



SYNTHESIS AND SPECTRAL STUDIES OF NOVEL PYRIDINE, PYRIDO[2,3-d]PYRIMIDINE AND PYRIDO[2,3-d]-3,1- OXAZINE DERIVATIVES

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Several novel pyridine, pyrido[2,3-d]pyrimidine and pyrido[2,3-d] 3,1-oxazine derivatives were prepared using the readily obtainable starting material 2-amino-6-aryl-4-(3,4,5-trimethoxyphenyl) pyridine-3-carbonitrile **1a,b** via the reaction with one carbon donors such as phenylisothiocyanate, carbon disulphide and formic acid. The IR, ¹H-NMR and mass spectra for the new synthesized compounds were discussed.

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Introduction

Within the framework of our research program¹⁻⁶ concerning the utility of activated nitriles, we turned our interest to 2-amino-4,6-diaryl pyridine-3-carbonitrile **1** as an example for heterocyclic compounds whose structure represents β-enaminonitrile incorporated with heterocyclic ring.

It has been reported a series of publications reflecting the importance and synthetic applications of aminonitriles bearing various heterocyclic nuclei.⁷⁻¹¹ Among those reports, there has been found different investigation concerning 2-amino-3-cyanofurans^{12,13} and pyrroles.¹⁴ On the other hand, few reports dealing with similar two bifunctional pyridines were submitted.¹⁵

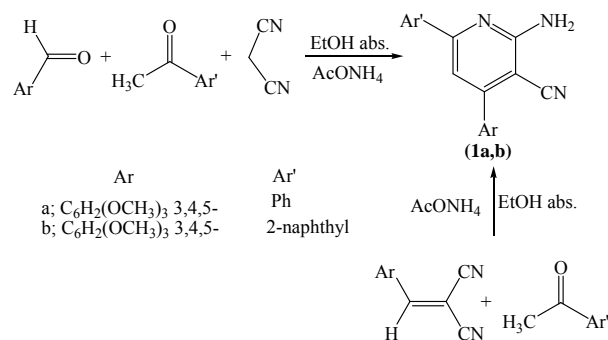
Results and Discussions

The titled compounds **1a, b** were successfully prepared by the following two attractive synthetic strategies. First, by the application of the reported one pot methodology used for the preparation of 2-aminopyridine-3-carbonitriles.¹⁶ Thus a mixture of equimolar amounts of 3,4,5-trimethoxybenzaldehyde, acetophenone (2-acetylnaphthalene), malononitrile and ammonium acetate in absolute ethanol was heated under reflux for 2 hrs. Second, by refluxing the arylidenemalononitrile, namely, 3,4,5-trimethoxybenzylidenemalononitrile with the coreactant ketone and ammonium acetate on molar ratios in absolute ethanol. The reaction readily proceeded to afford in each case an excellent yield of pyridine derivatives **1a, b**. (Scheme 1)

The structure of the products obtained was inferred from microanalytical and spectral data. Thus, the IR spectra of both compound showed two sharp absorption frequencies at 3496 and 3372 cm⁻¹ standing for the –NH₂ group absorption,

in addition to the vibrational frequency at 2207 cm⁻¹ indicating the presence of nitrile functionality.

Furthermore, the ¹H-NMR spectrum of compound **1a** in DMSO-d₆ exhibited signals from low to high field which were in agreement with the concerned structure. The aromatic protons of 6-substituted phenyl moiety displayed two multiplets at δ 8.8-8.40 ppm and 7.48-7.46 ppm integrating to two and three protons, respectively. However, the absorption singlet exhibited at δ 7.3 ppm integrating to one proton refers to the aromatic hydrogen located at C-5. Two magnetically equivalent protons at 2' and 6' positions of trimethoxyphenyl moiety displayed a singlet at δ 6.97 ppm. The amino group protons showed a singlet at δ 6.92 ppm (exch. in D₂O).

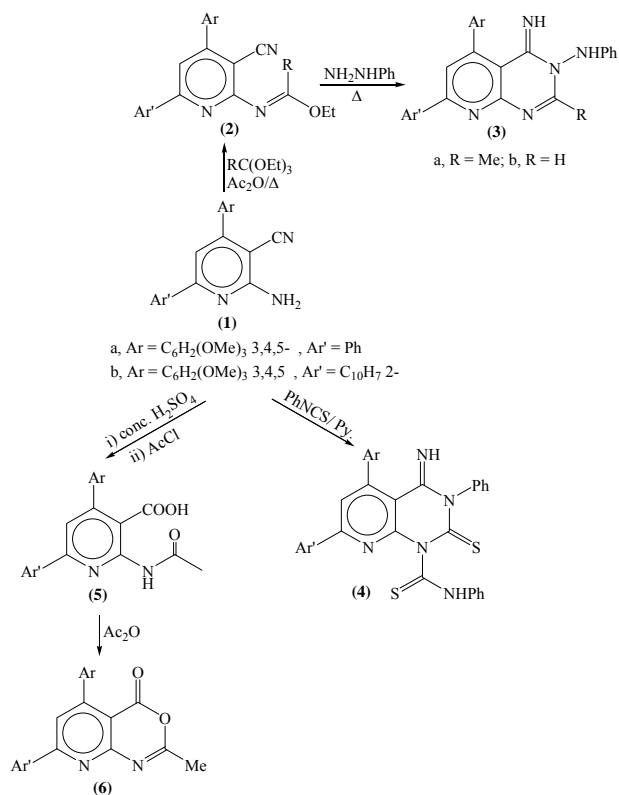


Scheme 1

Moreover, the 3,4,5-trimethoxy groups showed two singlets at δ 3.84 and 3.72 ppm, integrating to six and three protons of two magnetically equivalent –OCH₃ groups at 3'- and 5'- positions, while the latter corresponding to that one located at position 4'. Furthermore, structures **1a** and **1b** received a satisfactory support from the study of their mass spectra which were in full agreement with their assigned structure (c.f. Exp.).

It has been reported that the amino group bearing a heterocyclic ring readily reacts with triethylorthoformate or acetate to afford the corresponding ethoxyimine

derivatives.¹⁷ Thus, when conducting compound **1a** with triethylorthoacetate and/or compound **1b** with triethylorthoformate in refluxing acetic anhydride for 6 hrs. resulted in the formation of 4,6-diethoxymethyleneaminopyridine-3-carbo-nitriles **2a,b** in moderate yields. (Scheme 2)

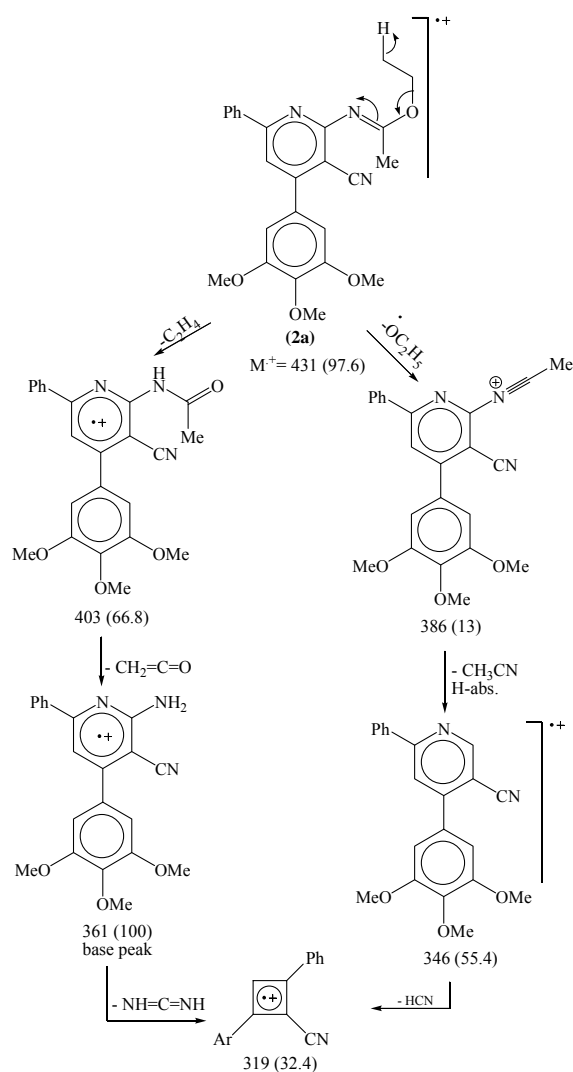


Scheme 2

The structure of products **2a,b** was inferred from microanalytical and spectral data. Thus, they lacked the coupling absorption bands characteristic to the –NH₂ group and acclaimed only the appearance of absorption frequencies of the nitrile and imino –C=N groups at 2209 cm⁻¹ and 1626 cm⁻¹.

Moreover, the structural features of both compounds **2a,b** received further support by a study of their mass spectra.

Furthermore, the mass spectrum of **2b** show a fragmentation pattern which very close to **2a** with the correct molecular ion at *m/z* = 467 (100%) which is the base peak (c.f. Exp.). Because of the presence of two almost similar electrophilic sites, the nitrile and its orthoethoxyisnitrile functionalities, it would be suitable to attempt its condensation with binucleophilic centers reagent e.g., phenylhydrazine. Thus, compounds **2a,b** were allowed to react with the latter reagent in refluxing ethanol for two hrs. It was proposed that the reaction proceeded via nucleophilic addition on the ethoxyisnitrile group followed by cyclization on the nitrile functionality to afford 5,7-diaryl-3-phenylamino-4-iminopyrido-[2,3-d](3H)pyrimidine derivatives **3a,b** in good yields. (Scheme 2)

Figure 1. EI fragmentation pattern of compound **2a**

The ¹H-NMR spectrum of compound **3a** in DMSO-*d*₆ clearly showed the absorption signals corresponding to each proton type in the assigned structure. Thus, the imino –NH proton displayed a singlet at δ 9.11 ppm integrating to one proton, however, the aromatic proton exhibited three multiplets in the range of δ 8.04-6.6 ppm integrating all thirteen protons, along with the anilino –NH proton appeared as abroad signal at δ 5.034 ppm. The trimethoxy group protons showed their absorption signal as two singlets at δ 4.03 ppm and 3.97 ppm integrating for six and three protons, respectively. In addition the two methyl proton type displayed a singlet at δ 2.30 ppm.

Moreover, the mass fragmentation pattern of compound **3b** presented a satisfactory support which was in full accordance with the proposed structure. It showed the fragment 529 (14.96%) corresponding to the parent peak.

When we devoted our efforts to the reactions **1a,b** with bifunctional reagents we thought that its treatment with phenyl isothiocyanate in refluxing pyridine would occur via initial attack of amino group followed by cyclization leading to addition of one molecule of the reagent.

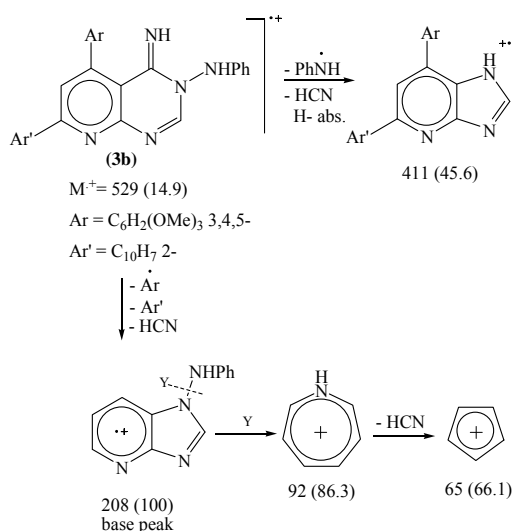


Figure 2. EI- fragmentation pattern of **3b**

By the study of their mass spectra it has been found that the molecular weight determination indicated the incorporation of two molecules of phenyl isothiocyanate in the formation of reaction product. It was proposed that the reaction involved the formation of 7-aryl-4-imino-3-phenyl-1-(N-phenylthiocarbox-amido)-5-(3,4,5-trimethoxyphenyl)-pyrido[2,3-d] pyrimidin-2-thione **4a,b**.

Examination of 1H -NMR spectrum of **4b** in DMSO- d_6 revealed two singlets, the former at δ 9.57 ppm integrating for one proton attributable to the exocyclic imino C=NH proton and the latter at δ 8.3 ppm stands for the thiocarboxamide proton absorption. The aromatic protons displayed signals in the range of δ 8.09-6.96 ppm, integrating totally for 20 protons of five aromatic rings existing in the concerned structure. Moreover, the three methoxy group protons located at 3', 4' and 5'-positions of the 5-substituted phenyl rings showed two singlets integrating to nine protons at δ 3.81 ppm and 3.78 ppm. The mass spectra of **4a** and **4b** were completely in accord with the proposed structures (C.F. Fig. 3,4).

Fused oxazinones are among the most important heterocycles which are required as synthons and their wide scope of biological activity.¹⁸⁻²⁵ Thus, the author intended to synthesize pyrido[2,3-d][3,1]oxazinone derivative **6** via two steps reaction involving hydrolysis of **1b** with the aid of concentrated sulphuric acid followed by refluxing in acetyl chloride to give 2-acetamidonicotinic acid derivative **5** which underwent cyclodehydration by treatment with acetic anhydride to afford 2-methyl-7-(2-naphthyl)-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-d][3,1]oxazin-4-one **6** in a moderate yield (Scheme 2).

The structure of the acetamidonicotinic acid derivative **5** was proven by solubility in aqueous sodium carbonate solution and its IR spectrum showed two broad vibrational bands at 3405 cm^{-1} and 3227 cm^{-1} attributable to the open amide -NH group and the carboxylic functionality existing in H-bonding that causes broadening of their absorption frequencies. Two strong absorption bands appeared at 1705 and 1662 cm^{-1} referring to the presence of carbonyl functionalities of both the carboxy and the open amide groups, respectively.

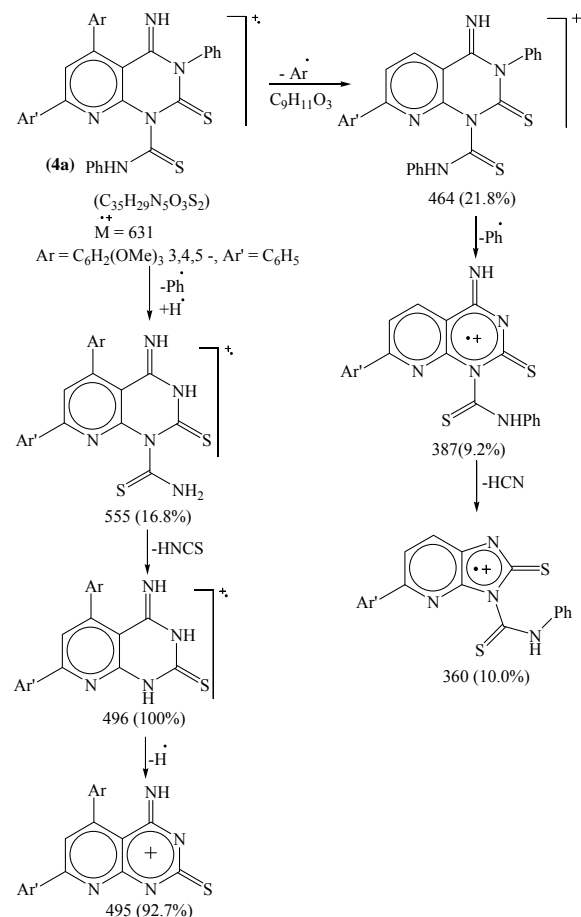


Figure 3. EI fragmentation pattern of compound **4a**

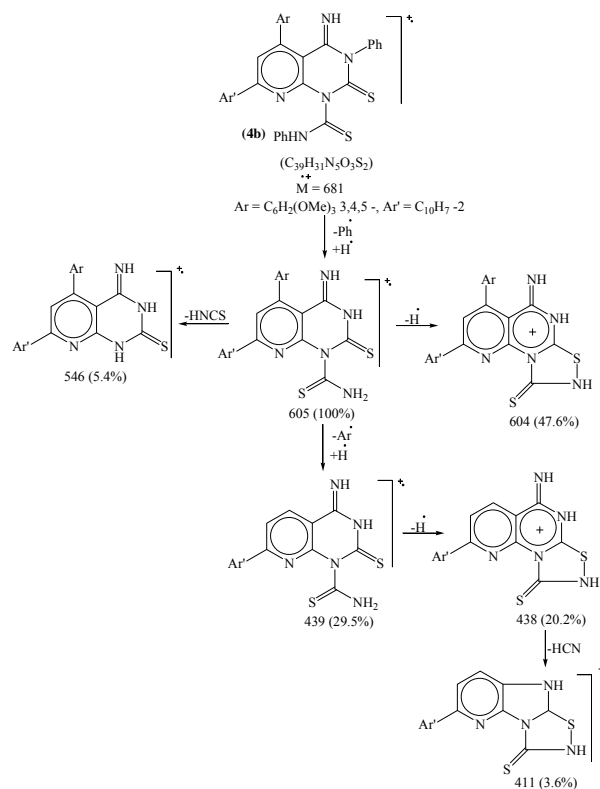


Figure 4. EI fragmentation pattern of compound **4b**

On the other hand, the structure of the product **6** was established from microanalytical and spectral data. Thus, its IR spectrum showed the lack of absorption bands of the amide –NH and acidic –OH groups that refers to their involvement in the cyclization process. The 6 μ m region revealed a stretching absorption frequency of 6-membered lactone at 1767 cm⁻¹ with the band appearing at 1663 cm⁻¹ which indicated the existence of C=N.

¹H-NMR of compound **6** in DMSO-d₆ show from low to high field signals characteristic for aromatic protons at δ ppm 8.1-7.5 (m, 10H), two singlet at δ 4.0, 3.8 ppm for the three methoxy protons in the ratio 6:3 and singlet at δ 2.3 for the three methyl protons.

Moreover, a full support of the proposed structure was provided by quantitative investigation of its mass fragmentation pattern (Fig. 5).

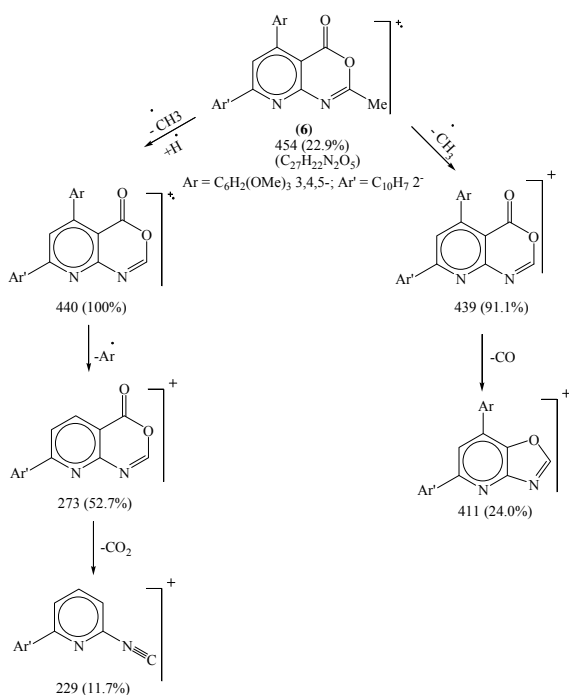
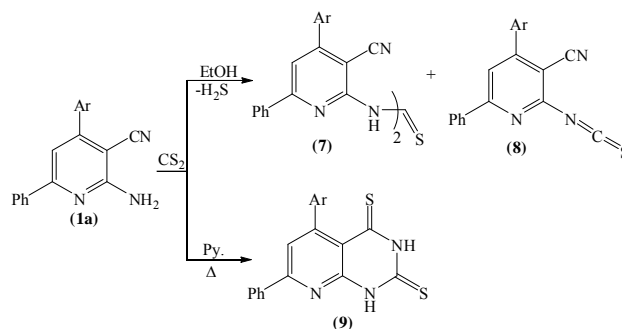


Figure 5. EI fragmentation of compound **6**

It has been reported that heterocyclic o-amino carbonitriles including furans, pyrimidines and quinazolines^{26,27} reacted with carbon disulphide under different reaction conditions to afford biologically interesting fused thiazines and/or pyrimidinedithione. However, when compound **1a** was treated with the reagent in ethanolic solution of KOH at refluxing temperature for 6hrs. The reaction fails to give the fused pyridine compound. Instead a semisolid product was separated out (two spots in TLC) and subjected to fractional crystallization, none of these products could be isolated in a pure state. Meanwhile, it was possible to detect in the crude reaction mixture by GC-MS technique two different compounds. The EI fragmentation pattern of one of them is completely in accord with N,N'-bis[4-aryl-3-cyano-6-phenyl pyridine-2-yl]thiourea **7** and the second showed completely different pattern whose highest m/z (relative intensity) peak is recorded at 403 (45.6) which is attributable to the isothiocyanate derivative **8** (Scheme 3). Tentative fragmentation which are in a good compatible with the proposed structures.



Scheme 3

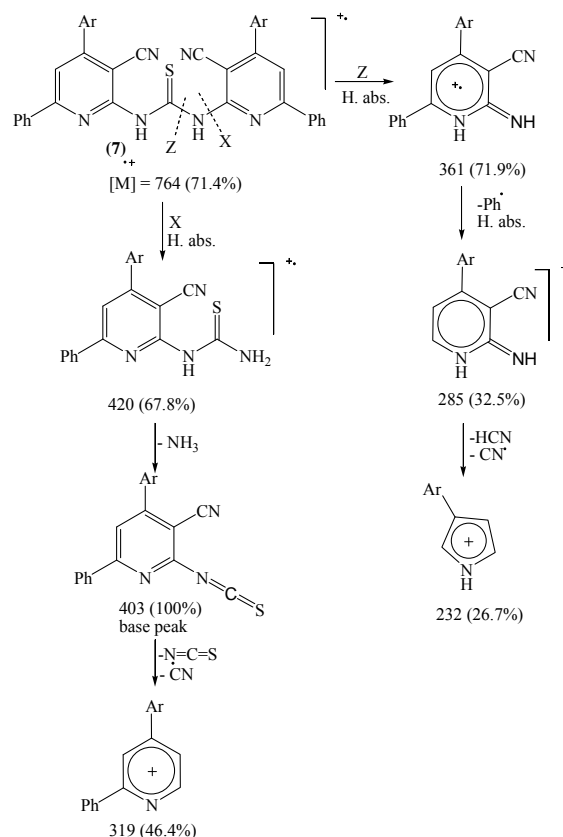
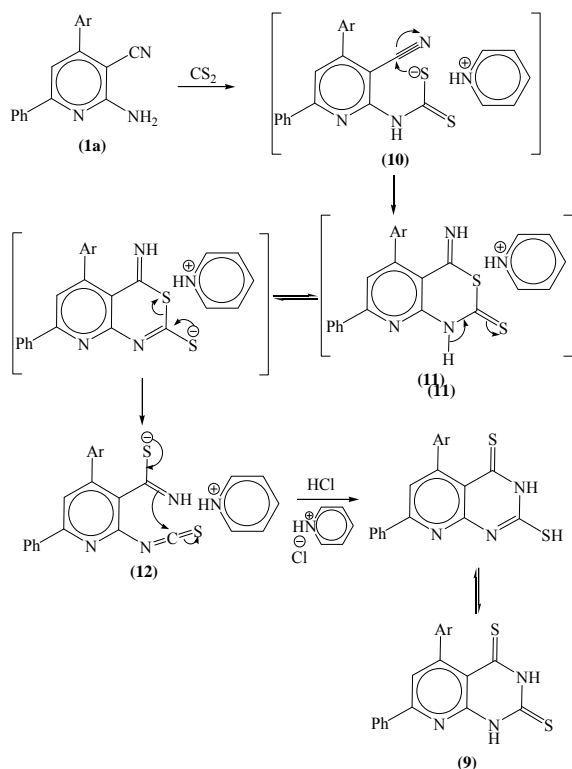


Figure 6. The main fragmentation pattern for **7**

Moreover, the highest recorded peak in the mass spectrum of **8** at m/z = 403 (45.6) represent the correct molecular ion peak which upon loss of methyl and cyanide radical afforded the radical cation at m/z = 362(100%) which represent the base peak.(c.f. Exp.).

By repeating the above reaction in pyridine under the same previous reaction conditions resulted in the formation of fused compound **9** whose structure was described as 5-aryl-7-phenylpyrido[2,3-d]pyrimidine-2,4-(1H,3H) dithione (Scheme 3). Now, it is postulated that the utility of pyridine is responsible for the existence of thiocarbamate intermediate **10** which in turn attacks the nitrile group to give the pyrimidine salt of 2-thio-1,3-thiazine derivative **11** which undergo rearrangement to the isothiocyanate derivative²⁸ **12** which underwent cyclization to give pyrido pyrimidine dithione derivative **9** (Scheme 4).

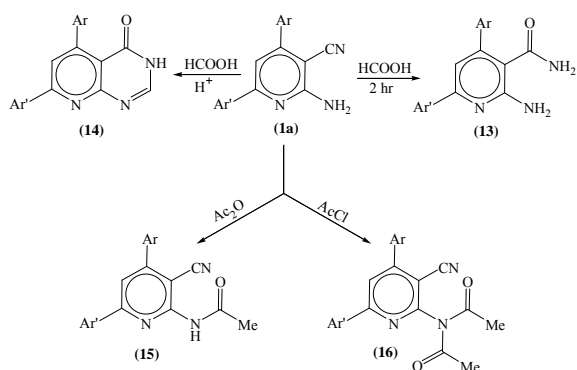


Scheme 4

The structure **9** was substantiated from the analytical and spectroscopic data. Moreover, its mass fragmentation pattern was in full harmony with the assigned structure. (c.f. Exp.).

Recently, there has been found a number of publications^{29,30} reported that the formation of fused pyrimidinones via condensation of variety of substituted 2-aminobenzonitriles and/or 2-aminopyrrolonitriles with formic acid is either an acid catalyzed or time dependent reaction.

We were able in our lab to obtain the intermediate substituted 2-aminopyridine-3-carboxamide derivative **13** by refluxing **1a** with formic acid in water bath for 2 hr. in absence of acid catalysis. Whereas, the reaction of **1a** with formic acid in the presence of concentrated sulphuric acid as acatalyst, afforded the cyclized product 5-aryl-7-phenylpyrido[2,3-d]pyrimidine-4(3H)one **14** in good yield (Scheme 5).



Scheme 5

The structure of pyridopyrimidinone **14** was proven on the basis of microanalytical and spectral data. Thus, their IR spectra revealed a broad band in the $3 \mu\text{m}$ region standing for stretching vibration of $\nu_{\text{NH,OH}}$, of the cyclic amide group. In addition, the $6 \mu\text{m}$ region exhibited the carbonyl vibrational band at 1680 cm^{-1} and/or 1659 cm^{-1} of cyclic 6-membered lactam ring.

Furthermore, the assigned structure of compound **14** received satisfactory support by the study of its mass fragmentation pattern which showed the correct molecular ion peak at 389 (45.7%).

The $^1\text{H-NMR}$ spectra of compound **14** in DMSO-d_6 revealed to doublets at $\delta 8.14 \text{ ppm}$ standing for the ring $-\text{NH}$ proton. However, the pyridyl H-2 proton displayed a singlet at $\delta 7.33 \text{ ppm}$ along with the phenyl group protons absorption shown as multiplet at $\delta 7.49 \text{ ppm}$ integrating to five protons, a singlet at $\delta 7.1 \text{ ppm}$ integrated for one proton (C6-H). The two protons at m-positions of 5-substituted 3,4,5-trimethoxyphenyl ring exhibited a singlet at $\delta 6.88 \text{ ppm}$, meanwhile the three methoxy group of the same ring displayed their absorption signals as two singlets at $\delta 3.84 \text{ ppm}$, and 3.75 ppm integrating for six and three protons located at 3'- and 5'- positions along with those substituted at 4'-position.

One of the historical beneficial roles of the amino group in organic chemistry is its susceptibility to be acylated upon treatment with various number of acylating agents, in easy going reactions. Of these reactions, the concerned compound **1a** was treated with acetyl chloride and/or acetic anhydride at the reflux temperature of the reagent. The reaction readily occurred via nucleophilic addition of the amino group on electronically deficient carbonyl carbon atom of the acetyl segment that led finally to the formation of monoacetyl derivative **15** in the first case and the diacetyl derivative **16** in the latter one (Scheme 5). The IR spectrum of **15** displayed ν_{NH} (sharp) at 3347 cm^{-1} , ν_{CN} at 2220 cm^{-1} and $\nu_{\text{CO(amide)}}$ at 1658 cm^{-1} . On the other hand, the latter product **16** exhibited vibrational coupling bands for a carbonyl groups at 1730 and 1700 cm^{-1} and show the absence of absorption bands for NH group.

Moreover, the $^1\text{H-NMR}$ spectrum of compound **16** in CDCl_3 displayed a singlet at $\delta 2.42 \text{ ppm}$ integrating to six protons indicates the presence of two symmetrical acetyl groups.

On the other hand, compound **16** received further support to its structure assignment from the study of its mass spectrum whose fragmentation pattern was in full agreement with the proposed structure.(c.f. Exp.)

Experimental

All melting points were taken on Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP1200 spectrophotometer using KBr Wafer technique. $^1\text{H-NMR}$ spectra were determined on a Varian Gemini 200 MHz, Bruker AC-200 MHz using TMS as internal standard (chemical shifts in δ -scale). EI-MS were measured on a Shimadzu-GC-MS instrument operating at 70 eV. Microanalysis measurements were carried out at Ain Shams University laboratory and satisfactory analytical data (± 0.4) were obtained for all compounds. $^1\text{H-NMR}$ spectra and EI-MS were run at Cairo University labs.

Condensation of 3,4,5-trimethoxybenzaldehyde, acetophenone, malononitrile and ammonium acetate; Formation of 2-amino-6-phenyl-4-(3,4,5-trimethoxy-phenyl)pyridine-3-carbonitrile (1a)

A mixture of malononitrile (0.66 g; 0.01 mol), acetophenone (1.2 g; 0.01 mol), 3,4,5-trimethoxybenzaldehyde (1.96 g; 0.01 mol) and ammonium acetate (1.15 g; 0.015 mol) in dry benzene (50 ml) was heated under reflux using water separator for 4 hrs, cooled and the crude solid was triturated with ethanol. The solid product so formed was collected by filtration, dried and recrystallized from ethanol giving **1a** as yellow crystals, 2.8 g (78%), mp 161-163°C, ir: NH₂ 3496, 3372, C≡N 2207, C=N 1630 cm⁻¹. ¹H nmr (DMSO-d₆) δ 8.8-7.4 (m, 5H_{arom.}), 7.3 (s, 1H, C₅-H), 6.97 (s, 2H_{arom.}), 6.9 (br.s, 2H, NH₂, exchangeable with D₂O), 3.84 (s, 6H, 2OMe), 3.72 (s, 3H, OMe). ms: m/z: 362 (M+1, 100), 347 (43), 319 (24.2), 286 (13.6), 234 (16.2). Anal. Calcd. for C₂₁H₁₉N₃O₃ (361): C, 69.8; H, 5.26; N, 11.63. Found: C, 69.73; H, 5.42; N, 11.46.

Condensation of 3,4,5-trimethoxybenzaldehyde, 2-acetylnaphthalene, malononitrile and ammonium acetate; Formation of 2-amino-6-(2-naphthyl)-4-(3,4,5-trimethoxyphenyl) pyridine-3-carbonitrile (1b)

A mixture of malononitrile (0.66 g; 0.01 mol), 2-acetylnaphthalene (1.7 g; 0.01 mol), 3,4,5-trimethoxybenzaldehyde (1.96 g; 0.01 mol) and ammonium acetate (1.15 g; 0.015 mol) in dry benzene (50 ml) was heated under reflux using water separator for 4 hrs, cooled and triturated with ethanol. The solid product so formed was collected by filtration, dried and recrystallized from ethanol giving **1b** as yellow crystals, 3.5 g (87%), mp 173-175°C, ir: NH₂ 3476, 3296, C≡N 2207, C=N 1642 cm⁻¹. ms: m/z: 412 (M+1, 100), 397 (19), 381 (12), 286 (13.6), 288 (12), 244 (13.3). Anal. Calcd. for C₂₅H₂₁N₃O₃ (411): C, 72.99; H, 5.1; N, 10.21. Found: C, 73.09; H, 5.32; N, 10.0.

Reaction of 1a with triethylorthoacetate; Formation of 2-ethoxyethylenamino- 6-phenyl-4-(3,4,5-trimethoxyphenyl)-pyridine-3-carbonitrile (2a)

A mixture of compound **1a** (3.61 g; 0.01 mol), triethylorthoacetate (5 ml) in freshly distilled acetic anhydride (5 ml) refluxed for 5 hrs. The solvent was removed under reduced pressure and the resulted solid was triturated with ether and recrystallized from ethanol giving **2a** as glassy yellow crystals, 2.28 g (53%), mp 158-160°C, ir: C≡N 2209 cm⁻¹. ms: m/z: 431 (M⁺, 97.6), 403 (66.8), 386 (13), 373 (30), 361 (100), 346 (55.4), 319 (32.4). Anal. Calcd. for C₂₅H₂₅N₃O₄ (431): C, 69.6; H, 5.8; N, 9.74. Found: C, 69.92; H, 5.66; N, 9.72.

Synthesis of 2-ethoxymethylenamino- 6-(2-naphthyl)-4-(3,4,5-trimethoxy-phenyl) pyridine-3-carbonitrile (2b)

A mixture of compound **1b** (4.11 g; 0.01 mol), triethylorthoacetate (10 ml) in acetic anhydride (5 ml) was refluxed for 5 hrs. The solvent was removed under reduced pressure and the resulted solid was triturated with ether and recrystallized from ethanol giving **2b** as buff crystals, 2.8 g

(61%), mp 143-145°C, ir: C≡N 2207 cm⁻¹. ms: m/z: 467 (M⁺, 100), 340 (M-C₁₀H₇, 22.8), 300 (M-Ar, 70.3), 421 (7.6), 395 (46.2), 167 (32.6), 77 (18.9). Anal. Calcd. for C₂₈H₂₅N₃O₄ (467): C, 71.94; H, 5.35; N, 8.99. Found: C, 72.08; H, 5.3; N, 8.73.

Reaction of 2 with phenyl hydrazine; Formation of 2-methyl-7-aryl-5-(3,4,5-trimethoxyphenyl)-3-phenylamino-4-imino-pyrido[2,3-d](3H)pyrimidine (3a) and (3b)

A mixture of compound **2** (0.01 mol) and phenyl hydrazine in ethanol (20 ml) was heated under reflux for 8 hrs. The reaction mixture was left to cool, poured into dilute hydrochloric acid; the solid product so formed was filtered off, dried and recrystallized from methanol giving **3a** as light brown crystals, 2.8 g (58%), mp 197 °C decomp., ir: NH 3383, C=N 1661 cm⁻¹. ¹H nmr (DMSO-d₆) δ 9.11 (s, 1H, =NH), 8.04-7.5 (m, 10H_{arom.}), 7.1 (s, 1H, C₆-H), 6.66 (s, 2H_{arom.}), 5.03 (br.s, 1H, NH, exchangeable with D₂O), 4.03 (s, 6H, 2OMe), 3.9 (s, 3H, OMe), 2.3 (s, 3H, Me). ms: m/z: 493 (M⁺, 100), 479 (22.8), 402 (70.3), 319 (44.8), 92 (83.6), 65 (33.6). Anal. Calcd. for C₂₉H₂₇N₅O₃ (493): C, 70.58; H, 5.47; N, 14.19. Found: C, 70.68; H, 5.34; N, 13.89.

3b: crystallized from dioxane to give buff crystals, 2.4 g (46%), mp 206-208°C, ir: NH 3376, C=N 1652 cm⁻¹. ms: m/z: 529 (M⁺, 4.9), 487 (17.8), 411 (45.6), 396 (15.5), 380 (8.1), 351 (14), 224 (12.6), 208 (100), 93 (33.6), 77 (44.1). Anal. Calcd. for C₃₂H₂₇N₅O₃ (529): C, 72.58; H, 5.10; N, 13.23. Found: C, 72.73; H, 5.0; N, 13.09.

Reaction of 1a,b with phenyl isothiocyanate; Formation of 7-aryl-4-imino-3-phenyl-1-[N-phenylthiocarboxamido]-5-(3,4,5-trimethoxy phenyl)pyrido[2,3-d]pyrimidine-2-thione (4a,b)

A mixture of compound **1a** (3.61 g; 0.01 mol) or **1b** (4.1 g; 0.01 mol) and excess phenyl isothiocyanate in pyridine (20 ml) was refluxed for 6 hrs. The reaction mixture was left to cool, acidified with dilute hydrochloric acid; the solid product so formed was filtered off, dried and recrystallized from the proper solvent to give **4a** and **4b**, respectively.

3,7-Diphenyl-5-(3,4,5-trimethoxyphenyl)-1-[N-phenylthiocarboxamido]-pyrido[2,3-d]pyrimidine-2-thione (4a)

Recrystallized from benzene as yellow crystals, 5.1 g (92%), mp 280-282°C, ir: NH 3357, 3376, C=N 1631, C=S 1259 cm⁻¹. ¹H nmr (DMSO-d₆) δ : 9.57 (s, 1H, =NH), 8.3 (s, 1H, NH), 8.09-6.96 (m, 15H_{arom.}), 7.2 (s, 1H, C₆-H), 6.7 (s, 2H_{arom.}), 3.81 (s, 6H, 2OMe), 3.78 (s, 3H, OMe). ms: m/z: 555 (M-Ph, 16.8), 497 (94.2), 496 (100), 466 (42.2), 387 (9.2), 360 (10). Anal. Calcd. for C₃₅H₂₉N₅O₃S₂ (631): C, 66.56; H, 4.59; N, 11.09; S, 10.14. Found: C, 66.91; H, 4.32; N, 10.88; S, 10.0.

7-(2-Naphthyl)-3-phenyl-5-(3,4,5-trimethoxyphenyl)-1-[N-phenylthio-carboxamido]pyrido[2,3-d]pyrimidine-2-thione (4b)

Recrystallized from benzene as greenish-yellow crystals, 5.9 g (87%), mp 236-238°C, ir: NH 3386, 3346, C=N 1644, C=S 1287 cm⁻¹. ms: m/z: 605 (M-Ph, 100), 546 (5.4), 439 (29.5), 411 (3.6), 304 (15.7), 135 (60.3), 92 (30.2), 65 (22.8).

Anal. Calcd. for $C_{39}H_{31}N_5O_3S_2$ (681): C, 68.72; H, 4.55; N, 10.27; S, 9.39. Found: C, 68.61; H, 4.4; N, 10.0; S, 9.23.

Formation of 2-acetylamino-6-(2-naphthyl)-4-(3,4,5-trimethoxyphenyl)pyridine-3-carboxylic acid (5)

A mixture of **1b** (4.11 g; 0.01 mol) in concentrated sulphuric acid (5 ml) was heated for 2 hrs, left to cool, neutralized by 5N sodium hydroxide solution and filtered. The clear filtrate was then acidified depositing an orange solid which was filtered off, dried then dissolved in acetyl chloride (5ml), refluxed for only 1 hr, left to cool, and poured into ice water. The separated solid was collected by filtration and dissolved in aqueous solution of sodium bicarbonate, filtered and the alkaline filtrate then acidified with dilute acetic acid. The deposited solid was filtered off, dried and recrystallized from methanol to give **5** as yellow crystals, 2.1 g (46%), mp 214-216°C, ir: NH 3405, 3227, CO acid 1705, CO amide 1662 cm^{-1} . ms: m/z: 472 (M^+ , 33.4), 454 (M-H₂O, 30.1), 430 (M-CH₂=C=O, 27.6), 384 (60.3), 181 (12.8). Anal. Calcd. for $C_{27}H_{24}N_2O_6$ (472): C, 68.64; H, 5.08; N, 5.93. Found: C, 68.83; H, 4.8; N, 5.77.

Synthesis of 2-methyl-7-(2-naphthyl)-5-(3,4,5-trimethoxyphenyl) pyrido [2,3-d]3,1-oxazin-one (6)

A solution of compound **5** (1 g) in freshly distilled acetic anhydride (5 ml) was heated under reflux for one hour, then left to cool and poured into ice water with stirring. The separated solid was collected by filtration, dried and recrystallized from light petroleum ether (b.p. 100-120°C) to give **6** as orange crystals, 2.08 g (46%), mp 98°C (decomp.), ir: CO oxazinone 1767, C=N 1663 cm^{-1} . ¹H nmr (DMSO-d₆) δ: 8.1-7.5 (m, 7H_{arom.}), 7.1 (s, 1H, C₆-H), 6.7 (s, 2H_{arom.}), 4.0 (s, 6H, 2OMe), 3.8 (s, 3H, OMe), 2.3 (s, 3H, C₂-Me). ms :m/z: 454 (22.9), 440 (M-Me, 100), 410 (12.4), 411 (24.0), 312 (11.9), 273 (52.7), 229 (11.7). Anal. Calcd. for $C_{27}H_{22}N_2O_5$ (454): C, 71.36; H, 4.84; N, 6.16. Found: C, 71.61; H, 4.9; N, 5.86.

Reaction of 1a with CS₂ / KOH; Formation of N,N-bis[4-aryl-3-cyano-6-phenylpyridin-2-yl]thiourea (7) & isothiocyanate derivative (8)

A mixture of compound **1a** (3.61 g; 0.01 mol), carbon disulphide (5 ml) in ethanolic KOH solution (20 ml) was refluxed for 5 hrs. The excess ethanol was evaporated, then reaction mixture was left to cool, acidified with dilute hydrochloric acid giving a semisolid paste which was triturated with ether, recrystallized by DMF to afford a non isolable mixture of two compounds which were identified by GC-MS as **7** and **8**.

Reaction of 1a with CS₂ / pyridine; Formation of 7-phenyl-5-(3,4,5-trimethoxyphenyl)-1H,3H-pyrido[2,3-d]pyrimidin-2,4-dithione (9)

A mixture of compound **1a** (3.61 g; 0.01 mol), carbon disulphide (10 ml) in pyridine (20 ml) was refluxed for 6 hrs. The reaction mixture was left to cool, acidified with dilute hydrochloric acid. The solid product so formed was filtered off, dried and recrystallized from acetic acid giving **9** as buff

crystals, 2.6 g (61%) mp 164-166°C, ir: NH 3424, 3329, C=S 1241 cm^{-1} . ms :m/z: 437 (M^+ , 17.6), 422 (M-Me, 100), 406 (M-OMe, 44.2), 363 (36.2), 348 (22.7), 319 (16.1), 182 (80.7). Anal. Calcd. for $C_{22}H_{19}N_3O_3S_2$ (437): C, 60.41; H, 4.34; N, 9.61; S, 14.64. Found: C, 60.78; H, 4.18; N, 9.37; S, 14.33.

Reaction of 1a with formic acid i) in absence of catalyst; Formation of 2-amino-3-carboxamide-6-phenyl-4-(3,4,5-trimethoxyphenyl)pyridine (13)

A solution of **1a** (3.61 g, 0.01 mol) in formic acid (10 ml) was refluxed for 2 hrs, cooled, diluted with cold water. The solid product so formed was then filtered off, washed with water, dried and recrystallized from DMF affording **13** as light brown crystals, 2.1 g (57%), mp 223-225°C, ir: NH₂ 3412, 3380, 3240, C=O amide 1659 cm^{-1} . ms: m/z: 379 (M, 78.1), 365 (70), 349 (33.1), 304 (22.8), 291 (20.2). Anal. Calcd. for $C_{21}H_{21}N_3O_4$ (379): C, 66.49; H, 5.54; N, 11.08. Found: C, 66.71; H, 5.32; N, 10.84.

ii) In presence of Conc. H₂SO₄; Formation of 7-phenyl-5-(3,4,5-trimethoxyphenyl)-3H-pyrido[2,3-d]pyrimidin-4(3H)one (14)

A solution of **1a** (3.61 g, 0.01 mol) in formic acid (10 ml) was refluxed in the presence of Conc. H₂SO₄ (1 ml) for 10 hrs. The reaction mixture was then cooled, neutralized by 1N NaOH. The solid product so formed was filtered off, washed with water, dried and recrystallized from DMF affording **14** as brown crystals, 1.59 g (41%); mp 211-213°C, ir: (br) NH₂OH 3271, C=O 1680 cm^{-1} . ¹H nmr (CDCl₃) δ: 8.14 (d, 1H, NH), 7.49 (m, 5H_{arom.}), 7.33 (s, 1H, C₂-H), 7.1 (s, 1H, C₆-H), 6.88 (s, 2H_{arom.}), 3.84 (s, 6H, 2OMe), 3.75 (s, 3H, OMe). ms :m/z: 389 (45.7), 388 (100), 374 (40.6), 357 (18.9), 299 (16). Anal. Calcd. for $C_{22}H_{19}N_3O_4$ (389): C, 67.86; H, 4.88; N, 10.79. Found: C, 67.67; H, 5.0; N, 10.66.

Formation of 2-acetylamino-6-phenyl-4-(3,4,5-trimethoxyphenyl)-pyridin-3-carbonitrile (15)

A mixture of compound **1a** (3.61 g, 0.01 mol) and acetyl chloride (10 ml) was heated on a water bath for one hour. The reaction mixture left to cool then poured drop wisely into ice-water with fast stirring. The solid formed was collected by filtration, washed several times with water, dried and recrystallized from chloroform affording **15** as yellow crystals, 3.38 g (84%), mp 218-220°C, ir: NH 3347, C≡N 2220, CO amide 1658 cm^{-1} . ms :m/z: 403 (100), 361 (90.3), 195 (21.7), 181 (16.2), 91 (30.3). Anal. Calcd. for $C_{23}H_{21}N_3O_4$ (403): C, 68.48; H, 5.21; N, 10.42. Found: C, 68.71; H, 5.0; N, 10.37.

Formation of 2-(N,N-diacetylamino)-6-phenyl-4-(3,4,5-trimethoxyphenyl)-pyridin-3-carbonitrile (16)

A mixture of compound **1a** (3.61 g, 0.01 mol) in freshly distilled acetic anhydride (10 ml) was refluxed for two hours, then left to cool, poured into ice cold water with stirring. The separated solid was filtered off, dried and recrystallized from light petroleum ether (b.p. 80-100°C) to give **16** as glassy pale brown crystals, 2.51 g (58%), mp 128-130°C, ir: CO coupling bands 1730, 1700 cm^{-1} . ¹H nmr (CDCl₃) δ:

8.10-8.05 (m, 5H_{arom.}), 7.01 (s, 1H, C5-H), 6.88 (s, 2H_{arom.}), 3.96 (s, 9H, 3OMe), 2.42 (s, 6H, 2MeCO). ms :m/z: 446 (M⁺+1, 70.1), 389 (100), 373 (82.6), 372 (82.5), 346 (22.6). Anal. Calcd. for C₂₅H₂₃N₃O₅ (445): C, 67.41; H, 5.16; N, 9.43. Found: C, 67.72; H, 5.0; N, 9.22.

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