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Synthesis of novel 1,2-disubstituted-6,7-dimethyl-1*H*,5*H*-thieno[2,3-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-ones

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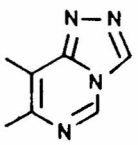
A facile and simple synthesis for 3-amino-2-thioxo-5,6-dimethyl-1,2,3,4-tetrahydrothieno[2,3-*d*]-pyrimidin-4(3*H*)-one **3a** is described and from this precursor, a series of hitherto unreported linear 1,2-disubstituted-6,7-dimethyl-[1*H*,5*H*]-thieno[2,3-*d*] [1,2,4]triazolo[1,5-*a*]pyrimidin-5-ones **6a-o** have been synthesised by the cyclocondensation of the corresponding 2,3-diamino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **5a,b** with various one carbon donors.

Condensed 1,2,4-triazolopyrimidines are biologically important compounds[1-3]. A number of literature reports are available on the synthesis[3-6] of the angular condensed [1,2,4]triazolo[4,3-*c*]pyrimidines(**I**) and [1,2,4]triazolo[4,3-*a*] pyrimidines[**II**]. However, the linear [1,24]triazolo[1,5-*a*]pyrimidines(**III**) have attracted relatively little attention. While a few reports[7,8] are available on the linear [1,2,4]triazoloquinazolines, their bioisoteric thieno-[1,2,4]triazolo[1,5-*a*]pyrimidines are relatively unexplored. The present paper deals with a facile and simple synthesis of a series of novel 1,2-disubstituted-6, 7-dimethylthieno[2, 3-*d*][1, 2, 4]-triazolo[1,5-*a*]pyrimidin-5-ones **6a-o**.

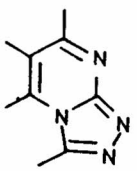
A large number of literature reports are available on the synthesis of various heterocyclic ring systems using *o*-aminomercapto compounds as synthons or precurssors for actual synthons[9-11]. Only a few reports are available in the literature on the synthesis of condensed 3-amino-2-thioxopyrimidin-4-ones. Santagati *et al.*[12], have reported the synthesis of 1, 2, 3, 4, 5, 6, 7, 8-octahydro-3-amino-2-thioxo[1]benzo-thieno[2,3-*d*]pyrimidin-4-one **3b** from the reaction of the corresponding 3-carbethoxy-2-isothiocyanatothiophene (R^1, R^2 = $(-CH_2-)_4$) with hydrazine hydrate. However, this route is not much attractive as it involves the use of a highly toxic chemical, thiophosgene making it less environment friendly. Moreover, it also gives the compound **3b** in a low yield (40%).

Herein, a novel, simple and more ecofriendly route for the preparation of 3-amino-2-thioxo-5,6-dimethyl-1,2,3,4-tetrahydrothieno [2,3-*d*]pyrimidin-4-one **3a** is described. This route not only curtails the use of thiophosgene, but also affords the desired *o*-aminothioxo compound **3a** in relatively good yields (79%).

Earlier, an alternate route reported from this laboratory[13], for the preparation of the bioisosteric, 3-amino-2-thioxoquinazolin-4-ones was adopted for preparing, **3a**. However, it yielded **3a** in negligible yields (10%). Hence improvisation was carried out on this method. Dimethylsulfoxide was substituted for acetone as the reaction solvent and aq. NaOH (20*M*) was used as the base instead of anhyd. K_2CO_3. Thiophene *o*-aminoester **1** was reacted with carbon disulfide to give dithiocarbamate salt **3a** which was methylated with dimethyl sulphate to



I



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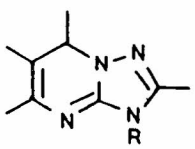
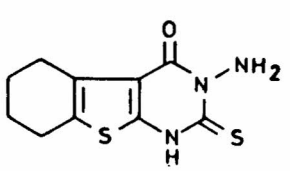
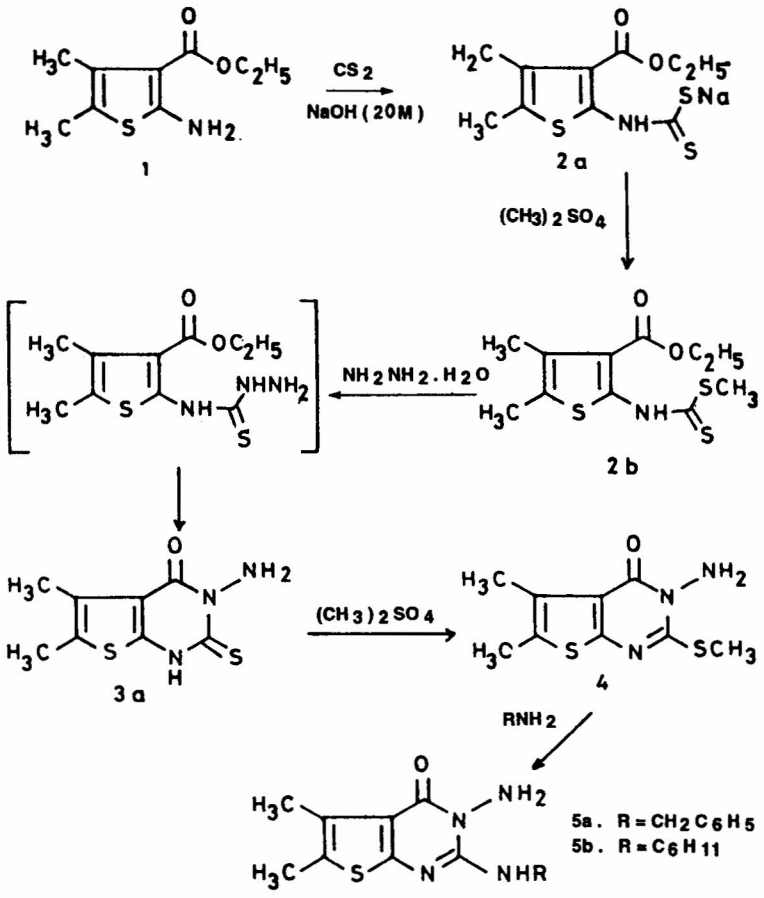


III



3a $R^1 = R^2 = CH_3$

3b $R^1 R^2 = -(CH_2)_4-$



Scheme I

afford the dithiocarbamate methyl ester **2b**. Compound **2b** on reaction with hydrazine hydrate yielded the desired **3a** in excellent yields and in very short reaction time (Scheme I). The use of DMSO, as the reaction solvent can exhance the rates of reactions, and, the use of alkali in higher concentration, helped in preventing the hydrolysis of the intermediate, **2a**, probably, due to less solvation.

Compound **3a** on methylation with dimethyl sulphate gave 3-amino-2-methyl thio-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-(3*H*)-one **4**, which on treatment with benzylamine and cyclohexylamine, afforded the corresponding *o*-amino diazines, *viz*; 2,3-diamino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-(3*H*)-ones **5a,b** (Scheme I, Table I).

The target compounds, 1,2`-disubstituted-6,7-dimethyl-1*H*, 5*H*-thieno[2,3-*d*]-[1,2,4]triazolo-[1,5-*a*]pyrimidin-5-ones **6a-o** were synthesised in fair to good yields through the cyclisation of the appropriate, **5a/5b**, with a variety of single carbon donors[15], such as carboxylic acids (formic, acetic, propionic and isobutryic acids); isothiocyanates (phenyl and benzyl isothiocyanates), cyanogen bromide and potassium ethyl xanthate (prepared from CS_2, KOH and ethanol) (*cf.* Scheme II, Table II).

Compounds **5a** and **5b**, on diazotisation with $NaNO_2$/HCl at 0-5°C afforded the 1-substituted-6,7-dimethylthieno[2, 3-*d*][1,2,3,4]tetrazolo[4, 5-*a*]pyrimidin-5(4*H*)-ones **7a** and **7b**, respectively (Scheme III, Table II).

Experimental Section

All the melting points are uncorrected. IR spectra were recorded in KBr on Perkin Elmer-841 Grating spectrometer (ν_{max} in cm^{-1}); mass spectra on Varian Atlas CH-7 mass sectrometer at 70 eV; UV spectra on a Hitachi-2000 spectrophotometer (λ_{max} in nm) and ^1H NMR spectra on a Varian A-60 or EM-360 spectrometer at 60 MHz (chemical shifts in δ, ppm) using TMS as internal standard.

Methyl *N*-(3-carbethoxy-4, 5-dimethylthienyl)-

Table I—Characterization data of compounds **3a, 4** and **5a,b**

Compd	R	m.p.(°C) (Solv. of crystallisation)†	Yield (%)	Mol. formula (Mol. Wt)‡	^{1}H NMR (δ ppm) in DMSO-d_6
3a	-SH	269-71 (ethanol-chloroform)	80	$C_8H_9N_3OS_2$	2.12(s,3H, 5-CH_3), 2.19(s,3H,6-CH_3), 3.10(s,1H,*SH*), 5.2(s,2H,NH_2,D_2O exchangeable).
4	-SCH3	194-96 (ethanol-chloroform)	78	$C_9H_{11}N_3OS_2$	2.20(s,3H,5-CH_3), 2.30(s,3H,6-CH_3), 4.20(s,3H,SCH_3), 6.5(s,2H,NH_2,D_2O exchangeable)
5a	$NHCH_2C_6H_5$	132-36 (benzene)	75	$C_{15}H_{16}N_4OS$ (300)	2.30(s,3H,5-CH_3), 2.40(s,3H, 6-CH_3), 4.40(t, 1H, $NHCH_2C_6H_5$, D_2O exchangeable), 5.20(s,2H,NH_2,*D2O (exchangeable)* 7.4-7.7 (m,5H,Ar*H*)
5b	$-NHC_6H_{11}$	99-100 (benzene)	66	$C_{14}H_{20}N_4OS$ (202)	2.40(s,3H, 5-CH_3), 2.50(s,3H,6-CH_3), 3.6-4.0(m,11H,NH-$CH(CH_2)_5$, 5.20(s,2H,NH_2D_2O exchangeable), 7.4-7.7 (m,5H,Ar*H*)

†All the compounds gave satisfactory elemental analysis; ‡Mol. wt. determination by mass spectra
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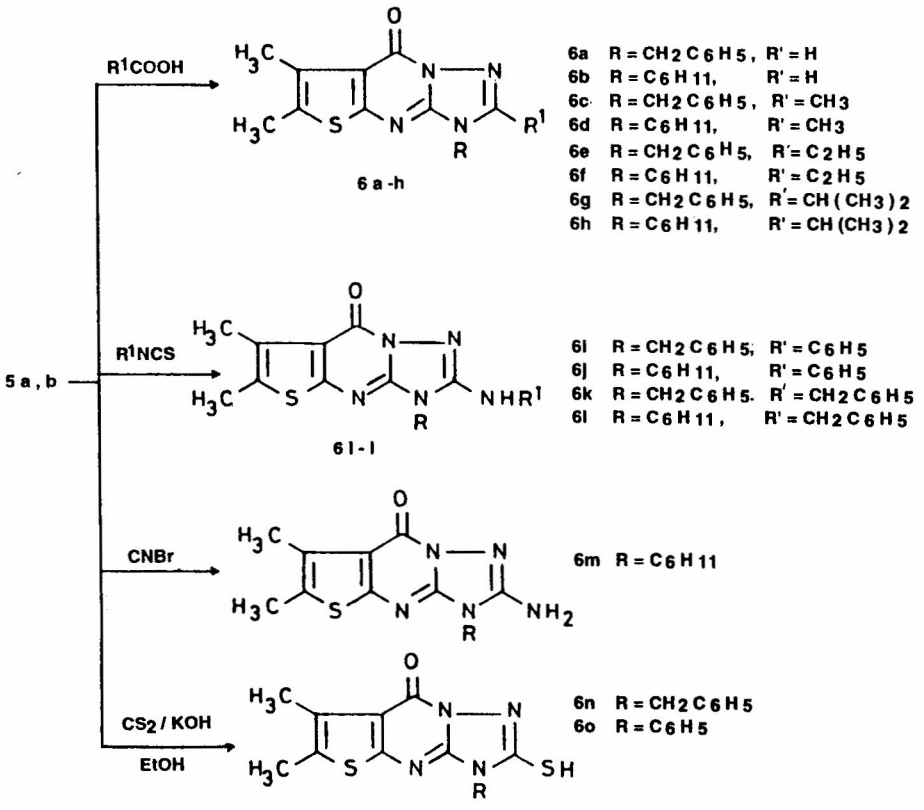


Scheme II

dithiocarbamate 2b. To a vigorously stirred solution of 2-amino-3-carbethoxy-4, 5-dimethylthiophene **1** (4.18 g, 0.02 mole) in DMSO (10 mL) at room temperature were added carbon disulphide (1.6mL, 0.26 mole) and aq. solution of NaOH (1.2 mL, 20 M). After stirring for 30 min., the reaction mixture was cooled in ice-bath (5-10 °C) and dimethyl sulphate (2.5g, 0.025 mole) was added

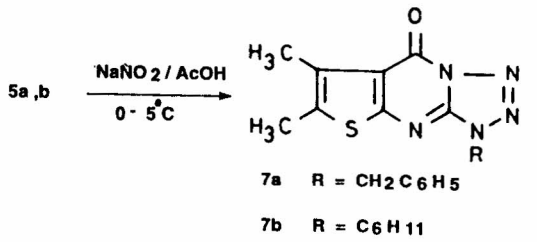
Table II—Characterization data of compounds **6a-o** and **7a,b**

Compd[†]	R	R[1]	m.p. °C (Solv. of crystallisation)[‡]	Yield (%) (reflux time in hr)	Mol. formula (Mol. wt)[§]
6a	$-CH_2C_6H_5$	H	259-61 (propanol)	80 (4)	$C_{16}H_{14}N_4OS$ (310)
6b	$-C_6H_{11}$	H	246-48 (methanol)	83 (4)	$C_{15}H_{18}N_4OS$
6c	$-CH_2C_6H_5$	CH_3	247-49 (propanol)	86 (8)	$C_{17}H_{16}N_4OS$ (324)
6d	$-C_6H_{11}$	CH_3	213-15 (ethanol)	76 (12)	$C_{16}H_{20}N_4OS$
6e	$-CH_2C_6H_5$	C_2H_5	189-91 (propanol)	76 (10)	$C_{18}H_{18}N_4OS$
6f	$-C_6H_{11}$	C_2H_5	190-92 (ethanol)	78 (10)	$C_{17}H_{22}N_4OS$
6g	$-CH_2C_6H_5$	*i*-C_3H_7	164-67 (ethanol)	76 (16)	$C_{19}H_{20}N_4OS$
6h	$-C_6H_{11}$	*i*-C_3H_7	157-59 (ethanol)	86 (10)	$C_{18}H_{24}N_4OS$
6i	$-CH_2C_6H_5$	C_6H_5NH	219-21 (ethanol)	70 (12)	$C_{22}H_{19}N_5OS$
6j	$-C_6H_{11}$	C_6H_5NH	207-09 (methanol)	78 (24)	$C_{21}H_{23}N_5OS$
6k	$-CH_2C_6H_5$	$CH_2C_6H_4NH$	203-05 (*i*-propanol)	58 (8)	$C_{23}H_{21}N_5OS$
6l	$-C_6H_{11}$	$CH_2C_6H_4NH$	168-70 (*i*-propanol)	56 (12)	$C_{22}H_{25}N_5OS$
6m	$-C_6H_{11}$	NH_2	168-69 (dmf)	78 (8)	$C_{15}H_{19}N_5OS$
6n	$-CH_2C_6H_5$	SH	136-37 (ethanol)	52 (8.5)	$C_{16}H_{14}N_4OS$
6o	$-C_6H_{11}$	SH	140-41 (ethanol)	54 (3.5)	$C_{15}H_{18}N_4OS_2$
7a	$-CH_2C_6H_5$		266-68 (ethanol)	76	$C_{15}H_{13}N_5OS$
7b	$-C_6H_{11}$		274-76 (ethanol)	74	($C_{14}H_{17}N_5OS$ (303)

[1]HNMR (δ, ppm) in DMSO-d_6: **6a**: 2.37 (s,3H,6-C*H*$_3$), 2.39 (s,3H,7-C*H*$_3$), 5.10 (s,2H,C*H*$_2$C$_6$H$_5$), 5.4 (s,1H,C*H*), 7.5 (m,5H,Ar-*H*); **6c**: 2.27 (s,3H,6-C*H*$_3$), 2.37 (s,3H,7-C*H*$_3$), 2.39 (s,3H,2-C*H*$_3$), 5.26 (s,2H,C*H*$_2$C$_6$H$_5$), 7.29 (m,5H,Ar-*H*); **6g**: 1.15 [d,6H,CH-(C*H*$_3$)$_2$], 2.30 (s,3H,6-C*H*$_3$), 2.38 (s, 3H,7-C*H*$_3$), 3.20 [(s,1H,C*H*-CH$_3$)$_2$] 5.32 (s,2H,C*H*$_2$C$_6$H$_5$), 7.23-7.29 (m,5H,Ar-*H*).

[‡]All the compounds gave satisfactory elemental analysis.

[§]Mol. wt. determination by mass spectra.



Scheme III

with stirring. The stirring was continued for additional 3 hr. and thereafter the reaction mixture was poured in ice-water mixture (1 L). The solid thus separated was filtered, dried and crystallised from ethanol to afford **2b** as yellow crystalline solid, yield 3.6 g (89%), m.p. 110-12 °C, (Found: C, 45.23; H, 5.35. $C_{11}H_{15}NS_3O$ requires C, 45.65; H, 5.22%); IR(KBr): 3180(NH), 2980(CH), 1680(C=O), 1060(C=S)cm^{-1}; ^{1}HNMR(CDCl$_3$): δ 1.95(t,3H, 2-COOCH$_2$C*H*$_3$), 2.20(s,3H,5-C*H*$_3$), 2.30(s,3H,6-CH$_3$, 4.20(q,2H,2-COOC*H*$_2$CH$_3$), 4.30(s, 3H, 1-SC*H*$_3$), 7.0 (s, 1H, 1-N*H*CSSCH$_3$, D$_2$O exchangeable).

3-Amino-2-thioxo-5,6-dimethylthieno [2,3-*d*]-pyrimidin-4-(3*H*)-one 3a. To a clear refluxing solution of **2b** (2.89 g, 0.01 mole) in ethanol (30 mL, 95%) was added hydrazine hydrate (5.0 g, 0.1

mole, 99% w/v) dropwise. After the addition was over, the reaction mixture was further refluxed for 3 hr. On cooling, the solid that separated out was filtered immediately, washed with ethanol and recrystallised from ethanol-chloroform mixture to yield **3a** as a colourless crystalline solid. Its characterisation data are given in Table I.

3-Amino-2-methylmercapto-5, 6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one 4. To an ice cold solution of **3a** (2.27 g, 0.01 mole) in DMF (45 mL) was added NaOH (0.4g, 0.01 mole) and the mixture was stirred for 30 min. To this was added dimethyl sulphate (1.26g, 0.01 mole) dropwise with constant stirring. After the addition was complete the reaction mixture was further stirred for additional 2 hr at room temperature. It was then poured into ice-water mixture and the solid separated out was filtered, washed, dried and recrystallised from ethanol-chloroform mixture to afford **4**, as white crystalline solid (Table I).

3-Amino-2-substituted-amino-5, 6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones 5a,b: General procedure. A mixture of 4(2.41 g, 0.01 mole) and the amine (0.02 mole) was refluxed for 34-36 hr, in an oil-bath maintained at the b.p. of the corresponding amine. The reaction mixture was then cooled to room temperature and poured in dil. aq. HCl solution (10% v/v). The solid separated was filtered, washed with water, dried and washed with pet. ether (40-60° C). It was recrystallised from benzene to yield **5a/5b**, as colourless solids (Table I).

Cyclisation of 5a,b with carboxylic acids to 1-alkyl-2*H*/2-substituted-6, 7-dimethyl-1*H*, 5*H*-thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-ones *6a-h*: General procedure. A mixture of 5(0.015 mole) and excess moles of the appropriate aliphatic carboxylic acid(10-15 mL) and *p*-toluenesulphonic acid(50 mg) was refluxed on an oil-bath for the time specified in Table II. Thereafter, the reaction mixture was poured into crushed ice and the solution basified (aq. NH_4OH, *p*H 8-9) and the solid separated was filtered, washed with water, dried and recrystallised from an appropriate solvent to give **6a-h** (Table II).

Cyclisation of 5a,b with isothiocyanates to the corresponding 1-aryl-2-aryl amino-6,7-dimethyl-1*H*,5*H*-thieno[2,3-*d*] [1,2,4]triazolo-[1,5-*a*]pyrimidin-5-ones *6i-l*: General procedure. A mixture of 5(0.01 mole) and the appropriate isothiocyanate (0.01mole) in 30 mL of pyridine (when aryl isothiocyanate was used) or ethanol (when aralkyl isothiocyanate was used) was refluxed for the time specified in Table II. The reaction mixture was cooled to room temperature, poured on crushed ice and the solid separated was filtered, dried and recrystallised from appropriate solvent to yield **6i-l** as the crystalline products (Table II).

2-Amino-1-cyclohexyl-6, 7-dimethyl-1*H*, 5*H*-thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-one *6m*. A solution of cyanogen bromide (1.15g, 0.01 mole) in ethanol (20 mL) was added dropwise to a well stirred suspension of **5b** (2.92 g, 0.01 mole) in methanol (25 mL). The reaction mixture was thereafter stirred for 4 hr, at room temperature. The solid obtained was filtered, washed with water, dried and recrystallised from DMF to yield colourless crystals of **6m** (Table II).

Cyclisation of 5a-b with potassium ethyl xanthate to the corresponding 1-substituted-2-mercapto-6, 7-dimethyl-1*H*, 5*H*-thieno[2, 3-*d*]-[1, 2, 4]triazolo[1, 5-*a*]-pyrimidin-5-ones *6n,o*: General procedure. A mixture of 5(0.01 mole) and potassium ethyl xanthate (3.2 g, 0.02 mole) prepared from KOH(4.2 g), CS_2 (4.5 g) and EtOH (19.5 mL) was refluxed on a water-bath for 8.5 hr. To this was added decolourising charcoal (1 g) and the reaction mixture was refluxed for an additional 30 min and filtered hot. The filtrate was cooled and acidified with aq. HCl (10% v/v). The solid separated was recrystallised from ethanol to yield colourless crystals of *6n-o* (Table II).

1-Substituted-6, 7-dimethyl-1*H*,5*H*-thieno[2,3-*d*]-1,2,3,4-tetrazolo[4,5-*a*]pyrimidin-5-ones *7a-b*: General procedure. To an ice cold suspension of **5a/5b** (0.01 mole) in glacial acetic acid (20 mL) was added with constant stirring a cold solution of sodium nitrite (0.01 mole) in water (5 mL) at 0-5° C. Thereafter reaction mixture was stirred at 5° C for 3 hr, and for additional 2 hr at room temperature. The solid separated was filtered, washed with cold water, dried and recrystallised from ethanol to give **7a,b** (Table II).

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