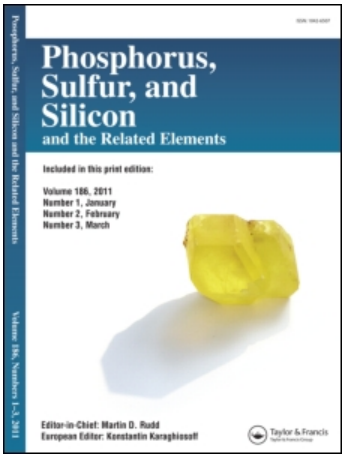

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THE USES OF POLYFUNCTIONALLY SUBSTITUTED THIOPHENES IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF BENZO[b]THIOPHENE, THIENO[2,3-b] PYRIDINE DERIVATIVES

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The reactivity of thiophene derivatives **1** and **2** towards cyanomethylenes, hydrazines, cinnamonitriles were studied to afford fused thiophene derivatives of potential biological activity.

Key words: Thiophenes, benzo[b]thiophene, thieno[2,3-b]pyridine.

INTRODUCTION

In the last few years we were involved in a program aiming to develop convenient synthetic routes for polyfunctionally substituted thiophenes, thiazoles and their fused derivatives.[1–5] These compounds are of potential biological activity having antiprotozoal,[6] antiviral,[7] bactericidal[8] and fungicidal properties.[9] In continuation of this work the uses of the thiophene derivatives **1** and **2** recently obtained by the reaction of acetylacetone or ethyl acetoacetate with malononitrile and elemental sulfur,[10] for the synthesis of fused thiophene derivatives of potential biological activity[11–14] are reported.

RESULTS AND DISCUSSION

Compound **1** reacts with malononitrile to form a product with molecular formula $C_{11}H_8N_4S$. Two possible isomeric structures **3** and **4** were considered. Structure **4** is established for the reaction product on the basis of analytical and spectral data.

The IR spectrum of the reaction product revealed the presence of two NH_2 groups at 3480–3320 cm^{-1}, two CN groups at 2225, 2220 cm^{-1}. The ^1H NMR spectrum showed the presence of one singlet at δ = 2.43 ppm for one CH_3 group and two singlets δ = 4.23, 5.21 ppm (D_2O exchangeable) for two NH_2 groups.

In a similar manner the reaction of **1** with ethyl cyanoacetate afford the benzo[b]thiophene derivative **6**. Formation of **6** takes place via the intermediate formation of **5**.

The reaction of **1** with benzaldehyde gave the benzal derivative **7**. Structure of **7** was established based on the obtained analytical and spectral data. The reaction of **7** with hydrazine hydrate and phenylhydrazine afford the phenyl hydrazone derivatives **8a,b**. Structures of **7** and **8a,b** were established based on analytical and spectral data.

The reaction of **1** with benzalmalononitrile yielded the thieno[2,3-b]pyridine derivative **10**. The structure of the latter was established based on analytical and spectral data. Thus, the IR spectrum of the product showed the presence of one NH_2 stretching at 3460–3330 cm^{-1}, one CN group stretching at 2220 cm^{-1} one C=O group stretching at 1680 cm^{-1}; ^1H NMR spectrum showed the presence of two singlets at δ = 2.22, 2.46 ppm for two CH_3 group, and one singlet at δ = 6.12

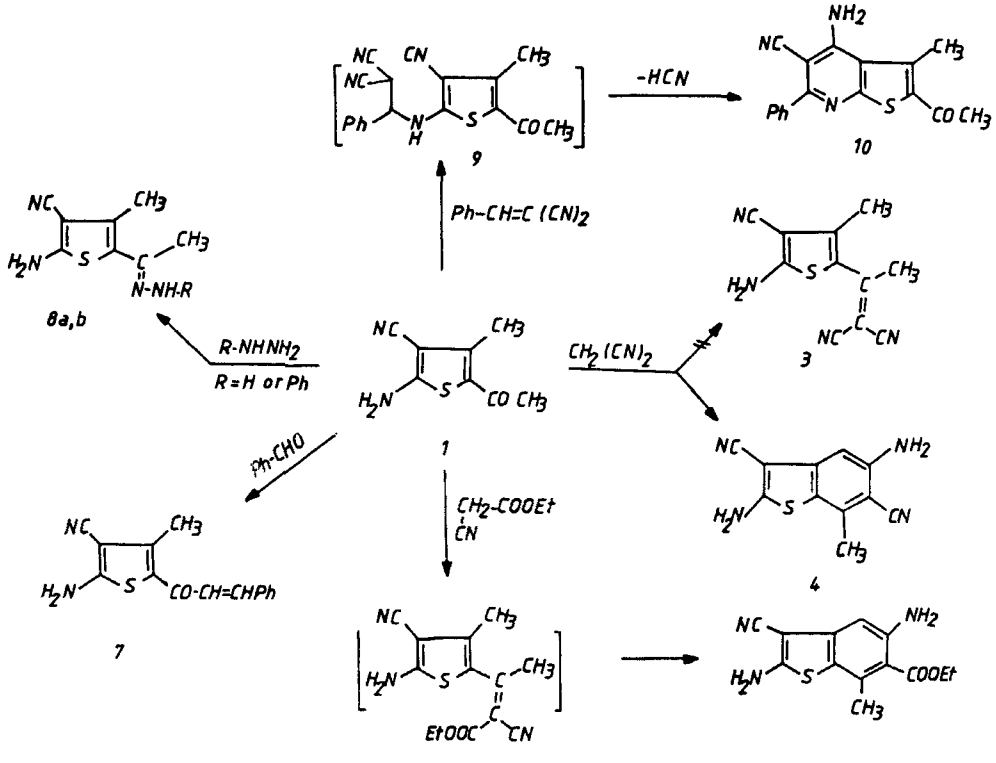

CHART 1

ppm (D_2O exchangeable) for NH_2 group and a multiplet at δ = 7.32–7.49 ppm corresponding to one phenyl group.

Reaction of compound **2** with malononitrile yielded a product with the molecular formula $C_{12}H_{12}N_4O_2S$. Two possible isomeric structures were considered, **11** and **12**. Structure **12** was established for the reaction product based on analytical and spectral data. The IR spectrum of the reaction product showed the presence of one CN group stretching at 2220 cm^{-1}; ^1H NMR spectrum revealed the presence of a triplet at δ = 1.16 ppm for one ester CH_3 group, a singlet at δ = 2.25 ppm for CH_3 group, a quartet at δ = 4.21 ppm for ester CH_2 group, two singlets at δ = 4.92, 5.63 ppm (D_2O exchangeable) corresponding to two NH_2 groups.

The reaction of **2** with ethyl cyanoacetate gave the thieno[2,3-b]pyridine derivative **14**. Formation of the latter product takes place through the intermediate formation of **13**.

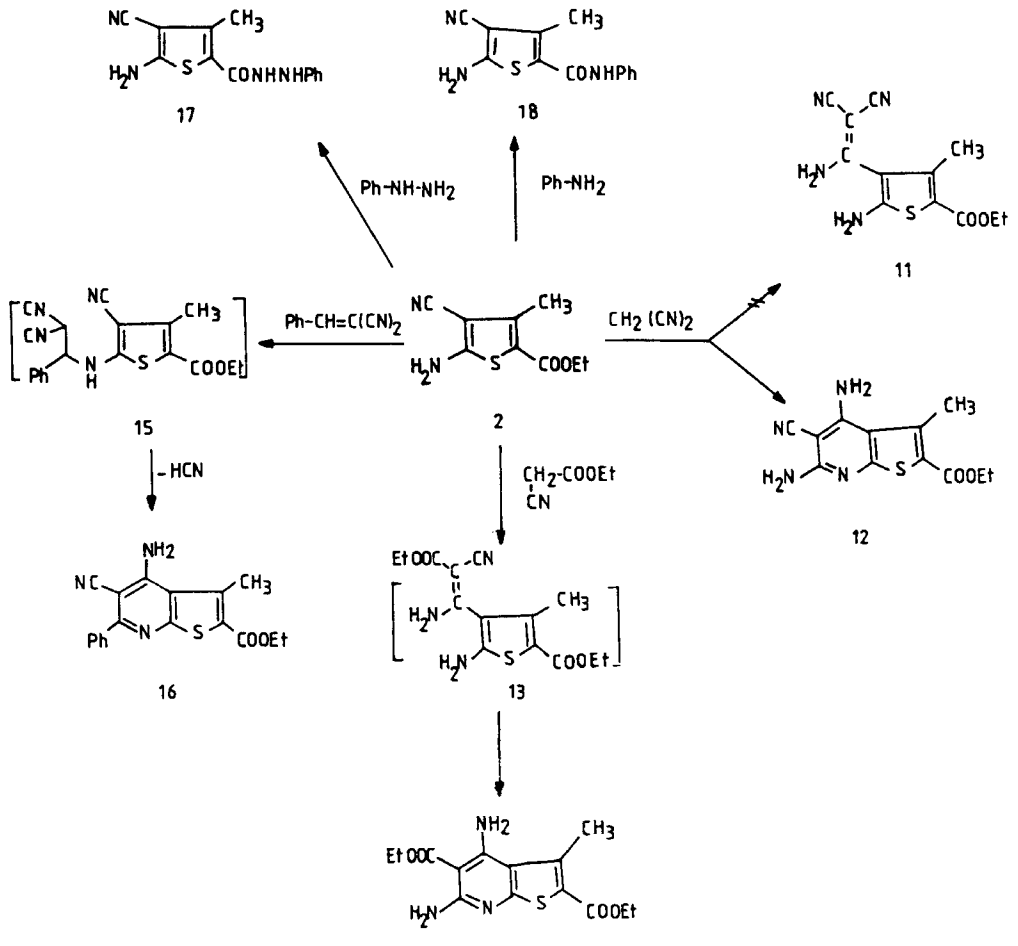

CHART 2

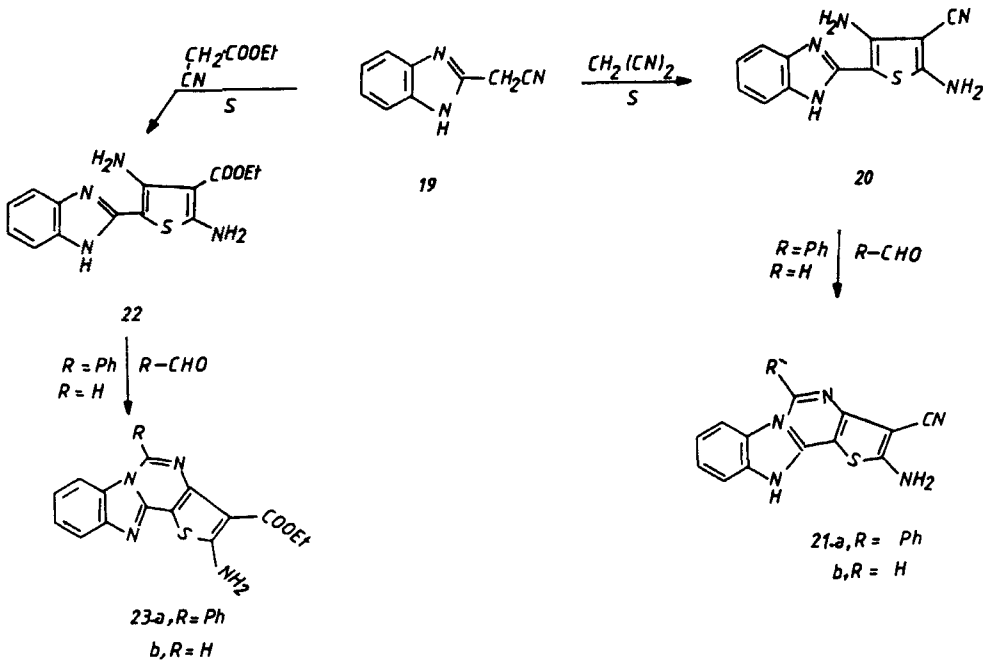

CHART 3

Reaction of **2** with benzalmalononitrile gave the thieno[2,3-b]pyridine derivative **16**. Formation of **16** takes place through the intermediate formation of **15** followed by loss of HCN and H_2.[15]

Reaction of **2** with phenylhydrazine gave the hydrazide derivative **17**. Moreover, with aniline gave the anilide derivative **18**. Structures of compounds **17** and **18** were established based on analytical and spectral data (Cf. experimental section).

The reaction of the cyanomethylene benzimidazole **19**[12] with sulfur and malononitrile in ethanolic triethylamine afforded the thiophene derivative **20** that was separated in good yield. Structure of **20** was established based on IR spectrum which showed one CN group stretching at 2200 cm^{-1}. ^1H NMR spectrum revealed the presence of two singlets at δ = 4.48 and 5.23 ppm (D_2O exchangeable) for two NH_2 groups, a multiplet at δ = 7.32–7.49 ppm for phenyl protons and a singlet (D_2O exchangeable) at δ = 8.42 ppm for one NH group.

The reaction of **20** with benzaldehyde and formaldehyde gave fused derivatives **21a,b**. Structures of latter derivatives was established based on analytical and spectral data. In a similar manner the reaction of **19** with sulfur and ethyl cyanoacetate afforded **22**, structure of which was based on analytical and spectral data. The reaction of **22** with each of benzaldehyde and formaldehyde gave **23a,b**.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye Unicam sp-100 spectrophotometer. ^1H NMR spectra (CD_3SOCD_3 as a solvent) were obtained on a varian A-90 spectrometer

using TMS as internal standard. Chemical shifts are expressed as δ (ppm). Analytical data were obtained from the Micro Analytical Data Unit at Cairo University.

2,5-Diamino-3,6-dicyano-7-methylbenzo[b]thiophene **4** *and Ethyl 2,5-diamino-3-cyano-7-methylbenzo[b]thiophen-6-carboxylate* **6**: *General procedure*: To a solution of **1** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) was added either of malononitrile (0.01 mol) or ethyl cyanoacetate (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product, formed upon dilution with water containing a few drops of hydrochloric acid, was collected by filtration.

2-Amino-5-cinnamoyl-3-cyano-4-methylthiophene **7**: To a solution of **1** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml), benzaldelyde (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product, formed upon dilution with water, was collected by filtration.

2-Amino-3-cyano-4-methyl-5-acetylhydrazonothiophene **8a** *and 2-Amino-3-cyano-4-methyl-5-acetylphenylhydrazonothiophene* **8b**: *General procedure*: To a solution of **1** (0.01 mol) in ethanol (30 ml), hydrazine hydrate (88%, 0.01 mol) or phenylhydrazine (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon pouring into ice/water containing a few drops of hydrochloric acid, was collected by filtration.

TABLE I

Physical and analytical data of the newly prepared compounds

Compd No.	Solvent	M.P. (°C)	Yield (%)	Mol-Formula (Mol.wt.)	Analysis (Calcd./Found)% C	H	N	S
4	EtOH	177	85	$C_{11}H_8N_4S$	57.8	3.5	24.5	14.0
				(228)	57.8	3.5	24.4	14.0
6	EtOH	135	78	$C_{13}H_{13}N_3O_2S$	56.7	4.7	15.2	11.6
				(275)	56.7	4.7	15.1	11.5
7	EtOH	300	81	$C_{15}H_{12}N_2OS$	76.1	4.4	10.4	11.9
				(268)	67.1	4.4	10.3	11.8
8_a	EtOH	300	90	$C_8H_{10}N_4S$	49.4	5.1	28.8	16.4
				(194)	49.4	5.1	28.7	16.4
8_b	EtOH	300	77	$C_{14}H_{14}N_4S$	62.2	5.1	20.7	11.8
				(270)	62.2	5.1	20.7	11.8
10	DMF	255	82	$C_{17}H_{13}N_3OS$	66.4	4.2	13.6	10.4
				(307)	66.4	4.2	13.6	10.4
12	MeOH	209	83	$C_{12}H_{12}N_4O_2S$	52.1	4.3	20.2	11.5
				(276)	52.1	4.3	20.2	11.4
14	EtOH	165	79	$C_{14}H_{17}N_3O_4S$	52.0	5.2	13.0	9.9
				(323)	52.0	5.2	13.0	9.8

TABLE I (*Continued*)

Compd No.	Solvent	M.P. (°C)	Yield (%)	Mol-Formula (Mol.wt.)	Analysis (Calcd./Found)% C	H	N	S
16	EtOH	182	69	$C_{18}H_{15}N_3O_2S$	62.0	4.4	12.4	9.2
				(337)	64.0	4.3	12.3	9.4
17	MeOH	215	82	$C_{13}H_{12}N_4OS$	57.3	4.4	20.5	11.7
				(272)	57.2	4.4	20.4	11.7
18	EtOH	206	86	$C_{13}H_{11}N_3OS$	60.7	4.2	16.3	12.4
				(256)	60.7	4.2	16.2	12.4
20	EtOH	225	78	$C_{12}H_9N_5S$	56.4	4.0	27.4	12.5
				(255)	56.3	4.0	27.3	12.5
21_a	DMF	185-90	70	$C_{19}H_{11}N_5S$	66.8	3.2	20.5	9.3
				(341)	66.7	3.2	20.5	9.3
21_b	MeOH	245	69	$C_{13}H_7N_5S$	58.8	2.6	26.4	12.0
				(265)	58.7	2.6	26.4	12.0
22	MeOH	145	82	$C_{14}H_{14}N_4O_2S$	55.6	4.5	18.4	10.5
				(302)	55.6	4.5	18.5	10.5
23_a	EtOH	252-254	83	$C_{21}H_{16}N_4O_2S$	64.9	4.1	14.4	8.2
				(388)	64.9	4.0	14.4	8.2
23_b	EtOH	195-7	80	$C_{15}H_{11}N_4O_2S$	57.8	3.5	18.0	10.2
				(311)	57.7	3.5	18.0	10.2

6-Acetyl-4-amino-3-cyano-5-methyl-2-phenylthieno[2,3-b]pyridine **10**: To a reaction of **1** (0.01 mol) in ethanol (30 ml), containing triethylamine (0.5 ml), benzalmalononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water, was collected by filtration.

Ethyl 3-cyano-2,4-diamino-5-methylthieno[2,3-b]pyridin-6-carboxylate **12** *and Diethyl 2,4-diamino-5-methylthieno[2,3b]pyridin-3,6-dicarboxylate* **14**: *General procedure*: To a solution of **2** (0.01 mol) in ethanol (30 ml) containing triethylamine there was added either malononitrile (0.01 mol), or ethyl cyanoacetate (0.01 mol). The reaction mixture was heated under reflux for 3 h and the solid product, formed upon dilution with water, was collected by filtration.

Ethyl 4-amino-3-cyano-5-methyl-2-phenylthieno[2,3-b]pyridin-6-carboxylate **16**: To a solution of **2** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml), there was added benzalmalononitrile (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water, was collected by filtration.

2-Amino-3-cyano-4-methyl-5-phenylhydrazidothiophene **17** *and 2-Amino-3-cyano-5-carboxanilido-4-methylthiophene* **18**: *General procedure*: To a solution of **2** (0.01 mol) in ethanol (30 ml), there was added either of phenylhydrazine (0.01 mol) or aniline (0.01 mol), the reaction mixture was heated under reflux for 3 h. The solid product formed, was collected by filtration.

2-(2',4'-Diamino-3'-cyano-thiophen-5'-yl)benzo[b]imidazole **20**: To a solution of **19** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml), there was added sulfur (0.01 mol) and malononitrite (0.01

TABLE II

I.R and ^1H NMR data of the newly prepared compounds

Compd No.	IR cm^{-1} (selected bands)	^1H NMR (δ ppm)
4	3460-3320 ($2NH_2$), 3050 (CH. aromatic), 2950 (CH_3), 2225,2220 (2CN), 1635(C = C).	2.25 (s, 3H, CH_3); 4.2 (s, 2H, NH_2); 6.52 (s, 2H, NH_2); 7.5 (s, 2H, NH).
6	3460-3340 ($2NH_2$), 3050 (CH. aromatic), 2950, 2895(CH_3,CH_2),2225 (CN), 1690(C = O), 1640 (C = C).	1.13 (t,3H,CH_3), 2.25 (q,2H,CH_2), 4.24(s, 3H, CH_3); 4.57 (s, 3H, NH_2); 5.33 (s, 2H, CH_2); 7.32 (s, 1H, CH).
7	3460,3340 (NH_2), 3050 (CH. aromatic), 2940 (CH_3), 2220 (CN), 1675(C=O),1640 (C=C).	1.13 (s, 3H, CH_3), 5.26 (s, 2H), NH_2), 6.28 (2d, 2H, J = 2.28 Hz, CH=CH), 7.23-7.41 (m, 5H, C_6H_5).
8_a	3450,3380 (NH_2), 2970 (CH_3), 2220 (CN), 1665 (C = N), 1645 (C=C).	2.23, 2.46 (2s,6H,2CH_3); 4.92 5.23 (25, 4H, $2NH_2$).
8_b	3455,3365 (NH_2), 3050 (CH aromatic); 2985 (CH_3), 2220 (CN), 1665 (C = N), 1640 (C=C).	2.20, 242(2s, 6H,2CH_3); 5.82 (s, 2H,NH_2); 7.32-7.52(m, 5H, C_6H_5); 8.25 (s, 1H, NH).
10	3460, 3330 (NH_2), 2980 (CH_3), 2220 (CN), 1675 (C=O).	2.22, 2.46 (2s, 6H, 2CH_3); 6.21 (2s, 2H, NH_2); 7.32-7.49 (m, SH, C_6H_5).
12	3450-3320 ($2NH_2$), 2980, 2895 (CH_3, CH_2); 2220 (CN), 1650 (C = N), 1645 (C=C).	1.16 (t,3H,CH_3); 2.25 (s, 3H,CH_3); 4.21 (q, 2H, CH_2), 4.92, 5.63 (2s, 4H, $2NH_2$).
14	3450-3330 ($2NH_2$), 2980, 2895 (CH_3, CH_2), 1650 (C=N), 1645 (C=C).	1.13, 1.16 (2t, 6H, 2CH_3); 2.21 (s,3H, CH_3); 2.21(s, 3H, CH_3), 4.22, 4.24 (m,4H, 2CH_2); 4.29, 4.59 (2s,4H, $2NH_2$).
16	3460,3350(NH_2), 3050 (CH aromatic); 2970, 2890(CH_3, CH_2); 2225(CN), 1660 (C=N), 1645 (C=C)	1.16(t,3H,CH_3); 2.22 (s,3H,CH_3); 4.24 (q, 2H,CH_2), 5.22(s,2H,NH_2), 7.32-7.51 (m,5H, C_6H_5).
17	3460-3300(NH_2-2NH), 3050 (CH aromatic); 2970(CH_3),2220(CN), 1690 (C=O), 1635 (C=C)	2.25 (s,3H,CH_3); 5.89 (s,2H,NH_2); 7.32-7.52 (m,5H,C_6H_5); 8.25, 8.82 (2s,2H,2NH);

TABLE II (*Continued*)

Compd. No.	IR cm^{-1} (selected bands)	^1H NMR (δ ppm)
18	3460-3300(NH_2, NH), 3050 (CH aromatic); 2970(CH_3), 2220(CN), 1690 (C=O), 1635 (C=C)	2.24 (s,3H,CH_3); 4.25 (s,2H,NH_2); 7.32-7.52(m,5H,C_6H_5);8.25 (s,1H,NH).
20	34605-3320(2NH_2, NH), 3050 (CH aromatic); 2970(CH_3), 2220(CN), 1650 (C=N), 1640 (C=C)	4.48 (s, 2H, NH_2); 5.23 (s, 2H, NH_2); 7.32-7.44 (m, 5H, C_6H_5); 8.42 (s, 1H, NH).
21_a	3465-3320 (2NH_2), 3050 (CH aromatic)2220 (CN), 165(C=N), 1640 (C=C).	4.48 (s, 2H, NH_2); 7.50-7.59 (m, 9H, C_6H_5,C_6H_4).
21_b	3465-3320 (2NH_2), 3050 (CH aromatic)2220 (CN), 165(C=N), 1640 (C=C).	4.49 (s, 2H, NH_2); 7.32-7.59 (m, 5H, C_6H_4, pyrimidin H-2).
22	3460-3320 (2NH_2), 3050 (CH aromatic)2980, 2865 (CH_3,CH_2), 1685 (C=O), 1655 (C=N), 1630 (C=C).	1.36 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 4.54 (s, 2H, NH_2); 7.32-7.45 (m,9H, C_6H_4,C_6H_5).
23_a	3460-3320 (2NH_2), 3050 (CH aromatic)2980, 2865(CH_3,CH_2),1685 (C=O),1655 (C=N), 1630 (C=C).	1.36 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 4.54 (s, 2H, NH_2); 7.32-7.45(m, 9H, C_6H_4, C_6H_5).
23_b	3470, 3460(NH_2), 3060 (CH aromatic),2975, 2890(CH_3,CH_2),1690 (C=O),1660(C=N),1635 (C=C).	1.36(t,3H,CH_3), 4.22 (q,2H,CH_2), 4.59 (s,2H,NH_2), 7.33-7.52 (m,5H,C_6H_4, pyrimidin C-H).

mol). The reaction mixture was heated under reflux for 3 h. The solid product, so formed, was collected by filtration.

5-Amino-4-cyano-2-phenyl-thieno[3,2-d]pyrimidino[1,7:1',2']benzimidazole **21a** *and 5-Amino-4-cyano-2[H]-thieno[3,2-d]pyrimidino[1,7:1'2'] benzimidazole* **21**: *General procedure*: To a solution of **20** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml), there was added either benzaldelyde (0.01 mol) or formaldehyde (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water, was collected by filtration.

2-(2',4'-Diamino-3'-ethoxycarbonyl-thiophen-5'-yl)benzo[b]imidazole **22**: To a solution of **19** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml), there was added sulfur (0.01 mol) and ethyl cyanoacetate (0.01 mol) and the reaction mixture was heated under reflux for 3 h. The solid product, so formed, was collected by filtration.

5-Amino-4-ethoxycarbonyl-2-phenylthieno[3,2-b]pyrimidino[1,7:1',2']benzimidazole **23a** *and 5-Amino-4-ethoxycarbonyl-2[H]-thieno[3,2-b]pyrimidino[1,7:1',2']benzmidazole* **23b**: *General procedure*: To

a solution of **22** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) there was added either benzaldehyde (0.01 mol) or formaldehyde (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with ice/water, was collected by filtration.

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