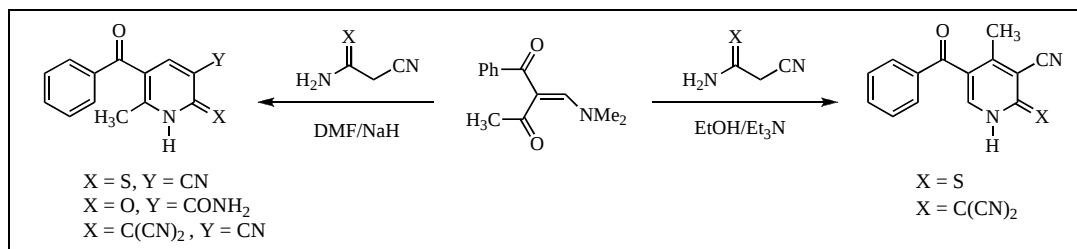


Fathi A. Abu-Shanab*, A. M. Hessen, and S. A. S. Mousa

Chemistry Department, Faculty of Science, Al-Azhar University, Assiut 71524, Egypt.

e-mail: fathorg82@hotmail.com

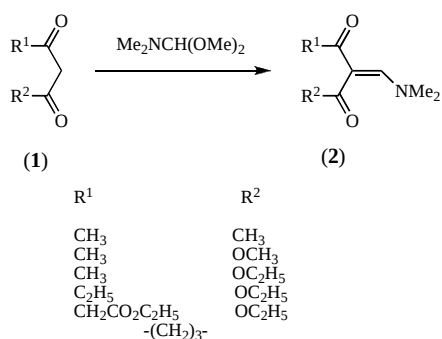
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Polysubstituted pyridines **11a,c** and **12** were prepared by the reaction of benzoylacetone with dimethylformamide dimethyl acetal followed by treatment with cyanothioacetamide **9a**, cyanoacetamide **9b** and the anion of malononitrile dimer **9c** in dry DMF. When the reaction was carried out in ethanol as a solvent and piperidine as a base afforded **14a,b**. Thienopyridines **16a,b** were prepared by the reaction of pyridinethiones **11a** and **14a** with 2-chloro-*N*-*p*-tolyl-acetamide (**15**). Further reaction of thienopyridines **16a,b** with either DMFDMA or nitrous acid to gave **17a,b** and **18a,b** respectively. The reaction of pyridine derivative **11c** with hydrazine and phenylhydrazine afforded the tricyclic compounds **19a,b**.

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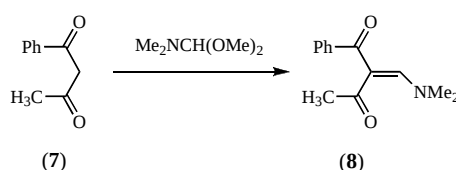
Formamide acetals are useful reagents; [3,4] their main application has been used for functional group transformations [5], but they may also be regarded as one-carbon synthons in the construction of carbon skeletons. One type of reaction, which is potentially valuable for the future purpose, is with 1,3-dicarbonyl compounds (**1**) to give enamines (**2**) [4].



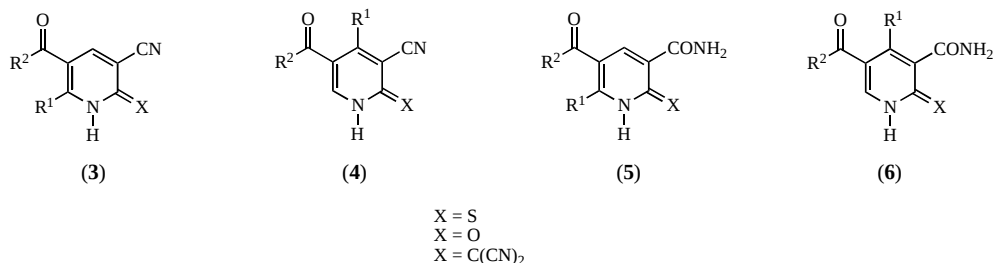
We have reported that these enamines (**2**) were used as precursors in the synthesis of pentasubstituted pyridines

(**3-6**) [6,7]. The structures of these compounds have been confirmed by X-ray crystallography [6,7].

In conjunction with our studies aimed at exploring the synthetic potential of enamine (**2**) we report here the reaction of benzoylacetone (**7**) with *N,N*-dimethylformamide dimethyl acetal (1:1) to give the corresponding enamine (**8**) [8].



This intermediate need not be isolated but can be reacted directly with cyanothioacetamide, cyanoacetamide or anion of malononitrile dimer in dry DMF and sodium hydride to give 2,3,5,6-tetrasubstituted pyridines (**10a-c**) or (**11a-c**) respectively as outlined in Scheme 1. In the first, initial Michael addition with elimination of dimethylamine followed by cyclization of the amino



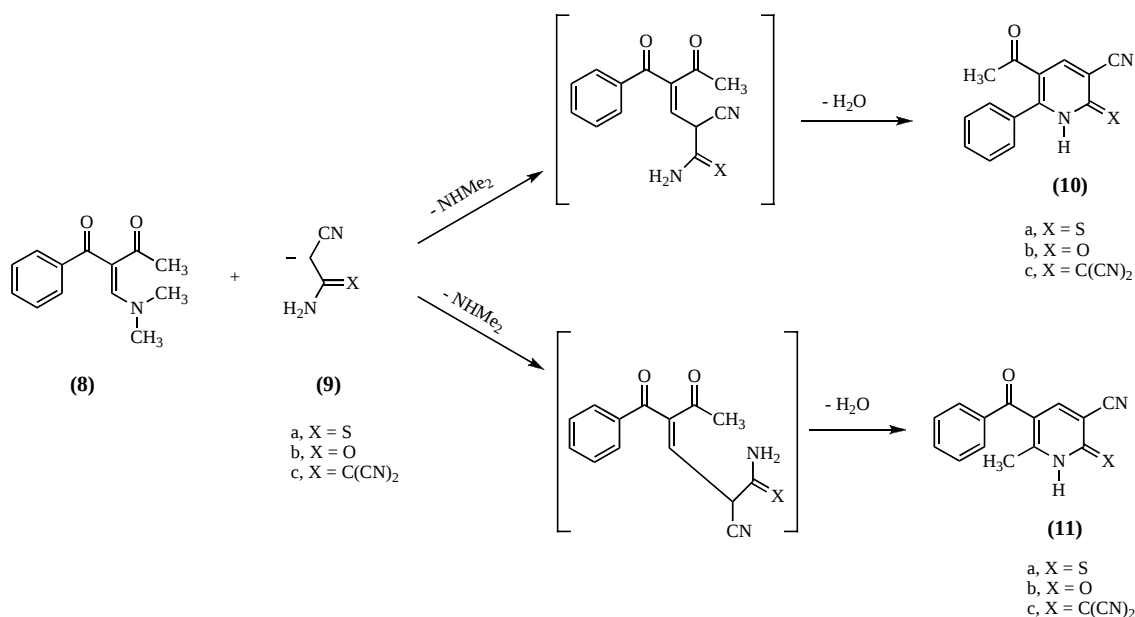
group with the carbonyl of the benzoyl moiety to give 2,3,5,6-tetrasubstituted pyridines (**10a-c**), whereas in the second initial Michael addition with elimination of dimethylamine followed by cyclization of the amino group with the carbonyl of the acetyl moiety gave 2,3,5,6-tetrasubstituted pyridines (**11a-c**). In practice, only one isomer was isolated in each case, but the ^1H NMR spectra show a singlet signal for the ring proton at δ_{H} 8.41, 7.51 and 8.3 ppm for compounds **11a**, **11c** and **12** respectively, did not enable the compounds to be identified unequivocally.

the cyano group so that the structure of (**11a**) becomes (**12**) up on hydrolysis.

On the other hand, reactions analogous to those reported above, but with ethanol as solvent and pepridine as a base [4], gave either (**13a,b**) or (**14a,b**) as outlined in Scheme 2.

The mass spectra of the isolated products show two peaks, one at m/z 105 corresponding to the benzoyl moiety and the other at m/z 77 corresponding to the benzene ring. This indicates that the molecule must contain the benzoyl moiety which corresponds to

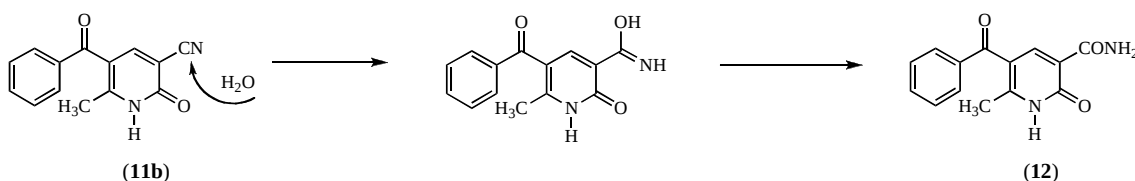
Scheme (1)

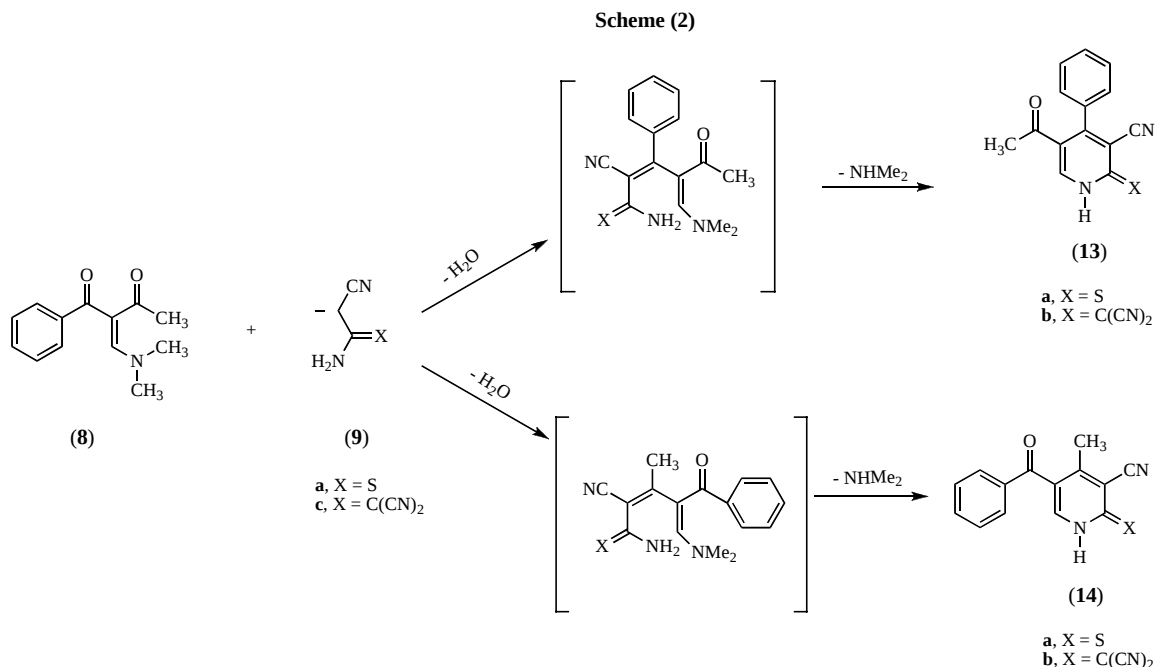


The mass spectra of the isolated products show two peaks at m/z 105 corresponding to the benzoyl moiety and at m/z 77 corresponding to the benzene ring. This indicates that the molecule must contain the benzoyl moiety which corresponding to structure (**11a-c**) not (**10a-c**). Hence, the isolated products have structures **11a-c**. The mass spectra of **11a** and **11c** show the molecular ions (m/z 254 and m/z 286) that fit to the structures **11a** and **11c** respectively, while the mass spectrum of **11b** shows a molecular ion peak (m/z 256) that is greater than the expected (m/z 238) by 18 units corresponding to a molecule of water. This confirms that the reaction was carried out with hydrolysis of the cyano group to amide group. Also the IR spectrum shows the disappearance of

structures (**14a,b**) not (**13a,b**). Hence, the isolated products have structures **14a,b**. Also the ^1H NMR spectra of these compounds show a singlet signal at δ 7.78 and 7.27 ppm corresponding to the ring proton.

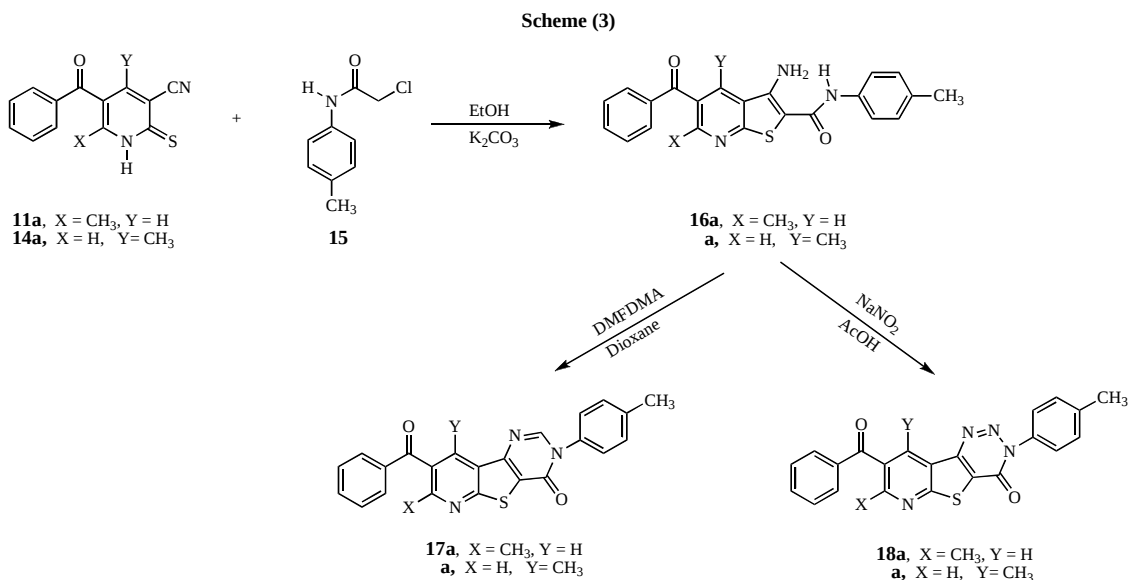
Some illustrative reactions, designed to demonstrate the potential usefulness of the products described above for further heterocyclic synthesis, are represented in Scheme 3 and Scheme 4. Thus, reaction of 5-benzoyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**11a**), and 5-benzoyl-4-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**14a**) with 2-chloro-*N-p*-tolyl-acetamide (**15**) and potassium carbonate in ethanol afforded 3-amino-5-benzoyl-6-methylthieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (**16a**) and 3-amino-5-benzoyl-4-methylthieno-

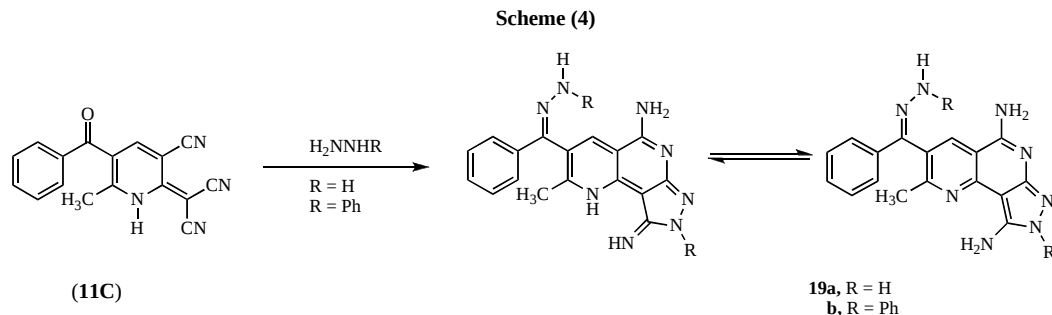




[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (**16b**) respectively. These compounds (**16a**) and (**16b**) upon treatment with dimethylformamide dimethyl acetal afforded 3-benzoyl-2-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,7-triaza-fluoren-8-one (**17a**) and 3-benzoyl-4-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,7-triaza-fluoren-8-one (**17b**) respectively. While on treatment of (**16a,b**) with sodium nitrite in acetic acid afforded 3-benzoyl-2-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,6,7-tetraaza-fluoren-8-one (**18a**) and 3-benzoyl-4-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,6,7-tetraaza-fluoren-8-one (**18b**) respectively as shown in Scheme 3. The structure of the isolated compounds was confirmed by elemental analysis as well as spectral analysis.

Further reaction of 5-benzoyl-2-dicyanomethylidene-6-methyl-1,2-dihydropyridin-3-carbonitrile (**11c**) with hydrazine and phenylhydrazine to give 3-(hydrazono-phenyl-methyl)-2-methyl-1*H*-pyrazolo[3,4-*h*][1,6]-naphthyridine-5,9-diamine (**19a**) and 9-imino-2-methyl-8-phenyl-3-[phenyl-(phenyl-hydrazono)-methyl]-8,9-dihydro-1*H*-pyrazolo[3,4-*h*][1,6]-naphthyridine-5-ylamine (**19b**) respectively as outlined in Scheme 4. IR spectra show the disappearance of the cyano groups and the carbonyl group and the appearance of amino groups. Also the mass spectra show the molecular mass corresponds to the proposed structures.





EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer as KBr disks. NMR spectra were recorded on Bruker AC300 spectrometer at 300 MHz for solutions of $[\text{H}_6]$ dimethyl sulfoxide with tetramethylsilane (TMS) as an internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometer using electron impact (EI). 2-Chloro-*N*-*p*-tolylacetamide (**15**) was prepared by literature method [9].

General Procedure for the Preparation of 2,3,5,6-Tetrasubstituted pyridines (11a,c and 12). In a dry flask a mixture of benzoylacetone (**7**) (1.62 g, 10 mmol), dry toluene (20 mL) and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (1.19 g, 10 mmol) was left stirring at room temperature for 24 h, and then refluxed for 2 h, the solvent evaporated to yield red oil which dissolved in dry DMF. In a second flask a mixture of anhydrous *N,N*-dimethylformamide (DMF) (10 mL), sodium hydride (0.24 g, 10 mmol) and active methylene (**9a-c**) (10 mmol) was allowed to stir at room temperature for 10 min. The contents of the second flask were transferred into the first flask and left stirring at room temperature overnight. The resulting mixture was poured into ice cold water and acidified with concentrated HCl. The solid product was recovered by filtration and recrystallized from the proper solvent.

5-Benzoyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (11a). This compound was prepared by the method described above using cyanothioacetamide (**9a**) (1.0g, 10mmol). The solid obtained in yield (1.85g, 72.83%) as greenish brown crystals (DMF/EtOH), m.p. 270-272°C, ir: NH 3170, CN 2227, and C=O 1662 cm^{-1} , ^1H nmr (DMSO- d_6) δ 2.46 (s, 3H, CH_3), 7.50-8.04 (m, 5H, phenyl protons), 8.41 (s, 1H, ring-H), 14.39 ppm (br., 1H, exch., NH), ms: m/z 254 (M^+). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{OS}$: C, 66.12; H, 3.96; N, 11.02. Found: C, 65.9; H, 3.8; N, 10.9.

5-Benzoyl-2-dicyanomethylidene-6-methyl-1,2-dihydropyridine-3-carbonitrile (11c). The title compound was prepared by the method described above using sodium salt of malononitrile dimer (1.54g, 10 mmol). The solid was obtained in yield (2.2 g, 76.92%) as brown crystals, m.p. 206-208°C (EtOH), ir: NH 3250, CN 2212, 2188, C=O 1660 cm^{-1} . ^1H nmr (DMSO- d_6): δ 2.22 (s, 3H, CH_3), 4.36 (br., 1H, exch., NH) 7.18-7.36 (m, 5H, phenyl protons), 7.51 ppm (s, 1H, ring-H), ms: m/z 286(M^+). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{10}\text{N}_4\text{O}$, C, 71.32; H, 3.52; N, 19.57. Found, C, 71.1; H, 3.4; N, 19.3.

5-Benzoyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (12). This compound was prepared by the method described above using cyanoacetamide (0.84 g, 10 mmol). The

solid obtained in yield (1.7 g, 71.43%) as yellow crystals (DMF/EtOH), m.p. 292-294°C, ir: NH 3368,3215; C=O 1668 cm^{-1} , ^1H nmr (DMSO- d_6) δ 2.49 (s, 3H, CH_3), 7.52-7.71 (m, 6H, phenyl protons + NH), 8.3 (s, 1H, ring-H), 8.80 (s, 1H, exch., NH), 12.86 ppm (br., 1H, exch., NH), ms: m/z 256 (M^+). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.4; H, 4.6; N, 10.8.

General Procedure for the Preparation of 2,3,4,5-Tetrasubstituted pyridines (14a,b). In a dry flask a mixture of benzoylacetone (**7**) (1.62 g, 10 mmol), dry toluene (20 mL) and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (1.19 g, 10 mmol) was left stirring at room temperature for 24 h, and then refluxed for 2 h, cooled and evaporated to yield red oil which dissolved in absolute ethanol. A solution of active methylene (**9a,c**) (10 mmol) in absolute ethanol (30 mL) was added followed by piperidine (0.5 mL), and the reaction mixture was left under reflux temperature for about 4 h. The reaction mixture was poured into ice cold water and acidified with concentrated HCl. The solid product was recovered by filtration and recrystallized from the proper solvent.

5-Benzoyl-4-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (14a). The title compound was prepared by the method described above using cyanothioacetamide (1.0 g, 10 mmol). The solid obtained in yield (1.92 g, 75.59%) as yellow crystals, m.p. 238-240°C (EtOH), ir: NH 3169, CN 2218 cm^{-1} . ^1H nmr (DMSO- d_6) δ 2.43 (s, 3H, CH_3), 7.50-7.76 (m, 5H, phenyl protons), 7.78 (s, 1H, ring-H), 14.08 ppm (br., 1H, exch., NH), ms: m/z 254 (M^+). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{OS}$, C, 66.12; H, 3.96; N, 11.02. Found, C, 65.9; H, 3.8; N, 10.9.

5-Benzoyl-2-dicyanomethylidene-4-methyl-1,2-dihydropyridine-3-carbonitrile (14b). The title compound was prepared by the method described above using sodium salt of malononitrile dimer (1.54 g, 10 mmol). The solid obtained in yield (2.03 g, 70.98%) as gray crystals, m.p. 145-147°C (EtOH), ir: NH 3337, CN 2190, 2156, C=O 1638 cm^{-1} . ^1H nmr (DMSO- d_6) δ 2.12 (s, 3H, CH_3), 4.16 (br., 1H, exch., NH) 7.05-7.24 (m, 5H, phenyl protons), 7.27 ppm (s, 1H, ring-H). ms: m/z 286(M^+). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{10}\text{N}_4\text{O}$, C, 71.32; H, 3.52; N, 19.57. Found, C, 71.0; H, 3.40; N, 19.3.

3-Amino-5-benzoyl-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (16a). A mixture of pyridine-2(1*H*)-thione (**11a**) (2.54 g, 10 mmol), 2-chloro-*N*-*p*-tolylacetamide (**15**) (1.83 g, 10 mmol) and sodium ethoxide (30 mL, 0.5 g sodium metal) was heated under reflux for about 2 h. The reaction mixture was poured on cold water, the solid product was recovered by filtration to give the title compound (**16a**) in yield (3.25, 81.05%) as reddish brown, m.p. 195-197°C (EtOH), ir: NH, NH_2 3435, 3317, 3203, C=O 1666, 1643 cm^{-1} , ms: m/z

401(M⁺). *Anal.* Calcd. for C₂₃H₁₉N₃O₂S, C, 68.81; H, 4.77; N, 10.47. Found, C, 68.5; H, 4.6; N, 10.2.

3-Amino-5-benzoyl-4-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (16b). The reaction was carried out by the method described above using pyridine-2(1*H*)-thione (14a) (2.54 g, 10 mmol) instead of (11a). The reaction was worked up as usual, and the solid obtained in yield (2.9 g, 72.32%) as yellow crystals, m.p. 230-232°C (EtOH), ir: NH, NH₂ 3489, 3401, 3341, C=O 1638 cm⁻¹, ms: m/z 401(M⁺). *Anal.* Calcd. for C₂₃H₁₉N₃O₂S, C, 68.81; H, 4.77; N, 10.47. Found, C, 68.6; H, 4.5; N, 10.3.

3-Benzoyl-2-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,7-triaza-fluorene-8-one (17a). 3-Amino-5-benzoyl-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (16a) (0.40 g, 1 mmol) in dry DMF (10 mL) was treated with DMFDMA (0.13 g, 1 mmol) portionwise with stirring at room temperature, and left stirring further 12 h. The solid obtained (0.33 g, 82.29%) as gray, m.p. 100-102°C (EtOH), ir: C=O 1684 cm⁻¹, ¹H nmr (DMSO-*d*₆) δ 2.39 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 7.32-7.78 (m, 9H, phenyl protons), 8.62 (s, 1H, pyridine-H) and 8.77 ppm (s, 1H, pyrimidine-H), ms: m/z 411(M⁺). *Anal.* Calcd. for C₂₄H₁₇N₃O₂S, C, 70.06; H, 4.16; N, 10.21. Found, C, 69.8; H, 4.0; N, 10.0.

3-Benzoyl-4-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,7-triaza-fluorene-8-one (17b). The reaction was carried out by the method described above using 3-amino-5-benzoyl-4-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (16b) (0.40 g, 1 mmol) instead of (16a). The reaction was worked up as usual, and the solid obtained (0.3 g, 74.81%) as yellow crystals, m.p. 200-202°C (EtOH), ir: C=O 1669, 1640 cm⁻¹, ¹H nmr δ 2.26 (s, 3H, CH₃), 2.84 (s, 3H, CH₃), 7.10, 7.13 (d, 2H, phenyl-AB), 7.38-7.55 (m, 5H, phenyl protons), 7.77 (s, 1H, pyridine-H), 8.12, 8.15 (d, 2H, phenyl-AB) and 9.36 ppm (s, 1H, pyrimidine-H), ms: m/z 411(M⁺). *Anal.* Calcd. for C₂₄H₁₇N₃O₂S, C, 70.06; H, 4.16; N, 10.21. Found, C, 69.7; H, 3.9; N, 10.1.

3-Benzoyl-2-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,6,7-tetraaza-fluorene-8-one (18a). 3-Amino-5-benzoyl-6-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (16a) (0.4 g, 1 mmol) in acetic acid (25 mL) was treated with sodium nitrite (0.14, 2 mmol) portionwise with stirring at room temperature, and left stirring further 1 h. The solid obtained (0.31 g, 77.31%) as gray, m.p. 135-137°C (EtOH), ir: C=O 1692 cm⁻¹, ms: (M⁺) at *m/z* 412. *Anal.* Calcd. for C₂₃H₁₆N₄O₂S, C, 66.98; H, 3.91; N, 13.58. Found, C, 66.6; H, 3.8; N, 13.3.

3-Benzoyl-4-methyl-7-*p*-tolyl-7*H*-9-thia-1,5,6,7-tetraaza-fluorene-8-one (18b). The reaction was carried out by the method described above using 3-amino-5-benzoyl-4-methyl-thieno[2,3-*b*]pyridine-2-carboxylic acid *p*-tolylamide (16b) (0.40 g, 1 mmol) instead of (16a). The reaction was worked up as usual, and the solid obtained (0.28g, 69.83%) as gray, m.p. 265-267°C (EtOH), ir: C=O 1675 cm⁻¹. *Anal.* Calcd. for

C₂₃H₁₆N₄O₂S, C, 66.98; H, 3.91; N, 13.58. Found, C, 66.7; H, 3.8; N, 13.4.

3-(Hydrazono-phenyl-methyl)-2-methyl-1*H*-pyrazolo[3,4-*h*][1,6]-naphthyridine-5,9-diamine (19a). A mixture of pyridine (11c) (2.86 g, 10 mmol), and hydrazine hydrate (1.5mL) in ethanol (30 mL) was heated under reflux for 2 h. The solvent was evaporated and the residue was recrystallized from ethanol to give 3-(hydrazono-phenyl-methyl)-2-methyl-1*H*-pyrazolo[3,4-*h*][1,6]naphthyridine-5,9-diamine (19a), (2.13 g, 64.16%) as brown crystals, m.p. 260-262°C (DMF/EtOH), ir: NH, NH₂ 3443, 3326, 3208 cm⁻¹, ¹H nmr (DMSO-*d*₆) δ 2.49 (s, 3H, CH₃), 2.92 (s, 2H, exch., NH₂), 5.48 (s, 2H, exch., NH₂), 6.58 (s, 2H, exch., NH₂), 7.55-7.95 (m, 5H, phenyl protons), 8.22 (s, 1H, ring-H), 11.64 ppm (br., 1H, exch., NH), ms: m/z 332 (M⁺). *Anal.* Calcd. for C₁₇H₁₆N₈, C, 61.43; H, 4.85; N, 33.71. Found, C, 61.2; H, 4.7; N, 33.5.

9-Imino-2-methyl-8-phenyl-3-[phenyl-(phenylhydrazono)-methyl]-8,9-dihydro-1*H*-pyrazolo[3,4-*h*][1,6]naphthyridine-5-ylamine (19b). A mixture of pyridine (11c) (2.86 g, 10 mmol), and phenylhydrazine (2.5mL) in ethanol (30 mL) was heated under reflux for 2 h. The solvent was evaporated and the residue was recrystallized from ethanol to give 9-imino-2-methyl-8-phenyl-3-[phenyl-(phenylhydrazono)-methyl]-8,9-dihydro-1*H*-pyrazolo[3,4-*h*][1,6]naphthyridin-5-ylamine in yield (19b) (2.54g, 52.48%) as gray crystals, m.p. 296-298°C (DMF/EtOH), ir: NH, NH₂ 3430, 3330, 3245 cm⁻¹, ¹H nmr(DMSO-*d*₆) δ 2.09 (s, 3H, CH₃), 3.37 (br., 2H, exch., NH₂), 6.36 (br., 1H, exch., NH), 6.65-7.32 (m, 17H, phenyl protons + 2NH), and 7.64 ppm (s, 1H, ring-H), ms: m/z 484 (M⁺). *Anal.* Calcd. for C₂₉H₂₄N₈, C, 71.88; H, 4.99; N, 23.12. Found, C, 71.6; H, 4.8; N, 22.9.

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