mmol) in dioxane (20 ml) and ethanol (10 ml) was stirred under reflux for 12 h. The reaction mixture was allowed to cool then poured into cold water (100 ml). The precipitate was filtered off, dried and cyrstallized.

2-(3,5-Dimethyl-1H-pyrazol-4-ylthio)-5,6-dimethyl-3, 4-dihydrothieno [2,3-d]pyrimidin-4-one (11a)

From hydrazine hydrate (99%) (5 ml). Yield 2.45 g, (80%) of white crystals, after crystallization from dioxane, mp. 300–302 °C; IR: 3400 (NH), 1650 (C=O), 1600 (C=N), 1550(C=C); ^{1}H-NMR (DMSO-d_6): δ 2.10–2.25 (methyl protons), 4.15 (br, NH), 5.25 (br, NH); $C_{13}H_{14}N_4S_2O$ (306.4): **C,** 50.96; **H,** 4.61; **N,** 18.29; **Found : C,** 51.02; **H,** 4.80; **N** 18.37.

2-(3,5-Dimethyl-1-phenylpyrazol-4-ylthio)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidin4-one (11b)

From phenylhydrazine hydrochloride (1.45 g, 10 mmol). Yield 2.30 g, (60%) of white crystals, after crystallization, mp. 312–314 °C; IR: 3250 (NH), 1670 (C=O), 1600 (C=N); ^{1}HNMR (DMSO-d_6): 6 2.20–2.50 (methyl protons), 5.20 (br, NH), 7.70–8.50 (phenyl protons); $C_{19}H_{18}N_4S_2O$ (382.5): **C,** 59.66; **H,** 4.74; **N,** 14.65; **Found: C,** 59.62; **H,** 4.75; **N,** 14.71.

2-(4,6-Dimethyl-2-thioxo-1,2-dihydropyrimidin-5-ylthio)-5, 6-dimethyl-3,4-dihydrothieno [2,3-d]pyrimidin-4-one (12)

A mixture of compound (**5**d) (3.10 g, 10 mmol) and thiourea (0.76 g, 10 mmol) was stirred under reflux in dioxane (30 ml) in the presence of catalytic amount of piperidine for 15 h. The reaction mixture was allowed to, poured into water (100 ml), the precipitate was filtered off, washed with ethanol (30 ml), dried and crystallized from hot ethanol in 2. 1 1 g, (60%) yield, mp. 205–207 °C; **IR:** 3423 (br, NH), 1663 (C=O), 1600 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.22, 2.27, 2.73, 2.89 (methyl protons), 4.80 (br, NH), 8.20 (br, NH); $C_{14}H_{14}N_4S_3O$ (350.5): **C,** 47.98; **H,** 4.03; **N,** 15.99; **Found: C,** 48.08; **H,** 4.14; **N,** 16.21.

2-Acetyl-3, 6, 7-trimethyl-5H -thiazolo[3,2-a] thieno[2,3-d] pyrimidin-5-one (13)

A solution of compound **5**d (3.10 g, 10 mmol) in a mixture of acetic anhydride/ pyridine (30ml, 2:1) was stirred under reflux for 3 h. The reaction mixture was allowed to cool, then poured into cold water (100 ml). The deposit was filtered off, dried and crystallized from dioxane in 2.34 g, (80%) yield of green crystals, mp. 210–212 °C: IR: 1725, 1650 (2C=O).

1540 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.30, 2.40 2.50, 3.10 (methyl protons);[1] ^{3}C-NMR ppm: 13.0, 13.3, 17.1 (CH_3), 30.9 (CH_3-CO), 118.5–158.4(7 signals), 162.5 (-N-CO), 190.4 (CO-CH_3) ; $C_{13}H_{12}N_2S_2O_2$ (292.3): **C,** 53.40; **H,** 4.14; **N,** 9.58; **Found:C,** 53.38; **H.** 4.14; **N,** 9.41.

2-(Acetoxime)-3,6,7-trimethyl-5H-thiazolo[3,2-d]thieno[2,3-d] pyrimidin-5-one (14)

A mixture of **13** (2.92 g, 10 mmol) and hydroxylamine hydrochloride (0.70 g, 10 mmol) in dioxane (30 ml) and catalytic amount of piperidine was added. The reaction mixture was stirred under reflux for 15 h, then allowed to cool, poured into water (100 ml). The precipitate was filtered off, dried and crystallized from acetic acid in 1.90 g, (62%) yield, mp. 274–276 °C; IR: 3300 (br, NH), 1700 (C=O), 1580 (C=N); ^{1}H-NMR ($CDCl_3$:DMSO -d_6(1:1)): δ 1.60, 2.10, 2.20, 2.30 (methyl protons), 10.78 (br, OH); $C_{13}H_{13}N_3S_2O_2$ (307.4): **C,** 50.80 ; **H,** 4.26; **N,** 13.67; **Found: C,** 50.57; **H,** 4.31; **N,** 14.01.

2-(Acetothiosemicarbazone)-3,6,7-trimethyl-5H-thiazolo [3,2- a]thieno[2,3-d]pyrimidin-5-one (15)

A mixture of **13** (2.92 g, 10 mmol) and thiosemicarbazide (0.91 g, 10 mmol) in dioxane (30 ml) and catalytic amount of piperidine was added. The reaction mixture was stirred under reflux for 12 h, the mixture was allowed to cool, poured into water (100 ml). The precipitate was filtered off, dried and crystallized from dimethyl-formamide, in 3.10 g, (85%) yield of white crystals, mp. 306–308 °C; IR: 3250 (br, NH), 1700 (C=O), 1550 (C=N),, 1200 (C=S); ^{1}HNMR ($CDCl_3$:DMSO-d_6(1:1)): δ 1.90 (br, NH_2,), 2.10, 2.20, 2.35, 2.55 (methyl protons), 9.50 (br, NH), 10.44 (br, NH); $C_{14}H_{15}N_5S_3O$ (365.5): **C,** 46.01; **H,** 4.14; **N,** 19.16**; Found: C,** 46.14**; H,** 4.11; **N.** 19.41.

2-Cinnamoyl(derivatives)-3,6,7-trimethyl-5H-thiazolo[3,2-a]thieno [2,3- d]pyrimidin-5-one (16a-d)

General procedure

A mixture of **13** (2.92 g, 10 mmol), the aromatic aldehyde (10 mmol) and a catalytic amount of piperidine was heated at 170–180 °C in test tube for 3 h. The product was solidified by cooling. The precipitate so-formed was collected by filtration and crystallized.

2-Cinnamoyl-3,6,7-trimethyl-5H-thiazolo[3,2-a]thieno[2,3- d] pyrimidin-5-one (16a)

From benzaldehyde (1.06 g, 10 mmol). Yield 2.59 g, (68%) of yellow crystals, after crystallization from dioxane, mp. 255–257 °C; IR: 1698, 1686 (2C=O), 1652 (C=N); $C_{20}H_{16}N_2S_2O_2$ (380.5): **C,** 63.13; **H,** 4.24; **N,** 7.36; **Found: C,** 62.93; **H,** 4.37; **N,** 7.11.

2-(4-Chlorocinnamoyl)-3,6,7-trimethyl-5H-thiazolo[3,2-a]thieno [2,3- d]pyrimidin-5-one (16b)

From 4-chlorobenzaldehyde (1.41 g, 10 mmol). Yield 2.82 g, (68%) of orange crystals, after crystallization from dimethylformamide, mp.250–252 °C; IR: 1700, 1685 (2C=O), 1594 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.55, 2.60, 2.75 (methyl protons), 7.65–7.70, 8.10–8.14 (AA'BB'system for phenyl protons), d 8.41 (d, vinyl protons); $C_{20}H_{15}N_2S_2O_2Cl$ (414.9): **C,** 57.89; **H,** 3.64; **N,** 6.75; **Found: C,** 57.78; **H,** 3.71; **N,** 6.53.

2-(4-Methoxycinnamoyl)-3,6,7-trimethyl-5H-thiazolo[3,2-a]thieno [2,3- d]pyrimidin-5-one (16c)

From 4-methoxybenzaldehyde (1.36 g, 10 mmol). Yield 2.59 g, (63%) of yellow crystals, after crystallization from dioxane, mp. 270–272 °C; IR: 1700, 1683 (2C=O), 1635 (C=N); $C_{21}H_{18}N_2S_2O_3$ (410.5): **C,** 61.44; **H,** 4.42; **N,** 6.82; **Found: C,** 61.58; **H,** 4.31; **N,** 6.53.

2-(2- Theinylamoyl)-3,6,7-trimethyl-5H-thiazolo[3,2-a]thieno [2,3- d]pyrimidin-5-one (16d)

From thiophene-2-carboxaldehyde (1.12 g, 10 mmol). Yield 2.40 g, (62%) brown crystals, after crystallization from dioxane, mp. 248–250 °C: IR: 1718, 1674 (2C=O). 1652 (C=N); $C_{18}H_{14}N_2S_3O_2$ (386.5) **C,** 55.93; **H,** 3.65; **N,** 7.25; **Found : C,** 56.18; **H,** 3 73; **N,** 7.13.

Acknowledgements
We would like to thank Prof. Dr. J. C. Jochims, Facultät für Chemie, Universität Konstanz (Germany), for helpfull discussion.

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