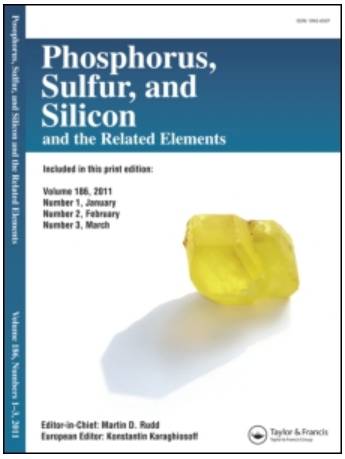

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SYNTHESIS OF POLYFUSED HETEROCYCLIC SYSTEMS DERIVED FROM FUNCTIONALLY SUBSTITUTED THIENO(2,3-b)THIOPHENE MOEITY

A. K. El-shafei[a]; A. M. M. El-saghier[a]; A. Sultan[a]; A. M. Soliman[a]
[a] Chemistry Department, Faculty of Science, Sohag, Egypt

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SYNTHESIS OF POLYFUSED HETEROCYCLIC SYSTEMS DERIVED FROM FUNCTIONALLY SUBSTITUTED THIENO(2,3-b)THIOPHENE MOEITY

A. K. EL-SHAFEI,† A. M. M. EL-SAGHIER, A. SULTAN
and A. M. SOLIMAN
Chemistry Department, Faculty of Science, Sohag, Egypt

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Diethyl 3,4-diaminothieno(2,3-b)thiophene-2,5-dicarboxylate **1** was converted into the sodium salt of the corresponding acid **2**. Compound **2** upon treatment with acetic anhydride furnished the bisoxazinone derivative **3**. The reaction of compound **3** with ammonium acetate, hydrazine hydrate or aniline afforded the bispyrimidine derivatives **4**, **5**, or **6** respectively. The reaction of compound **4** with phosphoryl chloride gave the corresponding chloro derivative **7** which was converted into the corresponding hydrazino derivative **8**. Treatment of compound **8** with acetylacetone or ethyl acetoacetate gave compounds **9** or **10**, respectively. On the other hand, the reaction of compound **1** with hydrazine hydrate gave the corresponding hydrazide derivative **11** which was also treated with acetylacetone, ethyl acetoacetate, formic acid or acetic anhydride to afford the described compounds **12**, **13**, **14**, or **15**, respectively.

Key words: Thienothiophene; bisthienoxazine; bisthienopyrimidine; bisthienopyrimidinone; pyrazine; pyrazinone.

INTRODUCTION

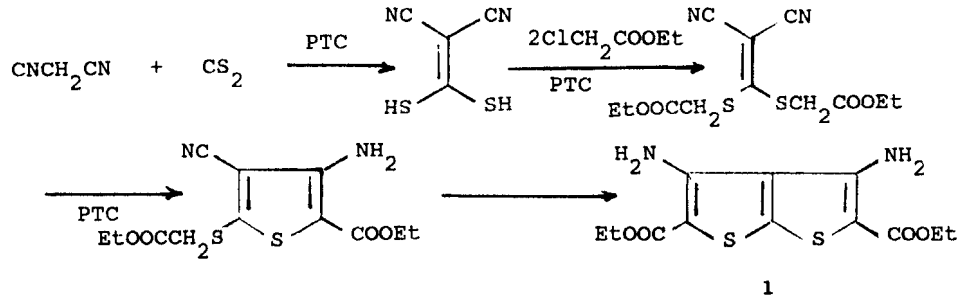
The reported biological activity of many heterocyclic compounds containing thiophene moeity[1,2] has prompted us to use a series of novel thieno(2,3-b)thiophenes[3] compound prepared in our laboratory as a building block for the synthesis of polyfused heterocycles containing oxazinone, pyrimidine, pyrimidinone, pyrazole, or pyrazolone nuclei.

RESULTS AND DISCUSSION

In an interesting study Makosza and Ladwikow[4] have found that carbanions of phenylacetonitrile, phenylacetone, ethyl cyanoacetate or ethyl acetoacetate generated in liquid-liquid or solid-liquid two phase systems react with CS_2 and dibromoethane to give substituted cyclic thioketals.

We have reported[3] the synthesis of a new series of functionally substituted thieno(2,3-b)thiophenes by using phase-transfer catalysis technique in a one pot reaction starting with malononitrile, CS_2 and ethyl chloroacetate in 1:1:2 molar ratio in K_2CO_3/ benzene/ in presence of tetrabutylammonium bromide catalyst. The following scheme represents the synthesis of our key compound, diethyl 3,4-diaminothieno(2,3-b)thiophene-2,5-dicarboxylate **1**.

†To whom all correspondence should be addressed.



1

Saponification of compound **1** in ethanolic sodium hydroxide solution afforded the sodium salt of the corresponding acid **2** which was treated with acetic anhydride where N-acetylation followed by dehydration was affected to give bis[2-methylthieno(3,2-d)oxazin-4-one] **3**.

The obtained oxazinone **3** was reacted with ammonium acetate, hydrazine hydrate or aniline where bis[2-methylthieno(3,2-d)-pyrimidin-4(3H)-one] **4**, bis[3-amino-2-methylthieno(3,2-d)pyrimidin-4(3H)-one] **5** or bis[2-methyl-3-phenylthieno(3,2-d)pyrimidin-4(3H)-one] **6**, were obtained, respectively. The reaction mechanism involves a nucleophilic attack of the amino group at the carbonyl carbon atom with subsequent fission of the C—O bond and formation of the C—OH bond. This was followed by another nuclephilic attack of the nitrogen atom at the C—OH bond and dehydration.

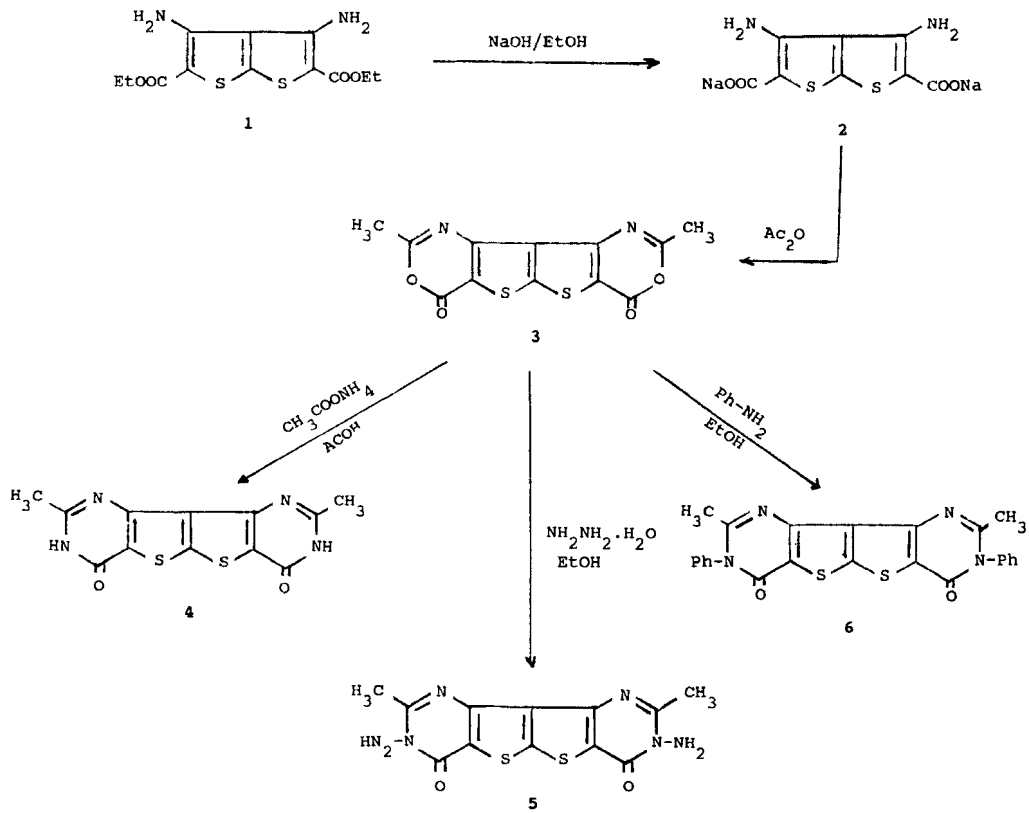


TABLE I

Physical and analytical data of the prepared compounds

Compound No	M.P °C	Yield %	Mol.Formula M.wt	Analytical data Calc./Found (%) C	H	N	S
1	201-202	88	$C_{12}H_{14}N_2S_2O_4$	45.84	4.48	8.91	
			(314.4)	45.42	4.50	8.78	
3	275	92	$C_{12}H_6N_2S_2O_4$	47.05	1.97	9.15	20.93
			(306.30)	46.85	1.73	8.78	21.10
4	>300	51	$C_{12}H_8N_4S_2O_2$	47.35	2.65	18.41	12.07
			(304.34)	47.12	2.48	18.22	11.70
5	239	87	$C_{12}H_{10}N_6S_2O_2$	43.10	3.01	25.14	19.18
			(334.37)	43.15	2.98	25.19	18.95
6	150-152	79	$C_{24}H_6N_4S_2O_2$	64.56	1.35	12.55	14.36
			(446.44)	64.32	1.40	12.12	14.45
7	139	55	$C_{12}H_6N_4S_2Cl_2$	42.23	1.77	16.42	18.79
			(341.23)	42.00	1.65	16.37	18.62
8	317	89	$C_{12}H_{12}N_8S_2$	43.36	3.64	33.71	19.29
			(332.40)	43.11	3.60	33.42	19.11
9	265	90	$C_{22}H_{18}N_8S_2$	57.62	3.96	24.44	13.98
			(458.55)	57.55	3.77	24.31	13.78
10	250	75	$C_{20}H_{12}N_8S_2O_2$	52.16	2.63	24.34	13.92
			(460.48)	52.21	2.46	24.11	13.80
11	332	88	$C_8H_{10}N_6S_2O_2$	33.55	3.52	29.35	22.39
			(286.33)	33.31	3.47	29.26	22.24
12	298[d]	95	$C_{18}H_{18}N_6S_2O_2$	52.15	4.38	20.28	15.47
			(414.49)	51.78	4.23	20.13	15.41
13	310	65	$C_{16}H_{14}N_6S_2O_4$	45.92	3.37	20.08	15.32
			(418.44)	45.67	3.16	20.12	15.15
14	284	86	$C_{20}H_{18}N_6S_2O_6$	47.79	3.61	16.72	12.76
			(502.51)	47.45	3.42	16.53	12.55
15	>300	89	$C_{12}H_6N_6S_2O_4$	39.77	1.67	23.19	17.69
			(362.34)	39.54	1.63	22.86	17.53

TABLE II

Important IR bands of the prepared compounds

Assignment	$\nu_{C=O}$	ν_{NH}	$\nu_{C=N}$	$\nu_{CH\ alif.}$	ν_{NH_2}
1	1730	--	--	2980-2950	3450,3350
3	1760	--	1600	2950-2900	--
4	1680	3290,3200	1600	2950-2920	--
5	1660	--	1600	2970-2950	3310,3200
6	1670	--	1620	2980-2960	--
7	--	--	1600	2960-2900	--
8	--	3200,3250*, 33400	1600	2970-2950	
9	--	--	1620,1600	2990-2900	--
10	1690	--	1620,1600	2970-2900	--
11	1630	3180,3250*, 3350			--
12	1640	--	1600	2950	3450,3350
13	1690,1670	--	1600	2980-2950	3450,3350
14	1740,1690	--	1600	2980-2950	--
15	1680	3180	1600	2970-2950	--

* Corrsponding to ν_{NH,NH_2}

TABLE III

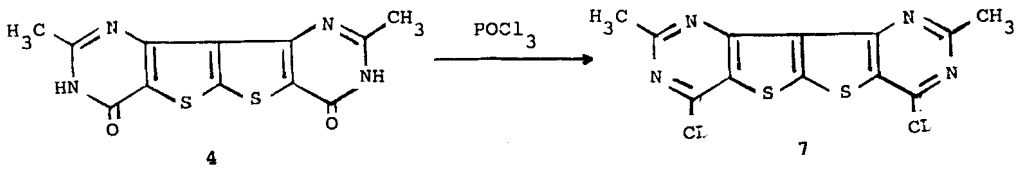
^{1}H-NMR spectra of the prepared compounds (chemical shifts in ppm)

Compound	$-CH_3$ at C-2 (s)	other signals
1	---	7.30(br,4H,NH_2), 4.60-4.10 (q,4H,$2CH_2$), 1.50-1.10(t, 6H,$2CH_3$).
3	2.65(6H)	-----
4	2.35(6H)	9.80(s,2H,2NH).
5	2.40(6H)	8.85(s,4H,$2NH_2$)
6	2.30(6H)	7.55-7.20(m,5H,CH-arom.).
7	2.42(6H)	----
8	2.45(6H)	8.75(s,2H,2NH), 6.70(s,4H, $2NH_2$
9	2.35(6H),2.65*(6H),3.00*(6H)	6.00(s,2-CH-pyrazole ring)
10	2.40(6H),3,00**(6H)	10.60(br,2H,2NH), 7.20(s, 2-CH-pyrazolinone ring)
11	------	9.10-8.70(br,2H,2NH of carbohydrazide group) 6.50 (s,4H,$2NH_2$), 4.70-4.10(br, 4H,$2NH_2$ of carbohydrazide group)
12	2.90*(6H),2.65*(6H)	7.30(s,2H,2CH of pyrazole ring), 6.50(s,4H,$2NH_2$) .
13	2.85**(6H)	11.10(br,2H,2NH), 7.90(s, 2H,2CH of pyrazolinone ring),6.60(s,4H,$2NH_2$).
14	2.40(6H),2.65***(12H)	----------
15	-------	11.30(br,2H,2NH),8.90(br, ,2H of formyl group), 6.80(s, 2H,2CH of pyrimidinone ring)

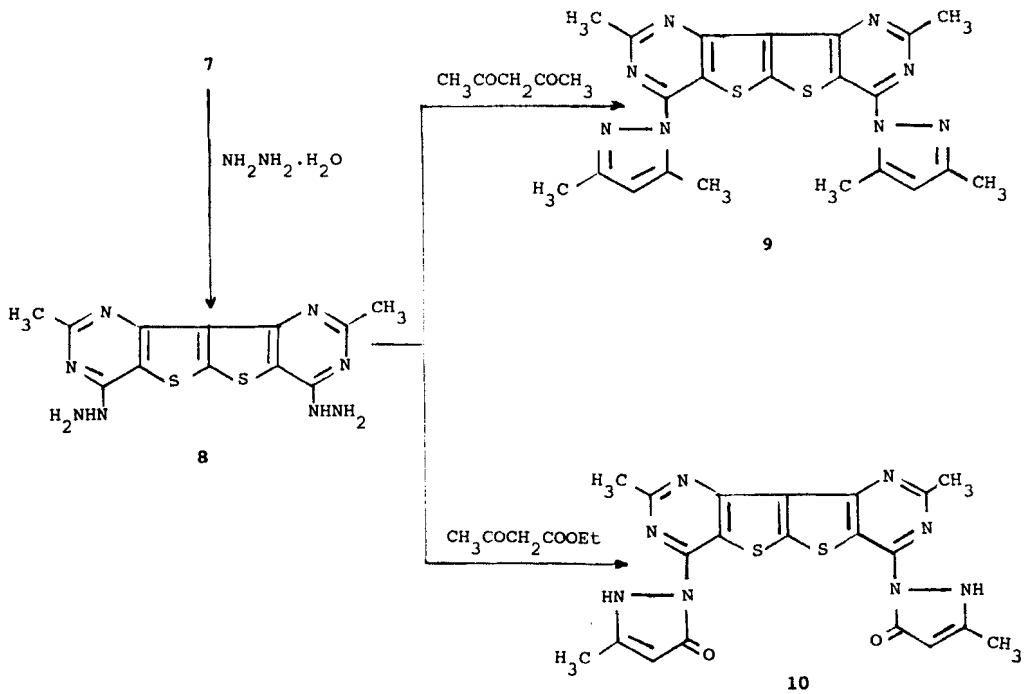
The solvent used in ^{1}H-NMR analyses is DMSO .

* at pyrazole ring ** at pyrazolone ring *** at $2N(COCH_3)_2$.

Chlorination of compound **4** with an excess amount of phosphoryl chloride yielded bis[4-chloro-2-methylthieno(3,2-d)pyrimidine] **7**.



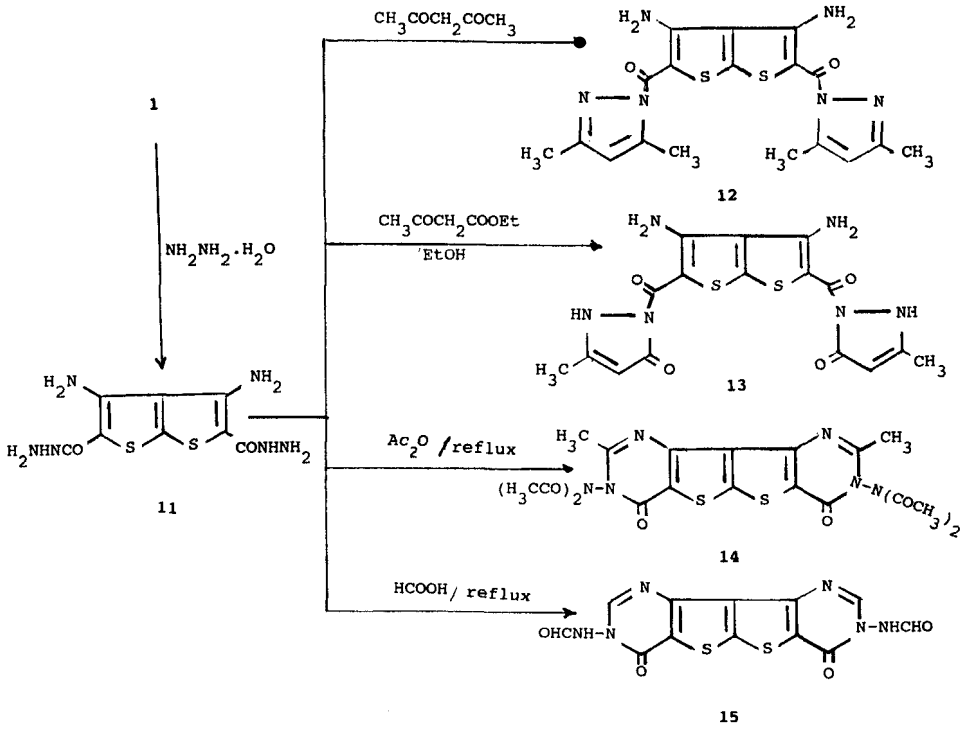
The chlorine atom in compound **7** was easily substituted by the hydrazino group on reaction with hydrazine hydrate. The obtained product, bis[4-hydrazino-3-methylthieno(3,2-d)pyrimidine] **8** was then condensed with acetylacetone or ethyl acetoacetate where an exocyclic pyrazole nuclei were formed and the reaction gave bis[4-(3,5-dimethylpyrazol-1-yl)2-methylthieno(3,2-d)pyrimidine] **9** or bis[3-methyl-1-(2-methylthieno(3,2-d)pyrimidin-4-yl)2-pyrazolin-5-one] **10**, respectively.



Compound **1** was also treated with hydrazine hydrate to give corresponding hydrazide 3,4-diamino-2,5-dihydrazidothieno-(2,3-b)thiophene **11** which was reacted with acetylacetone or ethyl acetoacetate where the hydrazide amino group was condensed with the carbonyl group followed by cyclization and dehydration into bis[(1-(3-aminothiophen-2-yl)carbonyl-)-3,5-dimethylpyrazole] **12** or bis[1-((3-aminothiophen-2-yl)carbonyl-)-3-methyl-2-pyrazolin-5-one] **13**, respectively.[5]

The reaction of compound **11** with acetic anhydride or formic acid yielded bis[3-diacetylamino-2-methylthieno(3,2-d)-pyrimidin-4(3H)-one] **14** and bis[3-formylaminothieno(3,2-d)-pyrimidin-4(3H)-one] **15**, respectively. The reaction pathway was

assumed to go through alkylation of both amino and hydrazide amino groups followed by cyclization via dehydration.



EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were obtained on a Pye-Unicam SP3-100 infrared spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 360 A at 60 MHz using TMS as internal standard. The elemental analyses were carried out on an elemental analyzer 240C.

Synthesis of bis[2-methylthieno(3,2-d)oxazin-4-one] **3**. Compound **1** (3.14 gm, 0.01 mol) was refluxed for one hour with ethanolic sodium hydroxide solution (50 ml, 4%). The precipitate sodium salt **2** was filtered off, washed with alcohol and left to dry. The sodium salt (3 gm) was refluxed for 3 hrs with acetic anhydride (20 ml). On cooling, the white precipitate was filtered off and used in the next step without further purification.

A sample was recrystallized from acetic acid as white needles.

Synthesis of bis[2-methylthieno(3,2-d)pyrimidin-4(3H)-one] **4**. A mixture of the oxazine derivative **3** (3.06 gm, 0.01 mol) and ammonium acetate (3.08 gm, 0.04 mol) in glacial acetic acid (50 ml) was refluxed for 3 hrs. The cooled reaction mixture was diluted with water whereby a white compound was precipitated. The solid product was collected by filtration, dried and recrystallized from absolute ethanol into white crystals.

Synthesis of bis[3-amino-2-methylthieno(3,2-d)pyrimidin-4(3H)-one] **5**. A mixture of the oxazine derivative **3** (3.06 gm, 0.01 mol) and hydrazine hydrate (2 ml, 0.04 mol) was refluxed in ethanol (50 ml) for 3 hrs. The obtained product was recrystallized from pyridine to give compound **5** as white needles.

Synthesis of bis[2-methyl-3-phenylthieno(3,2-d)pyrimidin-4(3H)-one] **6**. A mixture of the oxazine derivative **3** (3.06 gm, 0.01 mol) and aniline (4 ml, 0.04 mol) in acetic acid (20 ml) was refluxed for 3 hrs. On cooling and dilution with water, the precipitate solid was filtered off and recrystallized from ethanol as white needles.

Synthesis of bis[4-chloro-2-methylthieno(3,2-d)pyrimidine] **7**. Compound **3** (3.06 gm) was refluxed with an excess amount of phosphoryl chloride (20 ml) for 3 hrs. The cooled reaction mixture was slowly

added with stirring to an ice-cooled water whereby the product was separated out. The product was recrystallized from ethanol into brown needles.

Synthesis of bis[4-hydrazino-3-methylthieno(3,2-d)pyrimidine] **8**. A mixture of compound **7** (3.4 gm, 0.01 mol) and hydrazine hydrate (2 ml, 0.04 mol) in ethanol (30 ml) was refluxed for one hour. The solid product was recrystallized from ethanol into white needles.

Synthesis of bis[4-(3,5-dimethylpyrazol-1-yl)2-methylthieno-(3,2-d)pyrimidine] **9**. A mixture of compound **8** (3.3 gm, 0.01 mol) and acetylacetone (2 ml, 0.02 mol) were refluxed in ethanol (20 ml) for 3 hrs. The product was obtained by filtration of the cooled reaction mixture and was then recrystallized from methanol into white needles.

Synthesis of bis[3-methyl-1-(2-methylthieno(3,2-d)pyrimidin-4-yl)-2-pyrazolin-5-one] **10**. A mixture of compound **8** (3.3 gm, 0.01 mol) and ethyl acetoacetate (3 ml, 0.02 mol) were refluxed in ethanol (20 ml) for 3 hrs. On cooling, the precipitated solid was filtered off and was recrystallized from ethanol as pale yellow crystals.

Synthesis of 3,4-diamino-2,5-dihydrazido(2,3-b)thiophene **11**. A mixture of compound **1** (3.14 gm, 0.01 mol) and hydrazine hydrate (15 ml) were heated on a water bath for 3 hrs. The obtained solid product was washed with ethanol and was recrystallized from ethanol into white crystals.

Synthesis of bis[(1-(3-aminothiophen-2-yl)carbonyl-)-3,5-dimethylpyrazole] **12**. A mixture of compound **11** (2.85 gm, 0.01 mol) and acetylacetone (4 ml, 0.04 mol) was refluxed in ethanol for 5 hrs. On cooling, the precipitated solid was filtered off and was recrystallized from ethanol into pale yellow crystals.

Synthesis of bis[1-((3-aminothiophen-2-yl)carbonyl-)-3-methyl-2-pyrazolin-5-one] **13**. A mixture of compound **11** (2.85 gm, 0.01 mol) and ethyl acetoacetate (6 ml, 0.04 mol) were refluxed in ethanol (20 ml) for 5 hrs. On cooling the precipitated solid was filtered off and was recrystallized from DMF into white crystals.

Synthesis of bis[3-diacetylamino-2-methylthieno(3,2-d)pyrimidin-4(3H)-one] **14**. Compound **11** (2.85 gm) was refluxed for 4 hrs with acetic anhydride (20 ml). The solid precipitated on cooling was filtered off and was recrystallized from ethanol into white needles.

Synthesis of bis[3-formylaminothieno(3,2-d)pyrimidin-4(3H)-one] **15**. Compound **11** (2.85 gm) was refluxed for 5 hrs with formic acid (20 ml). The cooled reaction mixture was diluted with water, and the precipitated solid was filtered off and was recrystallized from ethanol into white needles.

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