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

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 was 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 becomes 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].

Multi-substituted 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 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, 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 aimed herein to synthesize new five-membered rings linked to 2-pyridone in addition to functionalized condensed tri- and tetracyclic pyridine ring systems.

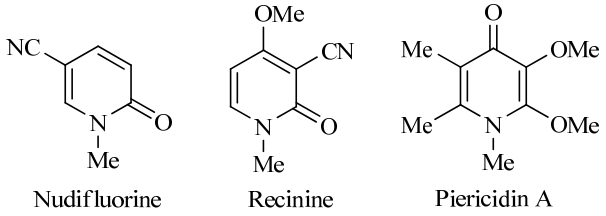
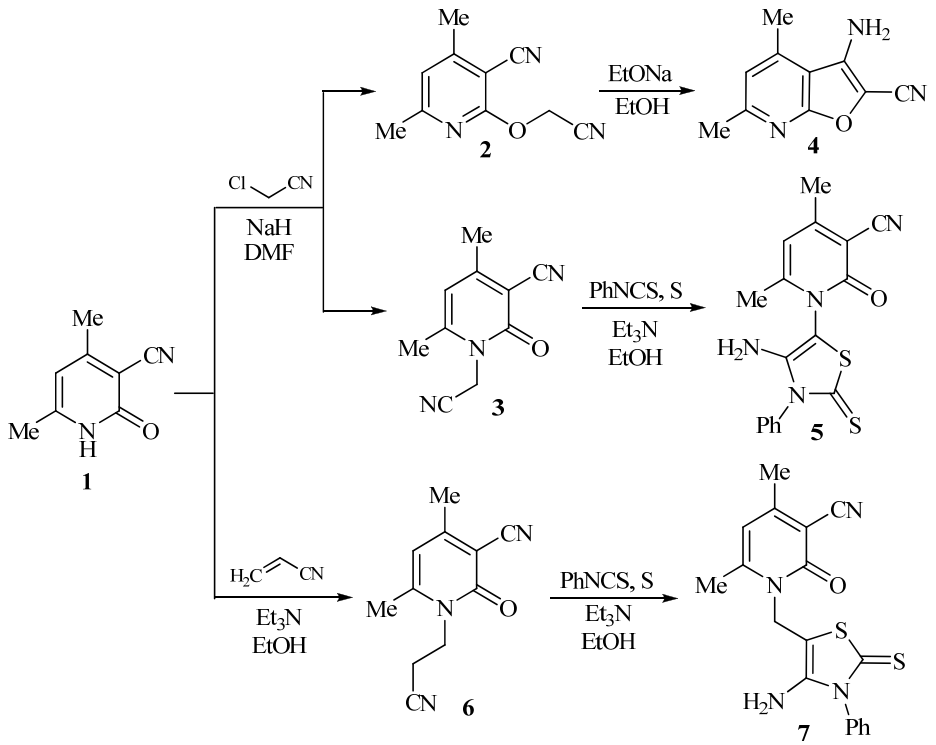


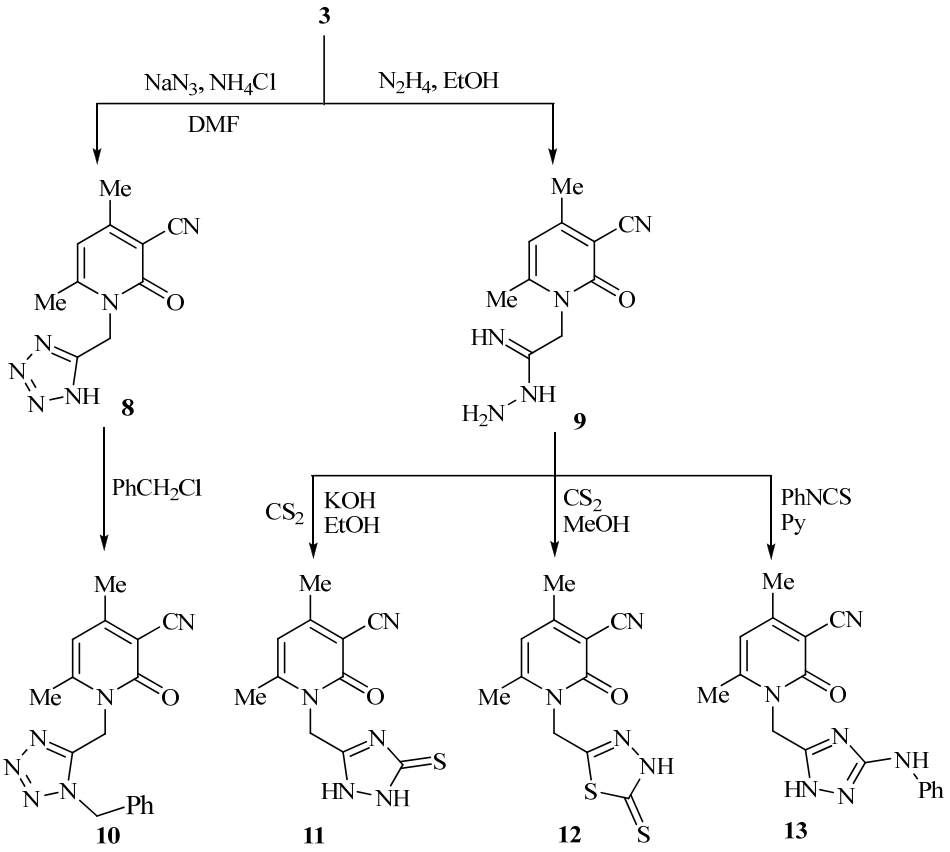
Fig. 1. Some natural derivatives of pyridones

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 ^{1}H 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 *O*-alkylated product and at 5.14 ppm for *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, ^{1}H NMR, and mass spectral data, which were in agreement with the assigned structure. Moreover, the signal of CH_2 protons was not seen in the ^{1}H 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 (NH_2) and 1342 (C=S) cm^{-1}. Its ^{1}H NMR spectrum showed new signals at 4.52 ppm for NH_2 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 in the same conditions used to synthesize compound **5**. The ^{1}H 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 presence of ammonium chloride. Concerning the intermolecular cycloaddition reaction of nitriles and azides, it was shown that in case of using azide salts, they react with nitriles through an anionic two-step mechanism leading regioselectively to 1*H*-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 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 lower the transition state is the activation of the nitrile by a proton which is provided by the ammonium salt [24].



Reaction of compound **3** with hydrazine hydrate in ethanol afforded the imidrazone derivative **9**. Confirmation of structures of compounds **8** and **9** were supported 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 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 separated by a methylene group which decreased the possibility of attachment at N(3) atom.

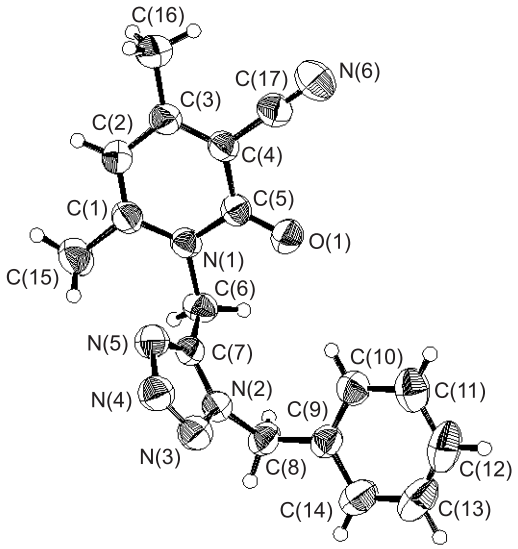
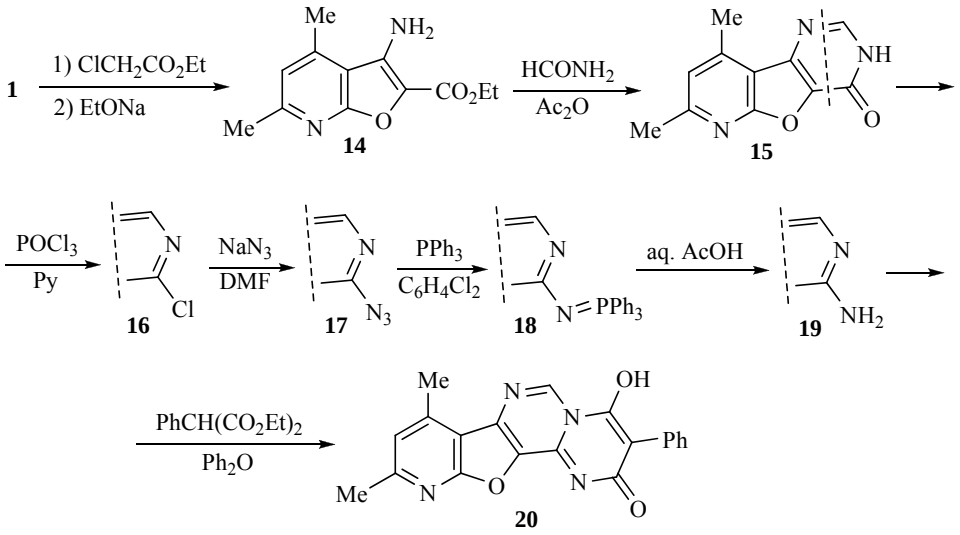


Fig. 2. The molecular structure of compound **10** with representation of the atoms by thermal vibration ellipsoids with 50% probability

Cyclization of the imidrazone **9** was performed by refluxing it with carbon disulfide in 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-thiadiazol-2-thione **12**, respectively, which is in agreement with previously reported results [23]. The 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 1,2,4-triazole ring system. The mass spectra for derivatives **11**–**13** showed the molecular ion peak in agreement with the assigned structure. The ^{1}H 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(3*H*)-one derivative **15**. Chlorination by treatment with phosphoryl chloride in dry pyridine afforded 4-chloro-7,9-dimethyl-3,4-dihydropyrido[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 the compound **17** presents in azide and not in tetrazole form. Refluxing the azidopyrido[3',2':4,5]-furo[3,2-*d*]pyrimidine derivative **17** with triphenyl phosphine, in 1,2-dichloro-benzene afforded the aminophosphorane **18**. Hydrolysis of the 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 mass-spectrum which showed the molecular ion peak corresponding to its molecular weight. The ^{1}H NMR spectrum of compound **20** showed a signal at 12.43 ppm due to OH group and absence of the broad signal at 7.53 ppm for NH_2 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 discs on a Pye Unicam SP 3300 spectrophotometer. The ^{1}H and ^{13}C 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 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–$CHCl_3$ (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_f 0.7 (EtOAc–$CHCl_3$, 1:10). IR spectrum, ν, cm^{-1}: 3060, 3009 (C–H), 2223 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.45 (3H, s, CH_3); 2.47 (3H, s, CH_3); 5.32 (2H, s, CH_2); 7.13 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.5 (CH_3); 23.8 (CH_3); 51.3 (CH_2); 83.0 (CH_2CN); 110.4 (CN); 113.4; 116.1; 119.4; 160.3; 160.6. Mass spectrum, *m/z* (I_{rel}, %): 187 $[M]^+$ (99). Found, %: C 64.22; H 4.66; N 22.61. $C_{10}H_9N_3O$. 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–$CHCl_3$, 1:10). IR spectrum, ν, cm^{-1}: 3076, 3041 (C–H), 2214 (CN), 1654 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm:

2.35 (3H, s, CH_3); 2.51 (3H, s, CH_3); 5.14 (2H, s, CH_2); 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. $C_{10}H_9N_3O$. 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, ν, cm^{-1}: 3410, 3350 (NH_2), 2210 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.50 (3H, s, CH_3); 2.61 (3H, s, CH_3); 6.27 (2H, br. s, NH_2); 7.01 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.3 (CH_3); 23.8 (CH_3); 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. $C_{10}H_9N_3O$. 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 Et_3N (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, ν, cm^{-1}: 3076, 3055 (C–H), 2944–2921 (C–H), 2252, 2225 (2CN), 1662 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.50 (3H, s, CH_3); 2.97 (2H, t, *J* = 6.9, $CH_2C\underline{H}_2CN$); 4.22 (2H, t, *J* = 6.9, $C\underline{H}_2CH_2CN$); 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. $C_{11}H_{11}N_3O$. 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), and solution of Et_3N (1.3 ml, 9.3 mmol) in abs. EtOH (30 ml), 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, ν, cm^{-1}: 3430, 3300 (NH_2), 2220 (CN), 1685 (C=O), 1342 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.29 (3H, s, CH_3); 2.42 (3H, s, CH_3); 4.52 (2H, br. s, NH_2); 6.99 (1H, s, H-5); 7.15–7.57 (5H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.2 (CH_3); 25.2 (CH_3); 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. $C_{17}H_{14}N_4OS_2$. 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-dihydropyridine-3-carbonitrile (7). Yield 1.9 g (55%). Pale yellow crystals. Mp 141–142°C. IR spectrum, ν, cm^{-1}: 3366, 3268 (NH_2), 2206 (CN), 1338 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.24 (3H, s, CH_3); 2.53 (3H, s, CH_3); 4.55 (2H, s, CH_2); 4.61 (2H, br. s, NH_2); 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. $C_{18}H_{16}N_4OS_2$. Calculated, %: C 58.67; H 4.38; N 15.20.

4,6-Dimethyl-2-oxo-1-(2*H*-tetrazol-5-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (8). A mixture of cyanomethylpyridine **3** (3.74 g, 20 mmol), NaN_3 (1.30 g, 20 mmol), and NH_4Cl (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 ice bath to precipitate the tetrazole **8** which then was recrystallized from MeOH. Yield 3.80 g (83%). Pale yellow crystals. Mp 216–217°C. IR spectrum, ν, cm^{-1}: 3429 (NH), 2216 (CN), 1621, 1598 (C=N), 1662 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34 (3H, s, CH_3); 2.51 (3H, s, CH_3); 5.50 (2H, s, CH_2); 6.98 (1H, s, H-5); 10.50 (1H, br. s, NH). ^{13}C NMR

spectrum (DMSO-d_6), δ, ppm: 20.3 (CH_3); 20.4 (CH_3); 42.2 (CH_2); 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. $C_{10}H_{10}N_6O$. 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, ?? 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, ν, cm^{-1}: 3387, 3295 (NH_2), 3226 (NH), 2215 (CN), 1655 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.32 (3H, s, CH_3); 2.48 (3H, s, CH_3); 3.18 (2H, br. s, NH_2); 4.60 (2H, s, CH_2); 5.34 (1H, br. s, N<u>H</u>NH_2); 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. $C_{10}H_{13}N_5O$. 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 onto 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, ν, cm^{-1}: 3074, 3051 (C–H), 2966–2922 (C–H), 2222 (CN), 1665 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34 (3H, s, CH_3); 2.46 (3H, s, CH_3); 5.50 (2H, s, NCH_2); 5.91 (2H, s, $PhCH_2$); 6.97 (1H, s, H-5); 7.33–7.68 (5H, m, H Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.4 (CH_3); 20.5 (CH_3); 37.8 (NCH_2); 59.0 (Ph<u>C</u>H_2); 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. $C_{17}H_{16}N_6O$. 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 CS_2 (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 2N aq. HCl. The solid product was collected and recrystallized from MeOH. Yield 0.40 g (75%). Yellow crystals. Mp 218–219°C. IR spectrum, ν, cm^{-1}: 3350 (NH), 2220 (CN), 1656 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.37 (3H, s, CH_3); 2.51 (3H, s, CH_3); 5.41 (2H, s, NCH_2); 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. $C_{11}H_{11}N_5OS$. 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), CS_2 (5 ml, 16 mmol) was added. The mixture was refluxed for 5 h, 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, ν, cm^{-1}: 2229 (CN), 1660 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.39 (3H, s, CH_3); 2.43 (3H, s, CH_3); 5.33 (2H, s, CH_2); 7.10 (1H, s, H-5); 12.82 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.8 (CH_3); 21.3 (CH_3); 46.6 (CH_2); 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. $C_{11}H_{10}N_4OS_2$. 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, ν, cm^{-1}: 3100 (NH), 2222 (CN), 1639 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.49 (3H, s, CH_3); 2.51 (3H, s, CH_3); 5.65 (2H, s, CH_2); 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. $C_{17}H_{16}N_6O$. 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 Ac_2O 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, ν, cm^{-1}: 3412 (NH), 3109–3064 (C–H), 2956, 2864 (C–H), 1703 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.57 (3H, s, CH_3); 2.75 (3H, s, CH_3); 7.24 (1H, s, H-8); 8.24 (1H, s, H-2); 9.84 (1H, br. s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 17.6, 24.0 ($2CH_3$); 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. $C_{11}H_9N_3O_2$. 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, $POCl_3$ (15 ml, 20.0 mmol) was added and the reaction mixture was refluxed for 4 h. The excess $POCl_3$ was removed under reduced pressure. The residue was dissolved in ice water (100 ml), the precipitate was collected by filtration and recrystallized from EtOH. Yield 2.60 g (73%). Colorless solid. Mp 167–168°C. IR spectrum, ν, cm^{-1}: 3100, 3050 (C–H), 2970, 2890 (C–H), 1608 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.71 (3H, s, CH_3); 2.92 (3H, s, CH_3); 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. $C_{11}H_8ClN_3O$. 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). NaN_3 (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 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, ν, cm^{-1}: 3090, 3033 (C–H), 2945, 2886 (C–H), 2140 (N_3). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.51 (3H, s, CH_3); 2.63 (3H, s, CH_3); 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. $C_{11}H_8N_6O$. 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 Ph_3P (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, ν, cm^{-1}: 3043, 3024 (C–H), 2985, 2918 (C–H), 1606 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.59 (3H, s, CH_3); 2.77 (3H, s, CH_3); 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. $C_{29}H_{23}N_4OP$. 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, ν, cm^{-1}: 3444, 3317 (NH_2), 3163 (C–H), 2953, 2852 (C–H), 1612 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.56 (3H, s, CH_3); 2.77 (3H, s, CH_3); 7.20 (1H, s, H-8); 7.53 (2H, br. s, NH_2); 8.40 (1H, s, H-2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 17.4 (CH_3); 23.9 (CH_3); 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. $C_{11}H_{10}N_4O$. 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 Et_2O and the obtained precipitate was filtered off, washed with Et_2O, dried, and recrystallized from DMF. Yield 0.50 g (75%). Brownish yellow crystals. Mp ~320°C. IR spectrum, ν, cm^{-1}: 3433–3298 (OH), 1665 (C=O), 1610 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 (3H, s, CH_3); 2.88 (3H, s, CH_3); 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 Structure Investigation of Compound 10. Crystal of compound **10** ($C_{17}H_{16}N_6O$, *M* 320.35) is block-shaped, colorless; crystal dimensions 0.3 × 0.3 × 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) $Å^3$; *Z* 4; d_{calc} 1.254 g/cm^{-3}; μ(MoKα) 0.838 cm^{-1}; *F*(000) 672.00. Measurements were carried out on R-Axis Rapid diffractometer. The data were collected to a maximum 2θ value of 50.6°. A total of 44 oscillation images were 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/grad. 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/grad. Of the 13526 reflections that were collected, 3088 were unique (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 "riding" 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 *R*1 0.0648 and R_w2 0.2423. All calculations were performed using the CrystalStructure [27] crystallographic software package except for refinement, which was performed using SHELXL-97 programm [28]. Crystallographic data of compound **10** has been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 864666).

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