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Phenyl Isothiocyanate in Heterocyclic Synthesis: Novel Synthesis of Thiazoles, Thieno[2,3-b]pyridine, Thiophene and Thieno[3,2-c]pyridazine Derivatives

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Summary. The enamino nitriles **1** and **2** react with phenyl isothiocyanate followed by cyclization with α-haloketones **3** and **10** to afford in each case the thiazole **5**, thiophene **11** and the thieno[2,3-b]pyridine derivatives **19** and **21**. Chemical and spectroscopic evidences for the structures of the new compounds are described.

Keywords. Thiazole; Thieno[2,3-b]pyridine; Thiophene; ^{1}H-NMR spectra.

Phenylisothiocyanate in der Heterocyclensynthese: Neue Synthesen für Thiazol-, Thieno[2,3-b]pyridin-, Thiophen- und Thieno[3,2-c]pyridazin-Derivate

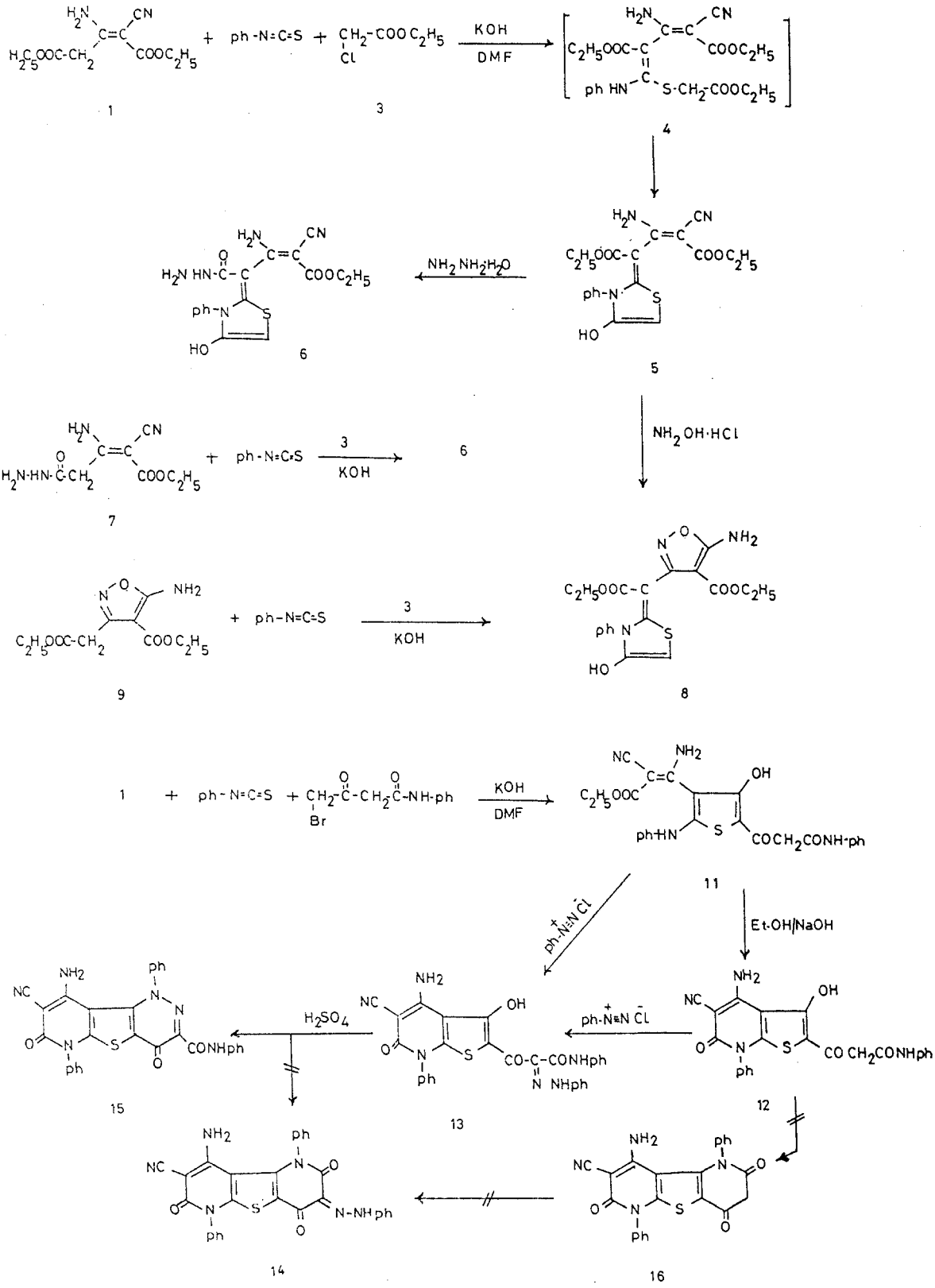
Zusammenfassung. Die Enamin-nitrile **1** und **2** ergaben nach Reaktion mit Phenylisothiocyanaten und nachfolgender Cyclisierung mit α-Halogenketonen **3** und **10** die entsprechenden Thiazole **5**, die Thiophene **11** und die Thieno[2,3-b]pyridine **19** und **21**. Chemische und spektroskopische Untersuchungen wurden als Strukturbeweise für die neuen Verbindungen herangezogen.

Introduction

The reaction of phenyl and benzoyl isothiocyanates with active methylene reagents has been recently investigated in our laboratories [1 – 3]. The products were heterocyclic ring systems which are expected to exhibit high biological activities [4 – 6], especially hypoglycemic [7] and anticonvulsant [8]. In this article we report the use of the title reagent for the synthesis of new heterocyclic ring systems through the reaction with some dimeric adducts followed by cyclization with α-halocarbonyl compounds.

Results and Discussion

Although diethyl 3-amino-2-cyano-2-penten-1,5-dicarboxylate (**1**) [9], 3-amino-2-propen-1,1,3-tricarbonitrile (**2**) [10] are interesting intermediates in heterocyclic synthesis [11 – 14] very little attention was paid to the potential utility of them for the synthesis of thiazoles and thiazolidenes. Thus, **1** reacts with phenyl isothio-



cyanate in dry *DMF* at room temperature to afford the nonisolable intermediate **4**. Treatment of **4** with ethyl chloroacetate **3** affords a single product in 80% yield to which we assign the thiazole structure **5**. The structure of **5** was based on the analytical and spectral data of the reaction product.

Thus, the IR spectrum revealed the presence of OH stretching at 3 550 – 3 320 cm^{-1}, CN group stretching at 2 220 cm^{-1}. ^{1}H-NMR spectrum revealed the presence of two triplets at $\delta = 1.65$, 1.68 ppm for 2 CH_3 groups, two quartets at $\delta = 4.23$, 4.30 ppm for two CH_2 groups, a D_2O exchangeable signal at $\delta = 5.58$ ppm for NH_2, a singlet at $\delta = 6.99$ ppm for thiazole H-5 and a singlet at $\delta = 10.11$ ppm for OH group.

Reaction of **5** with hydrazine hydrate affords the hydrazide derivative **6** as the product. Structure **6** was established based on its synthesis on another reaction route. Treatment of the hydrazide **7** [15] with phenyl isothiocyanate followed by cyclization with **3** in basic *DMF* solution affords the same product **6** (identical m. p. and mixed m. p.).

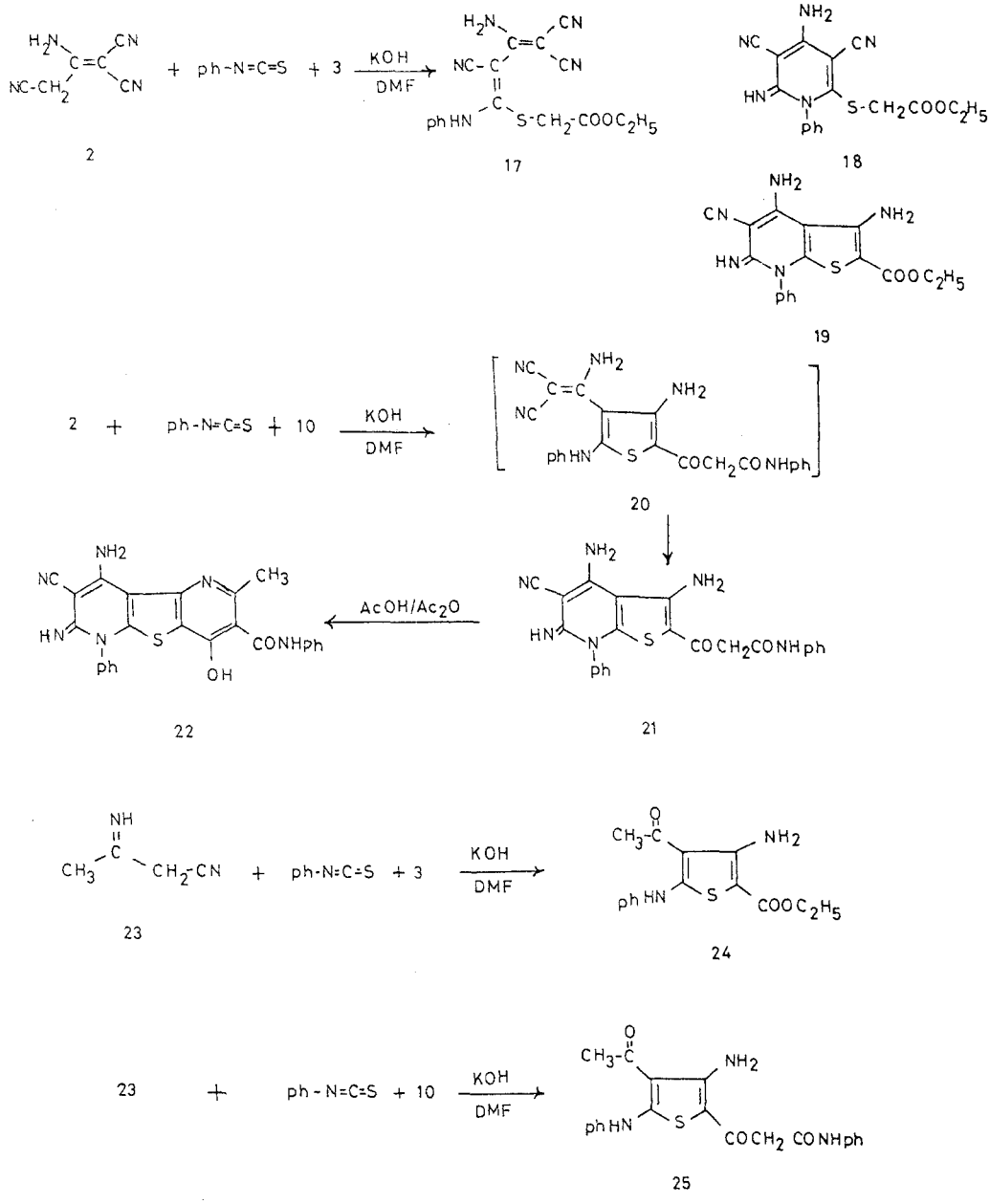
Reaction of **5** with hydroxylamine hydrochloride in *Et*OH/*Ac*ONa affords the isoxazole derivative **8**. Similarly, the structure of **8** was confirmed by an independent synthesis: reaction of the isoxazole derivative **9** [16] and phenyl isothiocyanate followed by cyclization with **3** gave the same product **8** (identical m. p. and mixed m. p.).

Reaction of **1** with phenyl isothiocyanate followed by reaction with γ-bromoacetoacetanilide **10** [17] affords the thiophene derivative **11**. The structure of **11** was confirmed based on analytical and spectral data. Heating of **11** in *Et*OH/NaOH solution yields the thieno[2,3-b]pyridine derivative **12**. Reaction of **12** with benzenediazonium chloride in *Et*OH/NaOH solution affords the phenyl hydrazone derivative **13**. The latter, upon treatment with conc. H_2SO_4 in a water bath, gave a product of the molecular formula $C_{29}H_{18}N_6O_3S$. Two possible isomeric structures (**14** and **15**) were proposed. The pyrido[2,3 : 2',3']thieno[4,5-c]pyridazine derivative **15** is established for the reaction product based on the failure to cyclize **12** to produce the pyrido[2,3 : 2',3']thieno[4,5-b]pyridine **16** which might be expected to react with benzenediazonium chloride to form **14**.

Reaction of **2** with phenyl isothiocyanate in dry *DMF* followed by cyclization with **3** afforded a single product of the molecular formula $C_{17}H_{15}N_5O_2S$. Three possible isomeric structures (**17** – **19**) were proposed for the reaction product. Structures **17** and **18** were ruled out based on the IR spectrum which revealed the presence of only one CN group stretching at 2 220 cm^{-1}. The ^{1}H-NMR spectrum revealed the absence of a CH_2 singlet which might be expected to appear if structures **17** and **18** were considered. Moreover, the presence of two D_2O exchangeable singlets at $\delta = 4.63$ and 5.24 ppm which are characteristic for the two NH_2 groups present in structure **19**, confirm the assignment.

In a similar way, the reaction of **2** with phenyl isothiocyanate followed by cyclization with **10** affords the thieno[2,3-b]pyridine derivative **21**. The latter is formed through the intermediate formation of the expected thiophene derivative **20**. The structure **21** was established based on analytical and spectral data (c. f. Exp. section). Reaction of **21** with acetic anhydride affords the pyrido[2,3 : 2',3']thieno[4,5-b]pyridine derivative **22**. The structure of **22** is based on its ^{1}H-NMR spectrum which revealed the presence of a singlet at $\delta = 1.68$ ppm characteristic for a CH_3 group and a broad singlet at 10.21 ppm for the OH group.

In analogy to the reactions of **1** and **2** with phenyl isothiocyanate followed by



the reaction with the halocarbonyl compounds **3** and **10**, the 3-iminobutyronitrile **23** [18] reacts with the same reagents to afford the thiophene derivatives **24** and **25**, respectively. The structures of **23** and **24** were established based on the analytical and spectral data (c. f. Exp. section).

Experimental Part

M. p. s are uncorrected. IR spectra (KBr): Pye Unicam SP-1000. ^{1}H-NMR spectra (*DMSO*): EM-300 MHZ, *TMS* as internal standard, chemical shifts in δ (ppm). Microanalytical data: Micro Analytical Data Unit at Cairo University.

Preparation of **5**, **11**, **19**, *and* **21** (*general procedure*)

To a cold suspension of powdered KOH (0.025 mol) in *DMF* (30 ml) were added each of the enaminonitriles **1** and **2** (0.025 mol), followed by phenyl isothiocyanate (0.025 mol). The mixture was stirred at room temperature overnight, then treated with the appropriate halogen compound **4** or **10** (0.025 mol) and left at room temperature for 24 h. The mixture was then triturated with cold H_2O (100 ml) containing HCl (0.1 mol, 5 ml). The resultant solid product was collected by filtration and crystallized from the proper solvent.

Diethyl 3-Amino-2-cyano-4-(3'-phenyl-4'-hydroxy-thiazol-2-yl)-2-pentene-1,5-dicarboxylate (**5**)

Yellow crystals from *Et*OH, yield 90%, m. p. 184°C. $C_{19}H_{19}N_3O_5S$ (401.3): Calc. C 56.8, H 4.7, N 10.4, S 8.0; found C 56.5, H 4.6, N 10.0, S 7.7. IR: 3550–3300 (OH, NH_2), 3050 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1700, 1690 (2 C=O), 1630 (C=C). ^{1}H-NMR: 1.65, 1.68 (2t, 6 H, 2 CH_3), 4.23, 4.30 (2q, 4 H, 2 CH_2), 5.58 (s, 2 H, NH_2), 6.99 (s, 1 H, thiazole H-5), 7.30–7.34 (m, 5 H, C_6H_5), 10.11 (s, 1 H, OH).

Ethyl 3-Amino-2-cyano-3-(2'-formanilidoacetyl-3'-hydroxy-5'-phenylaminothiophen-4'-yl)-acrylate (**11**)

Orange crystals from *Et*OH, yield 85%, m. p. 220°C. $C_{25}H_{22}N_4O_5S$ (490.4): Calc. C 61.2, H 4.5, N 11.4, S 6.5; found C 61.0, H 4.6, N 11.1, S 6.4. IR: 3570–3320 (OH, NH_2, NH), 3050 (CH aromatic), 2970, 2890 (CH_3, CH_2), 2220 (CN), 1710, 1690–1680 (3 C=O), 1630 (C=C). ^{1}H-NMR: 1.68 (t, 3 H, CH_3), 4.23 (q, 2 H, CH_2), 4.48 (s, 2 H, NH_2), 5.69 (s, 2 H, CH_2), 8.89, 9.91 (2s, 2 H, 2 NH), 10.21 (s, br, 1 H, OH).

3-Cyano-4,5-diamino-2-imino-6-ethoxycarbonyl-1-phenyl-thieno[2,3-b]pyridine (**19**)

Pale brown crystals from *Et*OH, yield 89%, m. p. 145°C. $C_{17}H_{15}N_5O_2S$ (353.3): Calc. C 57.7, H 4.2, N 19.8, S 9.1; found C 57.6, H 3.9, N 19.5, S 9.0. IR: 3450–3360 (NH_2, NH), 3050 (CH aromatic) 2965, 2890 (CH_3, CH_2), 2220 (CN), 1695 (C=O), 1665 (C=N). ^{1}H-NMR: 1.67 (t, 3 H, CH_3), 4.18 (q, 2 H, CH_2), 4.63, 5.24 (2 s, 4 H, 2 NH_2), 7.33–7.36 (m, 5 H, C_6H_5), 9.43 (s, br, 1 H, NH).

3-Cyano-4,5-diamino-2-imino-6-formanilidoacetyl-thieno[2,3-b]pyridine (**21**)

Yellow crystals from *DMF*, yield 78%, m. p. 160°C. $C_{23}H_{18}N_6O_2S$ (442.5): Calc. C 62.4, H 4.1, N 19.0, S 7.2; found C 62.1, H 4.3, N 19.2, S 6.8. IR: 3460–3300 (NH_2, NH), 3050 (CH aromatic), 2960, 2870 (CH_3, CH_2), 2220 (CN), 1700, 1685 (2 C=O), 1665 (C=N). ^{1}H-NMR: 4.24 (s, 2 H, NH_2), 4.98 (s, 2 H, NH_2), 5.21 (s, 2 H, CH_2), 7.32–7.36 (m, 10 H, 2 C_6H_5), 8.87, 9.21 (2 s, 2 H, 2 NH).

Ethyl 3-Amino-2-cyano-3-hydrazido-4-(4'-hydroxy-3'-phenylthiazol-2'-yl)-crotonoate (**6**)

Method (A): To a solution of **5** (0.01 mol) in *Et*OH (30 ml), hydrazine hydrate (0.01 mol) was added. The whole mixture was heated under reflux for 4 h. The solid formed upon dilution with H_2O containing few drops of HCl was collected and crystallized from *DMF*, yield 65%, m. p. >300°C. $C_{17}H_{17}N_5O_4S$ (387.4): Calc. C 52.7, H 4.4, N 18.1, S 8.3; found C 52.5, H 4.0, N 18.3, S 8.2. IR: 3560–3320 (OH, NH_2, NH), 3050 (CH aromatic), 2970, 2890 (CH_3, CH_2), 2220 (CN), 1710, 1690 (2 C=O), 1630 (C=C). ^{1}H-NMR: 1.68 (t, 3 H, CH_3), 4.21 (q, 2 H, CH_2), 5.21, 6.01 (2 s, 4 H, 2 NH_2), 6.98 (s, 1 H, thiazole H-5), 7.33–7.36 (m, 5 H, C_6H_5), 8.89 (s, 1 H, NH), 10.01 (s, br, 1 H, OH).
Method (B): The same experimental procedure used for the synthesis of **5** was carried out except for the use of **7** instead of **1**.

Ethyl (3-Amino-4-ethoxycarbonyl-isoxazolo-5-yl)-α-(4'-hydroxy-3'-phenyl-thiazolo-2'-yl)-acetate (**8**)

To a solution of **5** (0.01 mol) in ethanol (30 ml) containing *Ac*ONa (2 g), $NH_2OH \times HCl$ (0.01 mol) was added. The whole mixture was heated under reflux for 6 h and then poured into ice/H_2O mixture. The solid formed was collected and crystallized from dioxane: yield 68%, m.p. 270–273°C. $C_{19}H_{19}N_3O_6S$ (417.4): Calc. C 54.7, H 4.6, N 10.1, S 7.7; found C 54.6, H 4.4, N 10.4, S 7.2. IR: 3600, 3320 (OH, NH_2), 3045 (CH aromatic), 2970, 2890 (CH_3, CH_2), 1700, 1690 (2 C=0), 1640 (C=C). ^{1}H-NMR: 1.66–1.68 (2 t, 6 H, 2 CH_3), 4.20–4.25 (2 q, 4 H, 2 CH_2), 5.62 (s, 2 H, NH_2), 6.88 (s, 1 H, thiazole H-5), 7.33–7.36 (m, 5 H, C_6H_5), 10.21 (s, br, 1 H, OH).

4-Amino-3-cyano-6-formanilido-5-hydroxy-2-oxo-1-phenyl-thieno[2,3-b]pyridine (**12**)

A solution of **11** (0.01 mol) in *Et*OH (40 ml) containing NaOH (5 ml, 0.1 *N*) was heated under reflux for 2 h. The solid formed upon dilution with H_2O/HCl (till $pH = 6$) was collected and crystallized from dioxan to afford brown crystals, yield 76%, m.p. >300°C. $C_{23}H_{16}N_4O_4S$ (444.3): Calc. C 62.0, H 3.6, N 12.6, S 7.3; found C 62.0, H 3.5, N 12.3, S 6.9. IR: 3580–3300 (OH, NH_2, NH), 3050 (CH aromatic), 2890 (CH_2), 2220 (CN), 1700, 1690–1680 (3 C=0), 1635 (C=C). ^{1}H-NMR: 4.42 (s, 2 H, NH_2), 5.21 (s, 2 H, CH_2), 7.32–7.37 (m, 10 H, 2 C_6H_5), 8.89 (s, 1 H, NH), 10.25 (s, br, 1 H, OH).

4-Amino-3-cyano-5-hydroxy-6-(α-phenylhydrazo-formanilidoacetyl)-2-oxo-1-phenyl-thieno[2,3-b]pyridine (**13**)

To a solution of each **11** or **12** (0.1 mol) in *Et*OH (50 ml) containing NaOH (20 ml, 0.1 *N*), benzenediazonium chloride [prepared by addition of $NaNO_2$ solution (0.1 mol) to a cold solution of aniline (0.1 mol) containing the appropriate quantity of HCl at 0°C with stirring] was added. The reaction mixture was left at room temperature for 6 h and the solid product formed was collected and crystallized from *Et*OH to afford orange crystals, yield 90%, m.p. 152°C. $C_{29}H_{20}N_6O_4S$ (548.5): Calc. C 63.5, H 3.7, N 15.3, S 5.8; found C 63.1, H 3.6, N 15.3, S 6.0. IR: 3520–3300 (OH, NH_2, NH), 3050 (CH aromatic), 2220 (CN), 1710, 1700, 1680 (3 C=0), 1655 (C=N). ^{1}H-NMR: 4.86 (s, 2 H, NH_2), 7.32–7.38 (m, 15 H, 3 C_6H_5), 8.78, 8.98 (2 s, 2 H, 2 NH), 10.12 (s, br, 1 H, OH).

9-Amino-8-cyano-4,7-dioxo-3-formanilido-6-phenyl-pyrido[2,3:2',3']thieno[4,5-c]pyridazine (**15**)

Dry solid of **13** (0.01 mol) in conc. H_2SO_4 (5 ml) was heated in a boiling water bath for 4 h. The solid product formed upon dilution with ice/water mixture was collected and crystallized from *DMF*, yield 55%, m.p. >300°C. $C_{29}H_{18}N_6O_3S$ (530.5): Calc. C 65.6, H 3.4, N 15.8, S 6.0; found C 65.4, H 3.0, N 15.7, S 5.8. IR: 3460–3320 (NH_2, NH), 3045 (CH aromatic), 2220 (CN), 1710, 1690, 1680 (3 C=0), 1660 (C=N). ^{1}H-NMR: 4.89 (s, 2 H, NH_2), 7.30–7.36 (m, 15 H, 3 C_6H_5), 9.61 (s, 1 H, NH).

9-Amino-8-cyano-3-formanilido-4-hydroxy-7-imino-6-phenyl-2-methyl-pyrido[2,3:2',3']thieno[4,5-b]pyridine (**22**)

A solution of **21** (0.01 mol) in *Ac*OH (10 ml) and Ac_2O (5 ml) was heated under reflux for 4 h. The reaction mixture was poured into ice/water mixture and left in this medium overnight. The solid product formed was collected and crystallized from *DMF* to afford orange crystals, yield 50%, m.p. >300°C. $C_{25}H_{18}N_6O_2S$ (466.5): Calc. C 64.4, H 3.9, N 18.0, S 6.9; found C 64.3, H 4.1, N 17.8, S 7.2. IR: 3560–3300 (OH, NH_2, NH), 3045 (CH aromatic), 2960 (CH_3), 2220 (CN), 1695 (C=O), 1665 (C=N). ^{1}H-NMR: 1.68 (s, 3 H, CH_3), 5.23 (s, 2 H, NH_2), 7.34–7.37 (m, 10 H, 2 C_6H_5), 8.95, 9.30 (2 s, 2 H, 2 NH), 10.21 (s, br, 1 H, OH).

4-Acetyl-3-amino-2-ethoxycarbonyl-5-phenylamino-thiophene (**24**) and *4-Acetyl-3-amino-2-formanilidoacetyl-5-phenylaminothiophene* (**25**)

To a solution of **23** (0.01 mol) in *DMF* (20 ml) containing KOH (0.01 mol), phenyl isothiocyanate (0.01 mol) was added. The whole mixture was left at room temperature for 24 h with stirring. **3** or **10** (0.01 mol) was added and the whole mixture was heated in a boiling water bath for 4 h. The solid product formed upon dilution with H_2O containing HCl (till $pH=6$) was collected.

24 forms yellow crystals from dioxan, yield 72%, m. p. 164°C. $C_{15}H_{16}N_2O_3S$ (304.3): Calc. C 59.2, H 5.3, N 9.2, S 10.5; found C 59.0, H 5.4, N 9.5, S 10.5. IR: 3450–3320 (NH_2, NH), 3045 (CH aromatic), 2980, 2871 (CH_3, CH_2), 1690, 1685 (2 C=O). ^{1}H-NMR: 1.46 (s, 3 H, CH_3), 1.68 (t, 3 H, CH_3), 4.41 (q, 2 H, CH_2), 7.33–7.36 (m, 5 H, C_6H_5), 8.89 (s, br, 1 H, NH).

25 forms orange crystals from *DMF*, yield 81%, m. p. 235°C. $C_{21}H_{19}N_3O_3S$ (393.2): Calc. C 64.1, H 4.8, N 10.7, S 8.2; found C 64.0, H 4.5, N 10.4, S 8.0. IR: 3460–3320 (NH_2, NH), 3045 (CH aromatic), 2980 (CH_3), 1710, 1690–1675 (3 C=O). ^{1}H-NMR: 1.40 (s, 3 H, CH_3), 5.69 (s, 2 H, CH_2), 5.21 (s, 2 H, NH_2), 7.32–7.37 (m, 10 H, 2 C_6H_5), 8.81, 9.88 (2 s, 2 H, 2 NH).

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