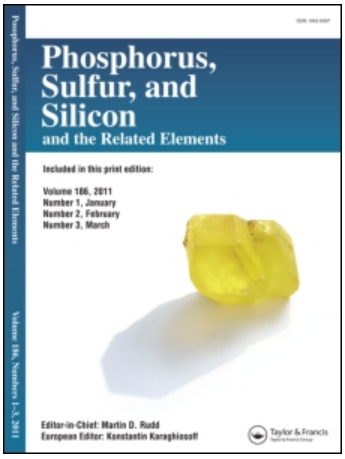

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Novel Synthesis of Thiazole, Coumarin, Pyridine, Thiophene and Thieno[2,3-b]Pyridine Derivatives

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NOVEL SYNTHESIS OF THIAZOLE, COUMARIN, PYRIDINE, THIOPHENE AND THIENO[2,3—b]PYRIDINE DERIVATIVES

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Several new thiazole, coumarin, pyridine, thiophene and thienopyridines were prepared from 4-chloroacetylantipyrine and activated nitriles as starting materials.

Keywords: Coumarin; thiazole; thienopyridine; thiophene

INTRODUCTION

In the past few years, we have been involved in a program directed towards developing new, simple, and efficient routes for the synthesis of polyfunctional azoles and fused azoles[1–12] as potential pharmaceuticals and biodegradable agrochemicals using readily available starting materials. This stimulated our interest for further studies on the chemistry of this class of compounds.

It has been found that 2-cyanoethanoic acid hydrazide **2** when treated with carbon disulfide in dimethylformamide under basic conditions in KOH/DMF solution gave the non-isolable intermediate **3**. The reaction of **3** with 4-chloroacetyl-l-phenyl-2,3-dimethyl-3-pyrazolin-5-one **1** afforded the thiazole derivative **5** (cf. Scheme 5). Structure 5 was elucidated by its analytical and spectral data. IR spectrum of the reaction product showed the presence of an NH group stretching at ν = 3470–3255 cm^{-1}, a cyano group at ν = 2260 cm^{-1}, an amidic carbonyl at ν = 1696 cm^{-1}, antipyrinyl carbonyl at ν = 1660 cm^{-1}, and thiocarbonyl at ν = 1244 cm^{-1}. The ^1H NMR spectrum of 5 showed, in addition to aromatic protons, the presence of a methylene group singlet at δ, = 4.43 ppm, a singlet at δ = 6.85 ppm for thiazole H-5 and a singlet at δ = 10.5 ppm for NH (cf. Tables I and II).

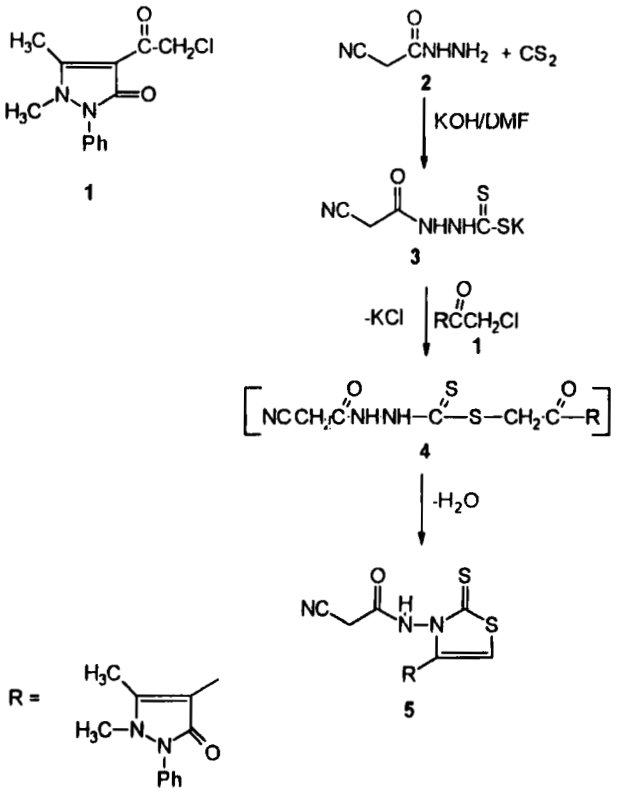
TABLE I Analytical Data and Physical Characteristics of Novel Compounds

Compd no.	Molecular formula (M.wt.)	M.p. (°C)	Color	Yield (%)	Elemental analysis (found) C	H	N
5	$C_{17}H_{15}N_5S_2O_2$ 385.46 ($M^+ = 385$)	145–147	Colorless	80	52.97 (53.60)	3.92 (4.41)	18.17 (18.11)
8	$C_{24}H_8N_4S_2O_4$ 490.56 ($M^+ = 490$)	180–182	Red	70	58.76 (58.65)	3.70 (3.83)	11.42 (11.53)
12a[b]	$C_{27}H_{19}N_7S_2O_2$ 537.62 ($M^+ = 537$)	210–212	Red	65	60.32 (60.10)	3.56 (3.75)	18.24 (18.36)
12b[b]	$C_{28}H_{21}N_7S_2O_3$ 567.65	180–182	Red	70	59.25 (59.35)	3.73 (3.87)	17.27 (17.36)
12c[b]	$C_{27}H_{18}ClN_7S_2O_2$ 572.07	205–207	Red	65	56.69 (56.73)	3.17 (3.32)	17.14 (17.11)
15	$C_{29}H_{24}N_4SO_3$ 508.60 ($M^+ = 508$)	228–230	Yellow	75	68.49 (68.80)	4.76 (4.18)	11.02 (11.24)
16	$C_{29}H_{22}N_4SO_4$ 490.59 ($M^+ = 490$)	255–257	Orange	65	71.00 (71.11)	4.52 (4.36)	11.42 (11.32)
23	$C_{28}H_{25}N_5SO_5$ 543.60	175–177	Yellow	80	61.87 (61.76)	4.64 (4.51)	12.88 (12.78)
24[c]	$C_{26}H_{19}N_5SO_4$ 497.53	255–257	Colorless	70	62.77 (62.81)	3.85 (3.90)	14.08 (14.13)
28	$C_{26}H_{21}N_7SO_2$ 495.56	138–140	Orange	75	63.02 (63.11)	4.27 (4.31)	19.79 (19.80)
30	$C_{26}H_{20}N_6SO_3$ 496.55	220–221	Colorless	65	62.89 (62.91)	4.06 (4.10)	16.93 (16.76)

[a] From EtOH unless otherwise stated.
[b] From dioxane.
[c] From DMF.

Structure **5** was also confirmed by its chemical reactivity towards different chemical reagents. Therefore, thiazole derivative **5** was condensed with 2-hydroxybenzaldehyde **6** in ethanol containing catalytic amount of piperidine to afford benzo[b]pyran **8**. Formation of **8** was assumed to proceed via first formation of the arylidene derivative **7** followed by addition of the hydroxyl group to the cyano group and ammonia elimination[11] (of Scheme 2).

Reaction of the thiazole derivative **5** with arylidenemalononitriles **9** in refluxing ethanol and in the presence of triethylamine as catalyst gave a product with addition and hydrogen elimination. Structure **12**



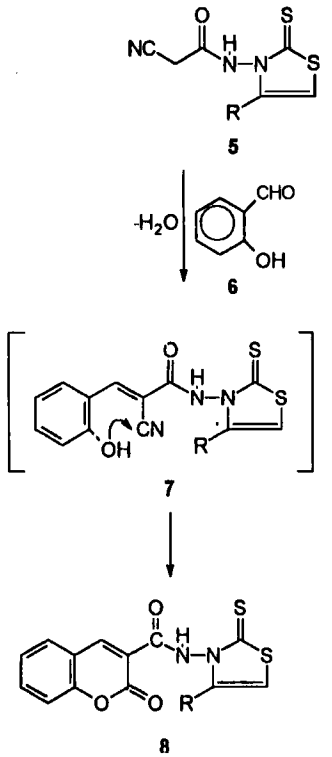
SCHEME 1

was suggested for the reaction product based on its elemental and spectral data. Formation of **12** was assumed to take place via a Michael type addition of the active methylene group of **5** to π-deficient centre in **9** to give the Michael adduct **10** which cyclized to the intermediate **11**. The latter readily eliminate one molecule of hydrogen to yield the pyridine derivative **12** (of Scheme 3).

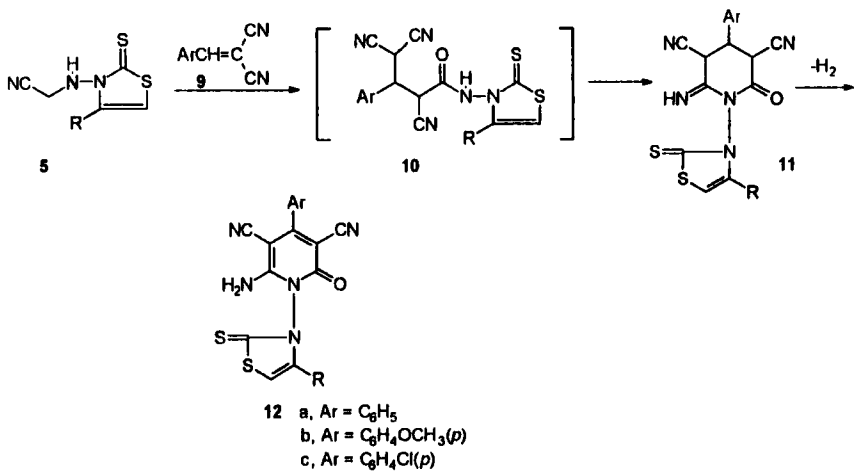
The *in situ* intermediate **14** was prepared from cyanoacetophenone **13** and phenylisothiocyanate in potassium hydroxide solution, which upon treatment with **1** afforded **15**.

Since the potassium salt of the enothiol **14** was thermally unstable, the freshly prepared crude product **14** was used without further purification. Elemental analysis and spectral data are in good agreement with the acyclic structure **15**.

In an attempt to prepare the thiophene **18** by refluxing **15** in ethanol containing few drops of triethylamine failed and a single



SCHEME 2



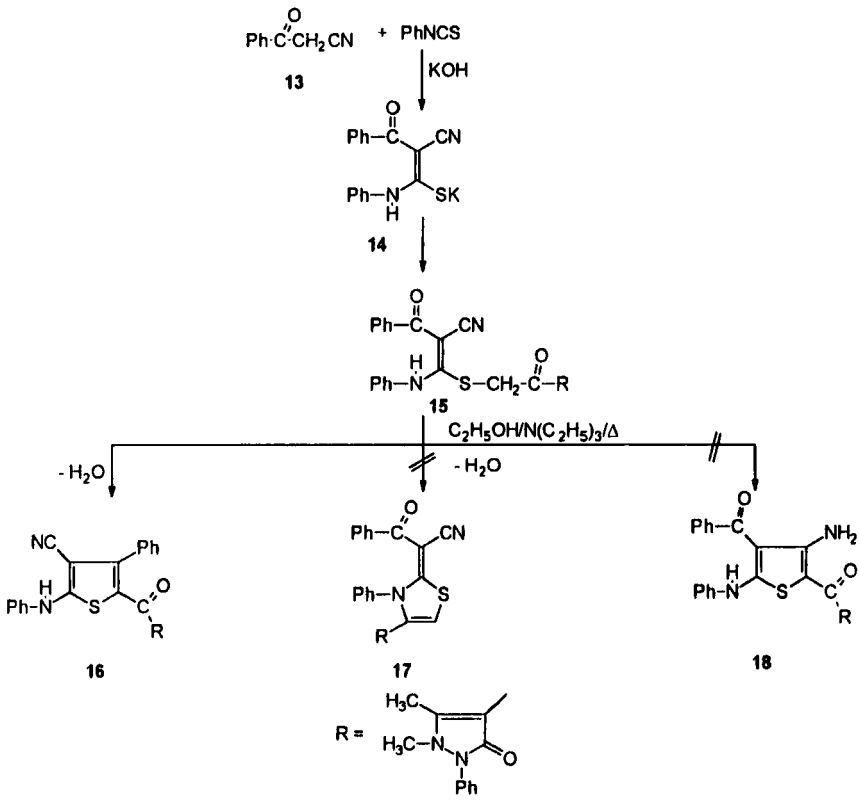
SCHEME 3

TABLE II Spectral Data of Newly Synthesized Compounds

Compd no.	IR (cm^{-1})	^1H NMR (δH)
5	3470, 3255 (NH), 2260 (CN), 1696 (CO), 1244 (CS)	2.4 (s, 3H, CH_3), 3.3 (s, 3H, N-CH_3), 4.43 (s, 2H, CH_2), 6.85 (s, 1H, thiazole H-5), 7.2–7.6 (m, 5H, aromatic), 10.5 (s, 1H, NH)
8	3440, 3330 (NH), 1700, 1690, 1665 (CO)	2.45 (s, 3H, CH_3), 3.31 (s, 3H, N-CH_3), 6.7 (s, 1H, thiazole H-5), 7.3–7.9 (m, 10H, aromatic), 10.2 (s, 1H, NH)
12a	3470, 3380 (NH_2), 2212 (CN), 1680, 1660 (CO)	2.52 (s, 3H, CH_3), 3.41 (s, 3H, N-CH_3), 7.38–7.54 (m, 11H aromatic), 8.2 (s, 2H, NH_2)
15	3360 (NH), 2210 (CN), 1680, 1674, 1665 (CO)	2.25 (s, 3H, CH_3), 3.4 (s, 3H, N-CH_3), 3.8 (s, 2H, CH_2), 7.1–7.6 (m, 10H, aromatic), 10 (s, 1H, NH)
16	3350, 3290 (NH), 2209 (CN), 1675, 1660 (CO)	2.4 (s, 3H, CH_3), 3.3 (s, 3H, N-CH_3), 7.4–8.1 (m, 15H, aromatic), 10.3 (s, 1H, NH)
23	3440, 3360, 3210 (NH_2, NH, OH), 2205 (CN), 1748, 1690, 1665 (CO)	1.1–1.3 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.22 (s, 3H, N-CH_3), 3.6–3.8 (q, 2H, CH_2), 6.45 (s, 2H, NH_2), 7.0–7.6 (m, 10H, aromatic), 8.0 (s, 1H, NH), 9.7 (s, 1H, OH)
24	3460, 3330 (NH2, OH), 2212 (CN), 1705, 1685, 1675 (CO)	
28	3450, 3370 (NH_2, NH), 2235, 2210 (CN), 1710, 1680 (CO)	2.47 (s, 3H, CH_3), 3.33 (s, 3H, N-CH_3), 3.73 (s, 2H, CH_2), 6.55 (s, 2H, NH_2), 7.25–7.65 (m, 10H, aromatic), 9.9 (s, 1H, NH)
30	3440, 3300 (NH_2), 2210 (CN), 1680, 1660 (CO)	

product via water elimination was obtained. However, the elemental analysis and spectral data of the reaction product were compatible only with the thiophene structure **16**. This assignment was supported by the appearance of NH, CN and carbonyl absorption at 3350 cm^{-1}, 2209 cm^{-1} and 1675 cm^{-1} respectively in the IR spectrum of the isolated product (cf. Tables I and II).

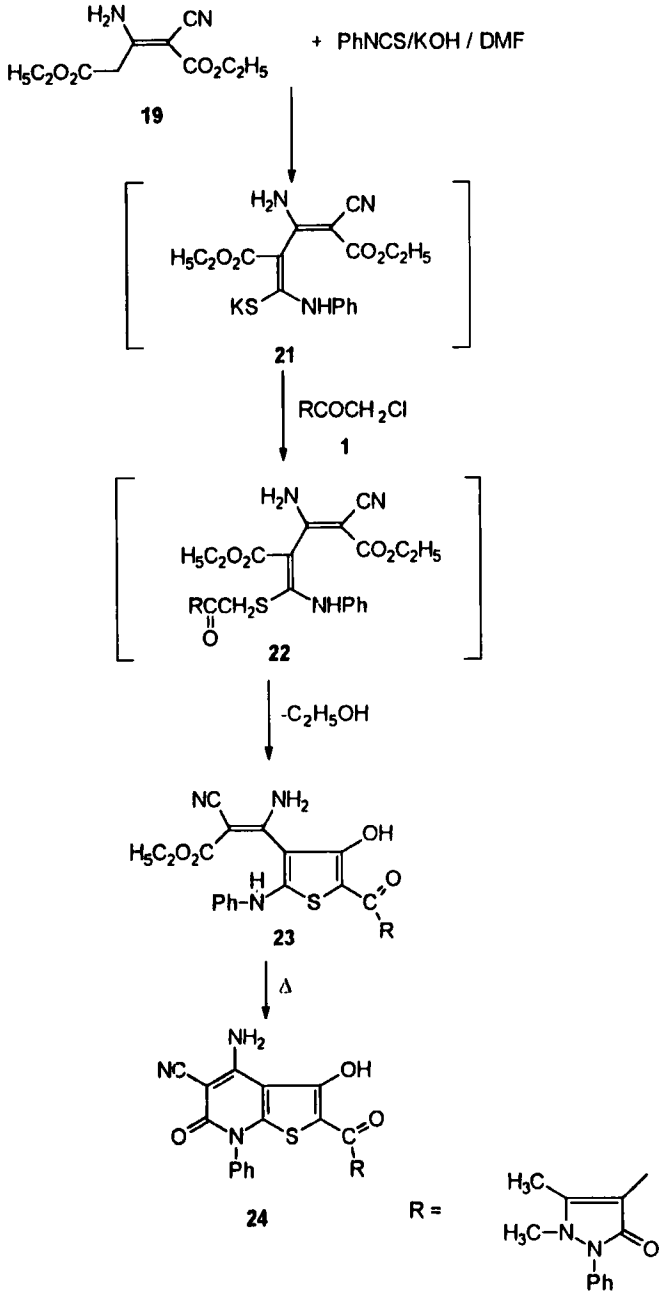
Similarly enaminonitriles **19** and **20** were used as starting materials in heterocyclic synthesis[12–15], a little attention was paid to their utility for synthesis of thiophenes and thienopyridines. Thus, 3-amino-2-cyano-2-pentene-1,5-dicarboxylate **19** was allowed to react with phenylisothiocyanate in dry dimethylformamide at room temperature



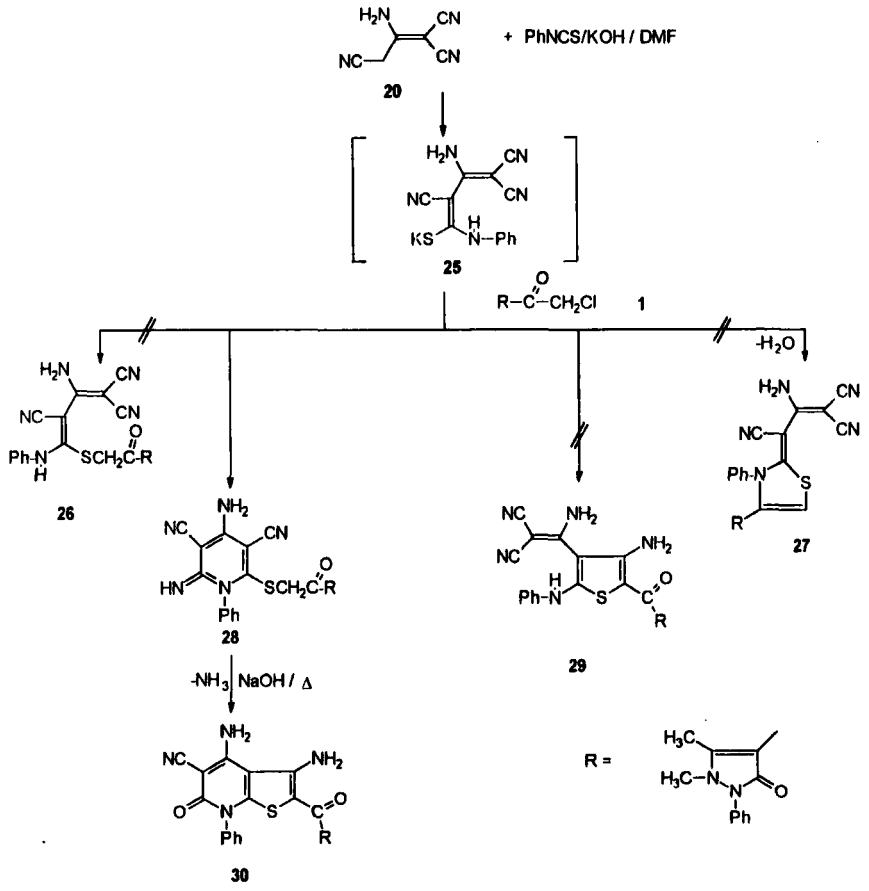
SCHEME 4

to give the non-isolable intermediate **21**. Treatment of **21** with **1** yielded a single product in good yield for which the thiophene structure **23** was established by analytical and spectral data (cf. Tables I and II).

The IR spectrum of the reaction product showed the presence of a cyano group stretching at $\nu = 2205\ cm^{-1}$, carbonyl groups at $\nu = 1748\ cm^{-1}$, $1690\ cm^{-1}$, and $1665\ cm^{-1}$, respectively. The ^1H-NMR spectrum revealed in addition to aromatic protons, the presence of triplet at $\delta = 1.2$ ppm (CH_3), singlet at $\delta = 2.3$ ppm (CH_3), singlet at $\delta = 3.22$ ppm (N-CH_3), quartet at $\delta = 3.75$ ppm (CH_2), two D_2O exchangeable singlets at $\delta = 6.45$ ppm (NH_2) and at $\delta = 8.0$ ppm (NH), and a singlet at $\delta = 9.7$ ppm (OH). These data agree with structure **23** which presumably was formed through the intermediacy of **22**. Heating of **23** in ethanol containing sodium hydroxide yielded the thienopyridine **24** (cf. Scheme 5). Its structure **24** was assigned as the cyclization product of **23**, based on its spectral data.



SCHEME 5



SCHEME 6

The reaction of 2-amino-1-propene-1,1,3-tricarbonitrile **20** with phenyl isothiocyanate in dimethylformamide followed by addition of **1** to the reaction mixture a product of molecular formula $C_{26}H_{21}N_7O_2S$ was formed. Four isomeric structures **26–29** can be considered for the reaction product (of Scheme 6). Structures **26** and **27** were ruled out based on the IR spectrum which showed the presence of two cyano groups stretching at $\nu = 2235\ cm^{-1}$, and $2210\ cm^{-1}$ respectively.

The distinction between structures **28** and **29** is based on the ^{1}H-NMR spectral data which showed the presence of $-SCH_2CO-$ methylene signal at $\delta = 3.73$ ppm. Thus, the pyridine structure **28** can be assigned to the reaction product.

Cyclization of **28** with ethanolic sodium hydroxide leads to the formation of the thienopyridine derivative **30** through ammonia liberation.

EXPERIMENTAL

All melting points are uncorrected and measured on Griffin & George MBF 010T (London) apparatus. Recorded yields correspond to the pure products. IR(KBr) spectra were recorded on a Perking Elmer SP-880 spectrophotometer and ^{1}H-NMR spectra were measured on a Varian 270 MHz spectrometer in DMSO-d_6 as solvent and TMS as an internal standard. (Chemical shifts were reported in δ units ppm. Microanalysis were performed on LECO CHN-932.)

Prepration of 2-cyano-N-(4-antipyrinyl)-2-thioxothiazol-3-yl)acetamide (5)

A solution of **2** (0.01 mol) in dimethylformamide (50 ml), carbon disulfide (0.01 mol), and potassium hydroxide (0.01 mol) in water (10 ml) were added. The reaction mixture was stirred for 3 h. To this solution (0.01 mol) of **1** was added. The reaction mixture was stirred overnight, poured on cold water and neutralized with HCl (10%). The solid product formed was collected by filtration and crystallized.

N-(4-Antipyrinyl-2-thioxothiazol-3-yl)-2H-2-oxobenzo[b]pyran-3-carboxamide (8)

A solution of (0.01 mol) of **5** and (0.01 mol) of salicylaldehyde in ethanol containing piperidine (0.1 ml) was refluxed for 1 h, then left to cool. The formed precipitate was collected by filtration and crystallized.

Preparation of 6-amino-1-(4′-antipyrinyl -2′-thioxothiazol-3′-yl)-4-aryl-3, 5-dicyanopyridine-2(1H) ones (12a-c). General procedure

A solution of **5** (0.01 mol) in absolute ethanol (50 ml) containing (0.1 ml) of triethylamine, was treated with (0.01 mol) of **9**. The reaction mixture was refluxed for 3 h, then left to cool. The solid product formed was collected by filtration and crystallized.

Preparation of 1-benzoyl-2-anilino-2-(antipyrinoylmethylthio)acrylonitrile (15)

A mixture of the appropriate cyanoacetophenone (0.01 mol), phenylisothiocyanate (0.01 mol) and potassium hydroxide (0.01 mol) dry in dimethylformamide (30 ml) was stirred for 5 h, at room temperature. The appropriate **1** (0.01 mol) was added and stirring was continued

for 2 hours. The mixture was diluted with water and the solid precipitate was collected and crystallized.

Formation of 2-antipyrinoyl-5-anilino-3-phenylthiophene-4-carbo-nitrile (16)

A solution of compound **15** (0.01 mol) in ethanol (50 ml) containing triethylamine (0.1 ml) was refluxed for 3 h, then left to cool at room temperature. The solid formed was collected by filtration and crystallized.

4-(3-Amino-2′-ethoxycarbonylacrylonitrilo)-2-antipyrinoyl-3-hydroxy-5-anilinothiophene (23)

To a cold suspension of finely ground potassium hydroxide (0.01 mol) in dry dimethylformamide (50 ml), **19** (0.01 mol) and phenylisothiocyanate (0.025 mol) were added in this order. The mixture was stirred over night at room temperature and then treated with **1** (0.01 mol) and stirred over night again. The reaction mixture was poured on cold water and the resulting precipitate was collected by filtration washed several times with water and crystallized.

Formation of 4-amino-2-antipyrinoyl-5-cyano-3-hydroxy-7-phenylthieno[2,3-b]pyridine-6(7H)-one (24)

A solution of **23** (0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.5 gm) was heated under reflux for 3 h. The reaction mixture was left to cool and poured into iced water. The formed precipitate was collected by filtration and crystallized.

4-Amino-1,2-dihydro-2-imino-1-phenyl-3,5-dicyano-6-antipyrinoyl-methylthiopyridine (28)

This compound was prepared according to the same procedure described for the synthesis of compound **23** using **20** instead of **19**.

3,4-Diamino-2-antipyrinoyl-5-cyano-7-phenylthieno [2,3-b]pyridine-6(7H)-one (30)

A solution of **28** (0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.01 mol) was heated under reflux for 2 h. The reaction mixture was poured on cold water, acidified with dilute HCl. The formed precipitate was collected by filtration and crystallized.

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