SYNTHESIS OF NEW ISOLATED AND FUSED TRI-AND TETRACYCLIC PYRIDINE DERIVATIVES

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A number of functionalized pyridine derivatives in which the pyridine ring is linked to triazole, thiadiazole, thiazole, and tetrazole moieties were synthesized by cyclization with carbon disulfide, phenylisothiocyanate, and sodium azide. Benzylation of the synthesized tetrazolylmethylpyridone derivative afforded the N(1)-benzylated product; its crystal structure is reported. The substituted fused tetracyclic pyridofuropyrimidine was synthesized by sequential reactions starting from the 2-pyridone derivative.

Keywords: pyridine, tetrazole, thiazole, triazole, alkylation, cyclization, tetracyclic system.

The synthesis of functionalized heterocycles, as well as tri- and tetracyclic nitrogen-containing compounds, is one of the major objectives for various laboratories because of their interesting biological properties. Derivatives of pyridones occur as alkaloids and have been isolated from the leaves and bark of various trees; for example, nudifluorine, recinine, and piericidin A (Fig. 1) have been isolated from *Trewia nudiflora* L., Cator plant, and mycelia of *Streptomyces mobaraensis* [1, 2], respectively. 2-Pyridones are biologically interesting molecules, and their chemistry has received considerable attention. Natural products with this structure have emerged as potent antitumor and antiviral agents, and 2-pyridones have proved useful as intermolecular connectors between building blocks in material science [3-9].

Multisubstituted pyridine derivatives and fused pyridines occupy a central position in modern heterocyclic chemistry, particularly in the pharmaceutical and agrochemical fields [10-14]. Furthermore, it has been reported that certain compounds bearing the thiadiazole, tetrazole, thiazole, and triazole nucleus possess significant anti-inflammatory activity [15-17]. The functionalization of pyridone and pyrimidine rings with substituents such as cyano, amino, and hydroxy groups and halogen permits cyclization to fused bi-, tri-, or tetracyclic systems. In view of these observations, and in continuation of our previous work on the synthesis of 2-pyridone derivatives [18-21] and other functionalized heterocycles, we aim herein to synthesize new five-membered rings linked to 2-pyridone in addition to functionalized condensed tri- and tetracyclic pyridine ring systems.

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Fig. 1. Some natural derivatives of pyridones.

In the present investigation, the pyridone derivative 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1), synthesized by treatment of acetylacetone with cyanoacetamide [22], was alkylated with 2-chloroacetonitrile to give two alkylnitrile derivatives, O- and N-alkylnitriles 2 and 3, respectively. The O- and *N*-alkylated derivatives were separated by column chromatography to give pure compounds 2 and 3 in 34 and 49% yields, respectively. The ¹H NMR spectrum of the carbonitrile 2 showed that the methylene group was shifted downfield compared to that of N-alkyl derivative 3. The methylene group singlet appeared at 5.32 ppm for the O-alkylated product and at 5.14 ppm for the N-alkylated one. Also, the IR spectra confirmed the absence of the carbonyl group in the O-alkylated derivative, which appeared at 1654 cm⁻¹ in the N-alkylated product. Compound 2 was cyclized by treatment with sodium ethoxide in absolute ethanol, affording the furopyridine derivative 4. The structure of furopyridine 4 was proved by IR, ¹H NMR, and mass spectral data, which were in agreement with the assigned structure. Moreover, the signal of CH₂ protons was not seen in the ¹H NMR spectrum, proving that the methylene group was involved in the cyclization step through addition to the nitrile group. The N-alkylated derivative 3 reacted with phenylisothiocyanate in the presence of sulfur, according to a reported method [23], to give the thiazolylpyridine 5. The IR spectrum of compound 5 showed absorption bands at 3300-3430 (NH₂) and 1342 (C=S) cm⁻¹. Its ¹H NMR spectrum showed new signals at 4.52 ppm for the NH₂ group and at 7.15-7.57 ppm for the phenyl group.



On the other hand, the substituted pyridine 1 reacted with acrylonitrile in the presence of triethylamine, affording 1-(2-cyanoethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6) in 95% yield. The aminothiazole derivative 7 was synthesized by the reaction of nitrile 6 with PhNCS and sulfur under the same conditions used to synthesize compound 5. The ¹H NMR spectrum of thiazole 7 showed two singlets at 4.25 and 4.61 ppm for CH_2 and NH_2 protons, respectively.

The tetrazole derivative **8** was prepared by treatment of nitrile **3** with sodium azide in DMF in the presence of ammonium chloride. Concerning the intermolecular cycloaddition reaction of nitriles and azides, it was shown that in the case of using azide salts, they react with nitriles through an anionic two-step mechanism leading regioselectively to 1H-tetrazoles [24]. The formation of tetrazoles from nitriles and azides was investigated regarding the scope and reaction kinetics. In the formation of the tetrazole using azide and ammonium salts, the proton transferred to the nitrile nitrogen in the formed intermediate originates from the ammonium azide. In previous studies the calculations showed that in reactions where a proton is available, a stepwise reaction through an intermediate is more favorable than the concerted spontaneous attack in [2+3] cycloaddition, either neutral or ionic. In this mechanism, the key to lowering the transition state is the activation of the nitrile by a proton, which is provided by the ammonium salt [24].



The reaction of compound **3** with hydrazine hydrate in ethanol afforded the imidrazone derivative **9**. The structures of compounds **8** and **9** were confirmed by their chemical reactions in addition to their spectral and analytical data. Benzylation of the NH group of the tetrazole derivative **8** by benzyl chloride afforded the *N*-benzylated tetrazole **10** as the only product in 82% yield. The structure of tetrazole **10** was also proved by single crystal X-ray structural analysis (Fig. 2), which showed that the benzyl group is located on N(2) and not on N(3) atom. This may be explained by the nature of the starting tetrazole in which the tetrazole ring is not directly attached to the pyridine ring and is separated by a methylene group, which decreased the possibility of attachment at the N(3) atom.



Fig. 2. The molecular structure of compound **10** with representation of the atoms by thermal vibration ellipsoids with 50% probability.

Cyclization of the imidrazone **9** was performed by refluxing it with carbon disulfide in an alcoholic solution of potassium hydroxide, carbon disulfide in methanol, or PhNCS in dry pyridine to afford the 1,2,4-triazole derivatives **11**, **13**, and 1,3,4-thiadiazole-2-thione **12**, respectively, which is in agreement with previously reported results [23]. Compounds **11** and **12** were obtained selectively. The presence of potassium hydroxide resulted, chemoselectively, in the formation of compound **11** in a base-catalyzed cyclization mechanism leading to the 1,2,4-triazole ring system. The mass spectra of derivatives **11-13** showed the molecular ion peak in agreement with the assigned structure. The ¹H NMR spectra revealed the chemical shifts corresponding to NH groups and the aromatic protons.



For the preparation of fused pyridofuropyrimidine derivatives, we examined the conversion of the furopyridine derivative 14, prepared according to the reported method [25], to the 4-aminopyridofuropyrimidine 19. The known aminoester 14 was cyclized by fusion with formamide to give the pyrimidin-4(3H)-one derivative

15. Chlorination by treatment with phosphoryl chloride in dry pyridine afforded 4-chloro-7,9-di-methyl-3,4dihydropyrido[3',2':4,5]furo[3,2-*d*]pyrimidine (**16**) in 73% yield. Compound **16** was treated with sodium azide in DMF at room temperature to give azide **17** in 65% yield. The IR spectrum of compound **17** showed absorption at 2140 cm⁻¹ due to the azide group, which indicated that compound **17** is in the azide and not the tetrazole form. Refluxing the azidopyrido[3',2':4,5]furo[3,2-*d*]pyrimidine derivative **17** with triphenyl phosphine in 1,2-dichlorobenzene afforded the aminophosphorane **18**. Hydrolysis of compound **18** with 80% aqueous acetic acid produced the amino derivative **19**. The structures of compounds **15-19** were confirmed by their analytical and spectral data. The structure of amine **19** was confirmed also by reaction with diethyl phenylmalonate to obtain the tetracyclic compound **20** [26]. The structure of pyrimido[3,2-*c*]pyrimidin-2-one derivative **20** was confirmed by the mass spectrum which showed the molecular ion peak corresponding to its molecular weight. The ¹H NMR spectrum of compound **20** showed a signal at 12.43 ppm due to the OH group and the absence of the broad signal at 7.53 ppm for NH₂ protons, which was present in the spectrum of compound **19**.

Thus, new pyridine derivatives, linked to triazole, thiadiazole, thiazole, and tetrazole ring systems, were synthesized. An efficient method to synthesize tricyclic and tetracyclic pyridine derivatives has been demonstrated. Benzylation of the synthesized tetrazolylmethylpyridone derivative afforded the N(1)-benzylated product.

EXPERIMENTAL

The IR spectra were recorded in KBr pellets on a Pye Unicam SP 3300 spectrophotometer. The ¹H and ¹³C NMR spectra were recorded on a Varian Mercury VX-300 spectrometer (300 and 75 MHz, respectively); residual signals of the solvent were used as the standard. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro Analytical Center of Cairo University, Egypt. Melting points were measured on an Electrothermal IA 9000 Series digital melting point apparatus. The progress of the reactions was monitored by TLC (silica gel 60 F254, Merck). The aminoester **14** was synthesized by the known method [25].

Alkylation of 4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1). A mixture of 2-pyridinone 1 (2.10 g, 14.0 mmol) and 60% NaH (0.56 g, 14.0 mmol) in anhydrous DMF (20 ml) was stirred at room temperature for 2 h. Then, 2-chloroacetonitrile (1.07 g, 14.1 mmol) was added dropwise at 0°C and the reaction mixture was stirred for an additional 12 h at room temperature. The solvent was removed by evaporation in *vacuo*, and the resulting residue was co-evaporated with anhydrous toluene (3×10 ml). The resulting residue was treated with ice-cooled water, with stirring, to crystallize the mixture of *O*- and *N*-alkylated compounds. The obtained compounds were separated by column chromatography using EtOAc–CHCl₃ (gradient 0-10% EtOAc) as eluent to give pure compounds 2 and 3.

2-(Cyanomethoxy)-4,6-dimethylnicotinonitrile (2). Yield 0.90 g (34%). Colorless powder. Mp 116-118°C. $R_{\rm f}$ 0.7 (EtOAc–CHCl₃, 1:10). IR spectrum, v, cm⁻¹: 3060, 3009 (C–H), 2223 (CN). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.45 (3H, s, CH₃); 2.47 (3H, s, CH₃); 5.32 (2H, s, CH₂); 7.13 (1H, s, H-5). ¹³C NMR spectrum (CDCl₃), δ , ppm: 19.5 (CH₃); 23.8 (CH₃); 51.3 (CH₂); 83.0 (CH₂<u>C</u>N); 110.4 (CN); 113.4; 116.1; 119.4; 160.3; 160.6. Mass spectrum, *m/z* ($I_{\rm rel}$, %): 187 [M]⁺ (99). Found, %: C 64.22; H 4.66; N 22.61. C₁₀H₉N₃O. Calculated, %: C 64.16; H 4.85; N 22.45.

1-(Cyanomethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3). Yield 1.30 g (49%). Pale-yellow crystals. Mp 230-231°C. R_f 0.2 (EtOAc–CHCl₃, 1:10). IR spectrum, v, cm⁻¹: 3076, 3041 (C–H), 2214 (CN), 1654 (C=O). ¹H NMR spectrum (CDCl₃), δ, ppm: 2.35 (3H, s, CH₃); 2.51 (3H, s, CH₃); 5.14 (2H, s, CH₂); 6.94 (1H, s, H-5). Mass spectrum, m/z (I_{rel} , %): 188 [M+H]⁺ (98). Found, %: C 64.33; H 4.71; N 22.59. C₁₀H₉N₃O. Calculated, %: C 64.16; H 4.85; N 22.45.

3-Amino-4,6-dimethylfuro[2,3-*b*]pyridine-2-carbonitrile (4). To a solution of *O*-alkylated compound **2** (1.89 g, 10 mmol) in abs. EtOH (30 ml), a few drops of NaOEt solution were added. The solution was refluxed for 30 min and left to cool. The solid obtained was filtered off and recrystallized from EtOH. Yield 1.70 g (88%). Pale yellow crystals. Mp 159-160°C. IR spectrum, v, cm⁻¹: 3410, 3350 (NH₂), 2210 (CN). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.50 (3H, s, CH₃); 2.61 (3H, s, CH₃); 6.27 (2H, br. s, NH₂); 7.01 (1H, s, H-5). ¹³C NMR spectrum (CDCl₃), δ , ppm: 22.3 (CH₃); 23.8 (CH₃); 105.4 (CN); 109.4; 114.0; 120.8; 142.5; 145.0; 158.1; 159.9. Mass spectrum, *m/z* (*I*_{rel}, %): 187 [M]⁺ (100), 147 (40), 240 (31). Found, %: C 64.28; H 4.69; N 22.59. C₁₀H₉N₃O. Calculated, %: C 64.16; H 4.85; N 22.45.

1-(2-Cyanoethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6). To a mixture of acrylonitrile (1.10 g, 20 mmol) and Et₃N (1.00 g, 10 mmol) in abs. EtOH (30 ml), 2-pyridone **1** (1.47 g, 10 mmol) was added. The reaction mixture was refluxed for 6 h, and the obtained precipitate, after cooling, was filtered off, dried, and recrystallized from EtOH. Yield 1.90 g (95%). White powder. Mp 133-134°C. IR spectrum, v, cm⁻¹: 3076, 3055 (C–H), 2944–2921 (C–H), 2252, 2225 (2CN), 1662 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm (*J*, Hz): 2.27 (3H, s, CH₃); 2.50 (3H, s, CH₃); 2.97 (2H, t, *J* = 6.9, CH₂CH₂CN); 4.22 (2H, t, *J* = 6.9, CH₂CH₂CN); 6.37 (1H, s, H-5). Mass spectrum, *m/z* (*I*_{rel}, %): 202 [M+H]⁺ (3), 201 (30), 148 (100), 120 (31), 77 (15). Found, %: C 65.73; H 5.38; N 20.94. C₁₁H₁₁N₃O. Calculated, %: C 65.66; H 5.51; N 20.88.

Synthesis of Compounds 5 and 7 (General Method). To a well-stirred solution of compound 3 or 6 (9.3 mmol), finely ground sulfur (0.3 g, 9.3 mmol), solution of Et_3N (1.3 ml, 9.3 mmol) in abs. EtOH (30 ml), and phenylisothiocyanate (1.3 g, 9.3 mmol) was gradually added. The reaction mixture was heated under reflux for 3-4 h, during which a yellowish-green crystalline compound separated. After cooling, the obtained solid was filtered, washed with Et_2O , dried, and recrystallized from MeOH to afford pure compound 5 or 7.

1-(4-Amino-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazol-5-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (5). Yield 1.6 g (50%). Yellow powder. Mp 180-182°C. IR spectrum, v, cm⁻¹: 3430, 3300 (NH₂), 2220 (CN), 1685 (C=O), 1342 (C=S). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.29 (3H, s, CH₃); 2.42 (3H, s, CH₃); 4.52 (2H, br. s, NH₂); 6.99 (1H, s, H-5); 7.15-7.57 (5H, m, H Ph). ¹³C NMR spectrum (CDCl₃), δ , ppm: 20.2 (CH₃); 25.2 (CH₃); 89.3 (C-5 thiazole); 105.0; 110.6; 113.1; 117.1; 120.4; 128.2; 129.5; 129.7; 133.2; 146.9; 156.1, 160.7; 163.1; 182.7 (C=S). Mass spectrum, *m*/*z* (*I*_{rel}, %): 354 [M]⁺ (15), 322 (30), 278 (5), 192 (100). Found, %: C 57.77; H 3.80; N 15.92. C₁₇H₁₄N₄OS₂. Calculated, %: C 57.61; H 3.98; N 15.81.

1-[(4-Amino-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazol-5-yl)methyl]-4,6-dimethyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (7). Yield 1.9 g (55%). Pale-yellow crystals. Mp 141-142°C. IR spectrum, v, cm⁻¹: 3366, 3268 (NH₂), 2206 (CN), 1338 (C=S). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.24 (3H, s, CH₃); 2.53 (3H, s, CH₃); 4.55 (2H, s, CH₂); 4.61 (2H, br. s, NH₂); 6.98 (1H, s, H-5); 7.68-7.80 (3H, m, H Ph); 7.89-8.08 (2H, m, H Ph). Mass spectrum, *m/z* (*I*_{rel}, %): 368 [M]⁺ (3), 278 (2), 256 (10), 192 (5), 160 (5), 96 (10), 64 (100). Found, %: C 58.75; H 4.26; N 15.33. C₁₈H₁₆N₄OS₂. Calculated, %: C 58.67; H 4.38; N 15.20.

4,6-Dimethyl-2-oxo-1-(*2H***-tetrazol-5-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (8)**. A mixture of cyanomethylpyridine **3** (3.74 g, 20 mmol), NaN₃ (1.30 g, 20 mmol), and NH₄Cl (1.10 g, 20 mmol) in DMF (10 ml) was heated for 7 h at 120-125°C. The solvent was removed under reduced pressure, and the residue was dissolved in water (100 ml) and carefully acidified with conc. HCl to pH 2. The solution was cooled to 5°C in an ice bath to precipitate the tetrazole **8**, which was then recrystallized from MeOH. Yield 3.80 g (83%). Pale-yellow crystals. Mp 216-217°C. IR spectrum, v, cm⁻¹: 3429 (NH), 2216 (CN), 1621, 1598 (C=N), 1662 (C=O). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.34 (3H, s, CH₃); 2.51 (3H, s, CH₃); 5.50 (2H, s, CH₂); 6.98 (1H, s, H-5); 10.50 (1H, br. s, NH). ¹³C NMR spectrum (DMSO-d₆), δ , ppm: 20.3 (CH₃); 20.4 (CH₃); 42.2 (CH₂); 99.2 (CN); 109.2; 115.6; 152.5; 153.0; 159.4; 161.0. Mass spectrum, *m/z* (*I*_{rel}, %): 231 [M+H]⁺ (2), 230 (15), 202 (10), 188 (8), 173 (20), 160 (50), 148 (30), 131 (30), 119 (60), 77 (65), 55 (100). Found, %: C 52.25, H 4.22; N 36.63. C₁₀H₁₀N₆O. Calculated, %: C 52.17; H 4.38; N 36.50.

2-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H***)-yl)ethanimidohydrazide (9).** To a solution of cyanomethylpyridine **3** (3.74 g, 20 mmol) in EtOH (20 ml), 80% hydrazine hydrate (2.00 g, 32 mmol) was added. The mixture was refluxed for 4 h, and the solvent was removed under reduced pressure. The precipitate was recrystallized from EtOH. Yield 3.50 g (81%). Yellow solid. Mp 249-250°C. IR spectrum, v, cm⁻¹: 3387, 3295 (NH₂), 3226 (NH), 2215 (CN), 1655 (C=O). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.32 (3H, s, CH₃); 2.48 (3H, s, CH₃); 3.18 (2H, br. s, NH₂); 4.60 (2H, s, CH₂); 5.34 (1H, br. s, N<u>H</u>NH₂); 7.17 (1H, s, H-5), 8.31 (1H, br. s, =NH). Mass spectrum, *m/z* (*I*_{rel}, %): 219 [M]⁺ (20), 204 (30), 188 (15), 173 (20), 149 (100). Found, %: C 54.88, H 5.79; N 31.99. C₁₀H₁₃N₅O. Calculated, %: C 54.78, H 5.98; N 31.94.

1-[(1-Benzyl-1*H***-tetrazol-5-yl)methyl]-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (10)**. To a stirred solution of tetrazole **8** (1.33 g, 5.8 mmol) and 60% NaH (0.08 g, 5.8 mmol) in anhydrous DMF (15 ml), benzyl chloride (0.74 g, 5.8 mmol) was slowly added dropwise. The mixture was stirred at room temperature for 8 h, then poured into ice water. After cooling the mixture, the resulting precipitate was collected by filtration and recrystallized from EtOH. Yield 1.50 g (82%). Colorless crystals. Mp 169-170°C. IR spectrum, v, cm⁻¹: 3074, 3051 (C–H), 2966-2922 (C–H), 2222 (CN), 1665 (C=O). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.34 (3H, s, CH₃); 2.46 (3H, s, CH₃); 5.50 (2H, s, NCH₂); 5.91 (2H, s, PhCH₂); 6.97 (1H, s, H-5); 7.33-7.68 (5H, m, H Ph). ¹³C NMR spectrum (DMSO-d₆), δ , ppm: 20.4 (CH₃); 20.5 (CH₃); 37.8 (NCH₂); 59.0 (Ph<u>C</u>H₂); 99.2 (CN); 109.4; 115.5; 120.3; 122.2; 124.3; 125.7; 127.9; 128.4; 128.6; 156.8. Mass spectrum, *m/z* (*I*_{rel}, %): 321 [M+H]⁺ (10), 320 (32), 245 (16), 217 (21), 203 (100), 177 (33). Found, %: C 63.81; H 4.98; N 26.41. C₁₇H₁₆N₆O. Calculated, %: C 63.74; H 5.03; N 26.23.

4,6-Dimethyl-2-oxo-1-[(5-thioxo-2,5-dihydro-1*H***-1,2,4-triazol-3-yl)methyl]-1,2-dihydropyridine-3-carbonitrile (11). To a stirred suspension of amidrazone 9** (0.48 g, 2.2 mmol) in EtOH (5 ml), KOH (1 mmol) and CS₂ (2 ml) were added gradually. The reaction mixture was then heated under reflux for 6 h. After cooling and evaporation of the solvent, the obtained potassium salt was dissolved in water and acidified with 2 N aqueous HCl. The solid product was collected and recrystallized from MeOH. Yield 0.40 g (75%). Yellow crystals. Mp 218-219°C. IR spectrum, v, cm⁻¹: 3350 (NH), 2220 (CN), 1656 (C=O). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.37 (3H, s, CH₃); 2.51 (3H, s, CH₃); 5.41 (2H, s, NCH₂); 6.99 (1H, s, H-5); 10.12 (1H, br. s, NH); 13.15 (1H, br. s, NH). Mass spectrum, *m/z* (*I*_{rel}, %): 262 [M+H]⁺ (80), 261 (80), 201 (25), 148 (100). Found, %: C 50.71; H 4.22; N 26.91. C₁₁H₁₁N₅OS. Calculated, %: C 50.56; H 4.24; N 26.80.

4,6-Dimethyl-2-oxo-1-[(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)methyl]-1,2-dihydropyridine-3-carbonitrile (12). To a solution of amidrazone **9** (1.75 g, 8 mmol) in MeOH (30 ml), CS₂ (5 ml, 16 mmol) was added. The mixture was refluxed for 5 h, and the solvent was removed under reduced pressure. The precipitate was recrystallized from MeOH. Yield 1.6 g (70%). Green powder. Mp 226-227°C. IR spectrum, v, cm⁻¹: 2229 (CN), 1660 (C=O). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.39 (3H, s, CH₃); 2.43 (3H, s, CH₃); 5.33 (2H, s, CH₂); 7.10 (1H, s, H-5); 12.82 (1H, br. s, NH). ¹³C NMR spectrum (DMSO-d₆), δ , ppm: 20.8 (CH₃); 21.3 (CH₃); 46.6 (CH₂); 101.0 (CN); 115.7; 118.5; 149.0; 151.2; 157.7; 163.1; 179.2 (C=S). Mass spectrum, *m/z* (*I*_{rel}, %): 279 [M+H]⁺ (10), 278 (100), 245 (23), 202 (20). Found, %: C 47.59; H 3.33; N 20.41. C₁₁H₁₀N₄OS₂. Calculated, %: C 47.46; H 3.62; N 20.13.

4,6-Dimethyl-2-oxo-1-[(3-phenylamino-1*H***-1,2,4-triazol-5-yl)methyl]-1,2-dihydropyridine-3-carbonitrile (13). A suspension of amidrazone 9 (0.22 g, 1 mmol) and phenylisothiocyanate (0.14 g, 1 mmol) in anhydrous pyridine (10 ml) was heated under reflux for 5 h. After cooling, the reaction mixture was poured into ice water and neutralized with diluted 10% HCl to give a buff solid precipitate. Triazole 13 was collected and recrystallized from EtOH–DMF (3:1). Yield 0.2 g (65%). Buff powder. Mp 116-117°C. IR spectrum, v, cm⁻¹: 3100 (NH), 2222 (CN), 1639 (C=O). ¹H NMR spectrum (DMSO-d₆), \delta, ppm: 2.49 (3H, s, CH₃); 2.51 (3H, s, CH₃); 5.65 (2H, s, CH₂); 6.46 (1H, s, H-5); 6.93-7.68 (5H, m, H Ph); 9.05 (1H, br. s, NH); 9.88 (1H, br. s, NH). Mass spectrum,** *m***/***z* **(***I***_{rel}, %): 320 [M]⁺ (15), 242 (33), 216 (10), 187 (70), 161 (100). Found, %: C 63.90; H 4.98; N 26.41. C₁₇H₁₆N₆O. Calculated, %: C 63.74; H 5.03; N 26.23.**

7,9-Dimethylpyrido[3',2':4,5]furo[3,2-*d***]pyrimidin-4(3***H***)-one (15). A suspension of ethyl 3-amino-4,6-dimethylfuro[2,3-***b***]pyridine-2-carboxylate (14) (2.34 g, 10 mmol) in formamide (5 ml) in the presence of 2-3 drops of Ac₂O was heated under reflux for 2 h. After cooling, the precipitate was triturated with MeOH to afford compound 15, which was recrystallized from AcOH. Yield 1.60 g (75%). Brownish-yellow solid. Mp ~320°C. IR spectrum, v, cm⁻¹: 3412 (NH), 3109–3064 (C–H), 2956, 2864 (C–H), 1703 (C=O). ¹H NMR** spectrum (DMSO-d₆), δ , ppm: 2.57 (3H, s, CH₃); 2.75 (3H, s, CH₃); 7.24 (1H, s, H-8); 8.24 (1H, s, H-2); 9.84 (1H, br. s, OH). ¹³C NMR spectrum (DMSO-d₆), δ , ppm: 17.6, 24.0 (2CH₃); 111.0; 121.7; 137.1; 143.2; 145.8; 146.9; 152.2; 158.8; 161.9. Mass spectrum, *m/z* (*I*_{rel}, %): 215 [M]⁺ (60), 187 (15), 168 (15), 153 (100). Found, %: C 61.51; H 4.13; N 19.64. C₁₁H₉N₃O₂. Calculated, %: C 61.39; H 4.22; N 19.53.

4-Chloro-7,9-dimethylpyrido[**3'**,**2':4,5**]**furo**[**3**,2-*d*]**pyrimidine (16)**. To a suspension of pyridofuropyrimidone **15** (3.29 g, 15.3 mmol) in anhydrous pyridine, POCl₃ (15 ml, 20.0 mmol) was added, and the reaction mixture was refluxed for 4 h. The excess POCl₃ was removed under reduced pressure. The residue was dissolved in ice water (100 ml), and the precipitate was collected by filtration and recrystallized from EtOH. Yield 2.60 g (73%). Colorless solid. Mp 167-168°C. IR spectrum, v, cm⁻¹: 3100, 3050 (C–H), 2970, 2890 (C–H), 1608 (C=N). ¹H NMR spectrum (DMSO-d₆), δ, ppm: 2.71 (3H, s, CH₃); 2.92 (3H, s, CH₃); 7.18 (1H, s, H-8); 8.68 (1H, s, H-2). Mass spectrum, m/z (I_{rel} , %): 234 [M+H]⁺ (40), 233 (20), 198 (100), 183 (19), 155 (20). Found, %: C 56.71; H 3.29; N 18.08. C₁₁H₈ClN₃O. Calculated, %: C 56.54; H 3.45; N 17.98.

4-Azido-7,9-dimethylpyrido[3',2':4,5]furo[3,2-*d***]pyrimidine** (17). NaN₃ (1.63 g, 25 mmol) was added to a stirred solution of compound **17** (1.17 g, 5 mmol) in DMF (20 ml). Stirring was continued for a further 10 h at room temperature. The reaction mixture was poured into ice-cooled water, and the precipitated solid was collected by filtration, washed with water, dried, and recrystallized from EtOH. Yield 0.90 g (76%). Pale-yellow crystals. Mp 160-161°C. IR spectrum, v, cm⁻¹: 3090, 3033 (C–H), 2945, 2886 (C–H), 2140 (N₃). ¹H NMR spectrum (DMSO-d₆), δ, ppm: 2.51 (3H, s, CH₃); 2.63 (3H, s, CH₃); 7.13 (1H, s, H-8); 8.56 (1H, s, H-2). Mass spectrum, m/z (I_{rel} , %): 240 [M]⁺ (11), 212 (20), 198 (100), 171 (31). Found, %: C 55.08; H 3.19; N 35.04. C₁₁H₈N₆O. Calculated, %: C 55.00; H 3.36; N 34.98.

7,9-Dimethy-3-(triphenylphosphoranylideneamino)pyrido[3',2':4,5]furo[3,2-*d***]pyrimidine (18). A solution of azide 17** (1.20 g, 5 mmol) and Ph₃P (1.31 g, 5 mmol) in 1,2-dichlorobenzene (10 ml) was heated under reflux for 40 min. The solvent was removed in vacuum, and the resulting solid was filtered and recrystallized from MeOH. Yield 2.00 g (85%). White powder. Mp 244-246°C. IR spectrum, v, cm⁻¹: 3043, 3024 (C–H), 2985, 2918 (C–H), 1606 (C=N). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.59 (3H, s, CH₃); 2.77 (3H, s, CH₃); 7.22 (1H, s, H-8); 7.60-7.66 (5H, m, H Ph); 7.75-7.89 (10H, m, H Ph); 8.76 (1H, s, H-2). Mass spectrum, *m/z* (*I*_{rel}, %): 474 [M]⁺ (14), 402 (10), 330 (9), 260 (10), 230 (100). Found, %: C 73.57; H 4.68; N 11.95. C₂₉H₂₃N₄OP. Calculated, %: C 73.41; H 4.89; N 11.81.

7,9-Dimethylpyrido[3',2':4,5]furo[3,2-*d***]pyrimidin-4-amine (19). A solution of iminophosphorane 18 (1.42 g, 3 mmol) in AcOH (80%, 20 ml) was heated under reflux for 5 h. The solvent was removed in vacuum, and the resulting solid product was digested with MeOH and collected by filtration, dried, and recrystallized from AcOH. Yield 0.50 g (78%). White prisms. Mp 293-294°C. IR spectrum, v, cm⁻¹: 3444, 3317 (NH₂), 3163 (C–H), 2953, 2852 (C–H), 1612 (C=N). ¹H NMR spectrum (DMSO-d₆), \delta, ppm: 2.56 (3H, s, CH₃); 2.77 (3H, s, CH₃); 7.20 (1H, s, H-8); 7.53 (2H, br. s, NH₂); 8.40 (1H, s, H-2). ¹³C NMR spectrum (DMSO-d₆), \delta, ppm: 17.4 (CH₃); 23.9 (CH₃); 110.6; 121.0; 132.1; 144.8; 145.5; 149.7; 153.4; 158.3; 161.9. Mass spectrum,** *m/z* **(***I***_{rel}, %): 214 [M]⁺ (4), 197 (0.4), 179 (0.5), 125 (4), 111 (10), 97 (20), 71 (60), 57 (100). Found, %: C 61.73; H 4.64; N 26.31. C₁₁H₁₀N₄O. Calculated, %: C 61.67; H 4.71; N 26.15.**

4-Hydroxy-7,9-dimethyl-3-phenylpyrido[3',2':4,5]furo[3,2-e]pyrimido[3,2-c]pyrimidin-2-one (20). A mixture of compound **19** (0.43 g, 2 mmol) and diethyl 2-phenylmalonate (0.47 g, 2 mmol) in diphenyl ether (5 ml) was refluxed in an oil bath for 20 min, using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was triturated with Et₂O and the obtained precipitate was filtered off, washed with Et₂O, dried, and recrystallized from DMF. Yield 0.50 g (75%). Brownish-yellow crystals. Mp ~320°C. IR spectrum, v, cm⁻⁰¹: 3433–3298 (OH), 1665 (C=O), 1610 (C=N). ¹H NMR spectrum (DMSO-d₆), δ , ppm: 2.55 (3H, s, CH₃); 2.88 (3H, s, CH₃); 7.33-7.63 (6H, m, H-8, H Ph); 8.62 (1H, s, H-5); 12.43 (1H, br. s, OH). Mass spectrum, *m*/*z* (*I*_{rel}, %): 359 [M+H]⁺, (20), 358 (50), 330 (20), 269 (10), 231 (100). Found, %: C 67.12; H 3.79; N 15.76. Calculated, %: C 67.03; H 3.94; N 15.63.

X-Ray Structural Investigation of Compound 10. The crystal of compound 10 ($C_{17}H_{16}N_6O$, M 320.35) is block-shaped and colorless; crystal dimensions $0.3 \times 0.3 \times 0.3$ mm. Crystal structure parameters at

20°C: crystal system monoclinic, space group $P2_1/c$. Unit cell dimensions: a 9.1474(9), b 12.206(2), c 15.334(2) Å; β 97.719(7)°; V 1696.5(3) Å³; Z 4; d_{calc} 1.254 g/cm⁻³; μ (MoK α) 0.838 cm⁻¹; F(000) 672.00. Measurements were carried out on an R-Axis Rapid diffractometer. The data were collected to a maximum 20 value of 50.6°. A total of 44 oscillation images was collected. A sweep of data was done using ω-scans from 130.0 to 190.0° in 5.0° step, at χ 45.0° and φ 0.0°. The exposure rate was 36.0 sec/deg. A second sweep was performed using ω scans from 0.0 to 160.0° in 5.0° step, at χ 45.0° and φ 180.0°. The exposure rate was 36.0 sec/deg. Of the 13526 reflections that were collected, 3088 were independent (R_{int} 0.0265); equivalent reflections were merged. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.836 to 0.975. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the "rider" model. The final cycle of full-matrix least-squares refinement on F^2 was based on 3088 observed reflections and 217 variable parameters and converged (largest parameter shift was 0.00 times its estimated standard deviation) with unweighted and weighted agreement factors R1 0.0648 and $wR_2 0.2423$. All calculations were performed using the CrystalStructure [27] crystallographic software package except for refinement, which was performed using the SHELXL-97 program [28]. Crystallographic data of compound 10 has been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 864666).

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