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# Synthesis and some chemical properties of 2-cyano-4-pyrone

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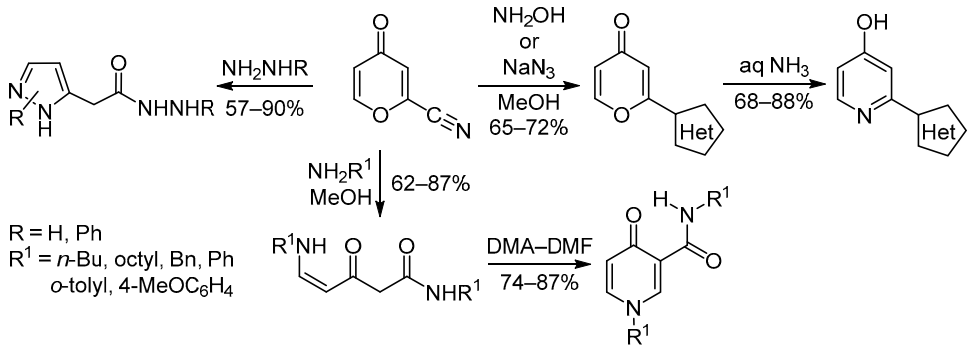


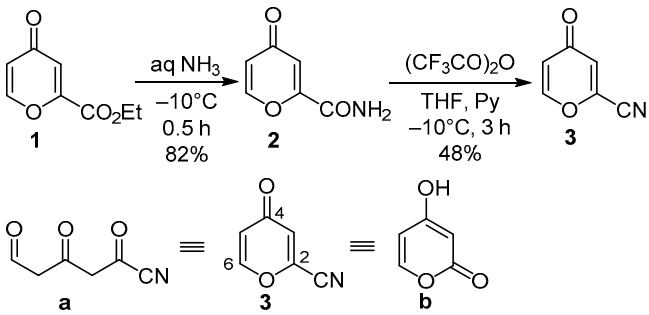

2-Cyano-4-pyrone obtained from comanic acid ethyl ester reacts with amines and hydrazines with the opening of the pyrone ring and substitution of the cyano group to form carbamoylated aminoenones (yields 62–87%) and pyrazolylacetic acid hydrazides. The reactions of 2-cyano-4-pyrone with hydroxylamine or sodium azide involve exclusively the cyano group, which makes it possible to obtain 2-heteroaryl-4-pyrones and 2-heteroaryl-4-hydroxypyridines.

**Keywords**: carbamoylated enaminones, 2-cyano-4-pyrones, 2-heteroaryl-4-hydroxypyridines, 2-heteroaryl-4-pyrones, 4-oxo-1,4-dihydropyridine-3-carboxamides, pyrazoles.

The search for novel molecules possessing low molecular weight and diverse reactivity is an important task of modern organic synthesis and is of great importance for medicinal chemistry and materials chemistry.[1] Pyrones containing a cyano group belong to polyelectrophilic substrates and are of interest for obtaining more complex heterocyclic structures.[2] Only substituted 2-cyano-4-pyrones are known in the literature, although the transformations described on their basis are limited to a small number of examples.[3,4] Thus it was previously shown that 6-aryl-2-cyano-4-pyrones react with $NaN_3$ at the cyano group to form tetrazolylpyrones exhibiting antiallergic activity.[4] We obtained also 2-cyano-6-(trifluoromethyl)-4-pyrone, which was subsequently in high demand for the construction of various fluorine-containing heterocycles.[5]

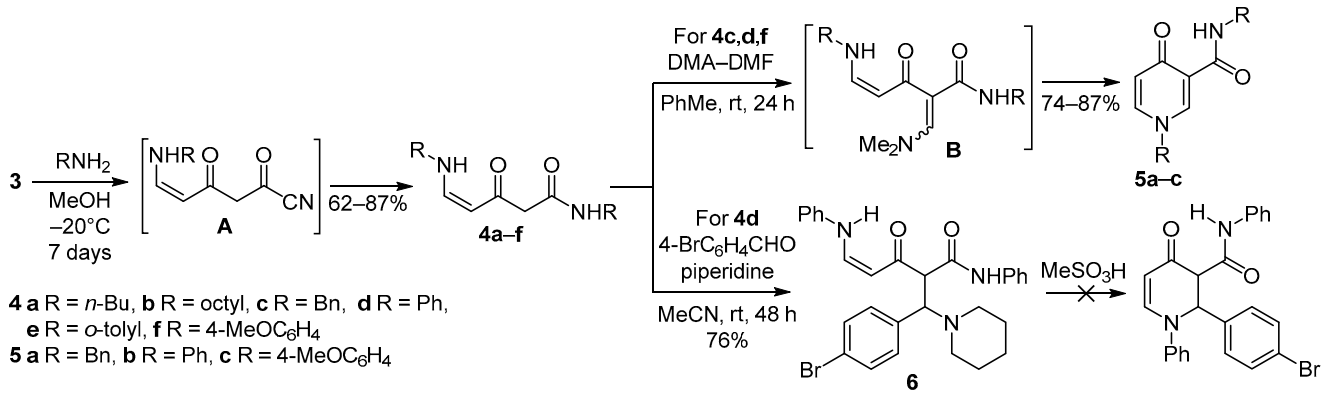
This work is devoted to unsubstituted 2-cyano-4-pyrone (**3**), which was described in our preliminary report[6] without carrying out a systematic study of its properties. This compound has four electrophilic centers (C-2, C-4, C-6 atoms, and CN group) and can be considered as a hidden triketo cyanide **a**, capable of reacting by the diketone fragment and with the simultaneous substitution of the cyano group or as a synthetic equivalent of still not described 4-hydroxy-2-pyrone (**b**) (Scheme 1).

**Scheme 1**




As starting material for the preparation of 2-cyano-4-pyrone (**3**), comanic acid ethyl ester (**1**) was used which was first converted to amide **2**.[7] It must be taken into account that the pyrone ring is easily opened by the action

**Scheme 2**



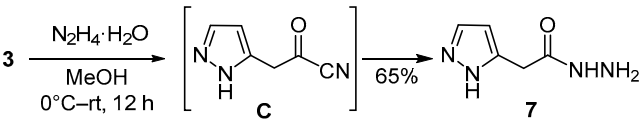

of ammonia with the formation of 4-pyridone. Despite this, we were able to find the reaction conditions allowing to access 2-cyano-4-pyrone from comanic acid ethyl ester in moderate yield: the reaction of ethyl comanate (**1**) under heterogeneous conditions with 20% aqueous $NH_3$ upon cooling (–10°C) hinders the opening the pyrone ring and affords 2-carbamoyl-4-pyrone (**2**) in 82% yield (Scheme 1). Subsequent treatment of amide **2** with $(CF_3CO)_2O$ in the presence of pyridine in absolute THF at –10°C leads to dehydration and the formation of 2-cyano-4-pyrone (**3**) in 48% yield. It should be noted that carrying out the reaction at room temperature, 2-cyano-4-pyrone (**3**) is obtained in trace amounts.

We further investigated the reaction of 2-cyano-4-pyrone (**3**) with various nucleophilic reagents. It was found that the reaction of 2-cyano-4-pyrone (**3**) with primary aliphatic and aromatic amines in anhydrous MeOH at –20°C for 7 days results in the opening of the pyrone ring and the formation of carbamoylated enaminones **4a**–**f** in 62–87% yields (Scheme 2). It follows from the structure of the resulting product that the attack of the amine molecule occurs at position C-6 of the pyrone ring. A possible intermediate of this reaction is acyl cyanide **A**, which is able to react with a second amine molecule resulting in substitution of the cyano group. The structure of the employed amine practically does not affect the course of the reaction, and even in the case of sterically hindered *o*-toluidine, the yield of enaminone **4e** decreases only slightly (62%). When this reaction is carried out in EtOH, the yields are reduced by about 20%, which is explained by the competing reaction of intermediate **A** with water present in EtOH.

Enaminones are polyfunctional substrates, which allows us to consider them as precursors for the synthesis of various compounds.[5,6,8,9] Thus, they undergo cyclization with the formation of 4-oxo-1,4-dihydropyridine-3-carboxamides **5a**–**c** in 74–87% yields under the action of DMA-DMF in dry PhMe for 24 h at room temperature (Scheme 2). We assume that this reaction proceeds with the formation of intermediate **B**, which then cyclizes to pyridones **5a**–**c**. The reaction of enaminone **4d** with 4-bromobenzaldehyde in the presence of piperidine at room temperature leads to the Mannich reaction product **6** (Scheme 2). The resulting product **6** does not form the corresponding dihydropyridone in the presence of $MeSO_3H$, although such a cyclization reaction was previously observed for 5-substituted enaminones.[9]

The reaction of 2-cyano-4-pyrone (**3**) with hydrazine hydrate proceeds in anhydrous MeOH at 0°C *via* the opening of the pyrone ring and the formation of pyrazole **7** in 65% yield (Scheme 3). Carrying out the reaction in EtOH gives the target product, but in a lower yield (26%). By analogy with amines, pyrazolylacetyl cyanide **C** is formed during the reaction, which reacts with hydrazine to replace the cyano group (Scheme 3).

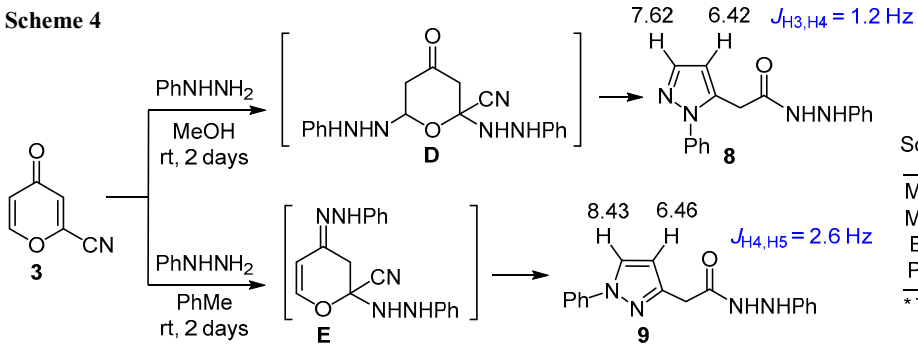
**Scheme 3**




The reaction of 2-cyano-4-pyrone **3** with phenylhydrazine in MeOH proceeds nonselectively forming a mixture of pyrazoles **8** and **9**. Probably, the nucleophilic attack of phenylhydrazine occurs not only at the position C-6 of 2-cyano-4-pyrone, but also at its carbonyl group. Optimization of the reaction conditions showed that the temperature and nature of the solvent affect the regioselectivity of the process (Scheme 4). Thus, polar protic solvents favor the formation of the 1,4-addition product at the C-6 atom (intermediate **D**, pyrazole **8**). In PhMe, the main isomer was the product of the 1,2-addition (intermediate **E**, pyrazole **9**). The obtained result is consistent with the data on the reaction of 2,6-disubstituted 4-pyrones with hydrazines.[10] By recrystallization of the mixture of regioisomers from EtOH, pyrazole **9** was isolated in pure form in 46% yield.

The structures of pyrazoles **8** and **9** were established using the spin-spin coupling constants and the values of chemical shifts of protons. In the case of regioisomer **8**, the pyrazole protons H-3 and H-4 appear at 7.62 and 6.42 ppm, respectively. A characteristic signal of pyrazole **9** is the downfield doublet of the H-5 proton at 8.43 ppm, which is a consequence of the deshielding effect of the phenyl substituent (Scheme 4). It is known from the literature that, for 3-substituted pyrazoles, the spin-spin coupling constant of the H-3 and H-4 protons is greater than for 5-substituted pyrazoles.[10] Thus, it was found that

**Scheme 4**




| Solvent | Tempe-rature, °C | Time, days | Ratio **8**:**9*** | Total yield, % |
|---|---|---|---|---|
| MeOH | –20 | 7 | 50:50 | 71 |
| MeOH | rt | 2 | 67:33 | 57 |
| EtOH | rt | 2 | 50:50 | 69 |
| PhMe | rt | 2 | 15:85 | 90 |

* The ratio of regioisomers determined on the basis of $^1$H NMR spectra.

for pyrazole **9** $J_{H4,H5}$ = 2.6 Hz, and for pyrazole **8** $J_{H3,H4}$ = 1.2 Hz, which is consistent with the proposed structures.

It should be noted that the reaction of 2-cyano-4-pyrone (**3**) with hydroxylamine, in contrast to the reaction with hydrazines, does not lead to the product of ring opening, but proceeds with the participation of the cyano group to form amidoxime **10** (yield 72%). The observed change in the course of the reaction is probably a consequence of the coordination of the OH and CN groups (intermediate **F**), which leads to an attack at the cyano group. As a result of acylation of amidoxime **10** with $(CF_3CO)_2O$ in the presence of pyridine, oxadiazolylpyrone **11** is formed in 41% yield (Scheme 5).

2-Cyano-4-pyrone (**3**) also enters the [3+2] cycloaddition reaction with $NaN_3$ in the presence of $NH_4Cl$ in aqueous THF solution to form 2-tetrazolyl-4-pyrone (**12**) in 65% yield (Scheme 5). The reaction proceeds selectively at the cyano group, without affecting the pyrone ring. When heating under reflux in $Ac_2O$, tetrazolylpyrone **12** undergoes the Huisgen rearrangement, which leads to the formation of oxadiazolylpyrone **13** in 66% yield (Scheme 5).

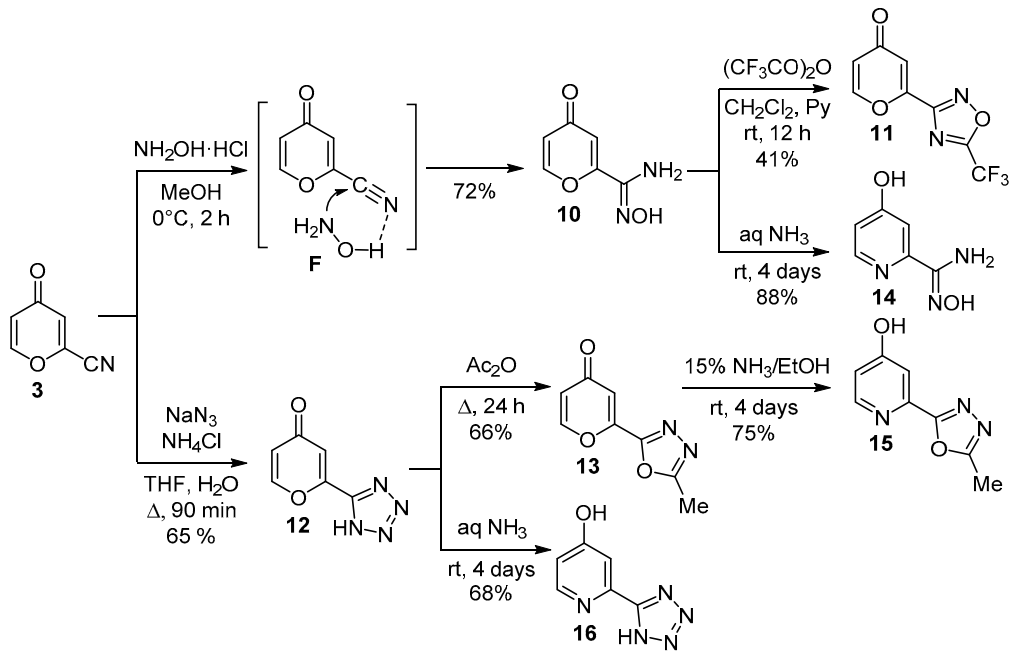
Next, we investigated the possibility of obtaining the corresponding 2-substituted pyridines starting from pyrones **10**, **12**, and **13** that are of interest as coordination structures.[11] It was found that pyrones **10**, **12**, **13** react with $NH_3$ *via* opening of the pyrone ring and subsequent closure to previously unknown pyridines **14**–**16** at room temperature for 4 days (Scheme 5). In the $^1$H NMR spectra of compounds **14**–**16**, the signals of the protons of the pyridine ring are shifted downfield in comparison with similar protons of the pyrones, which indicates that the obtained products are found in the 4-hydroxypyridine rather than 4-pyridone form. The largest value $\Delta\delta = \delta_H(\text{pyridine}) - \delta_H(\text{pyrone})$ was found for protons H-3 and H-5 – 0.5–1.0 ppm, while for proton H-6, the value $\Delta\delta$ lies in the range of 0.05–0.36 ppm.

To conclude, the synthesis of 2-cyano-4-pyrone, which is the active substrate in reactions with N-nucleophiles for the construction of diverse azaheterocycles, was carried out. Depending on the nature of the nucleophile, reactions proceed either with the opening of the pyrone ring and substitution of the cyano group or selectively at the cyano group. In the latter case, it becomes possible to access such important classes of heterocycles as 2-heteroaryl-4-pyrones and 2-heteroaryl-4-hydroxypyridines.

## Experimental

IR spectra were registered on a Shimadzu IRSpirit-T spectrometer with the ATR. $^1$H and $^{13}$C NMR spectra were

**Scheme 5**



acquired on Bruker Avance II (400 and 101 MHz, respectively) or Bruker Avance-500 (500 and 126 MHz, respectively) spectrometers in pulse Fourier transform mode in $CDCl_3$ or DMSO-$d_6$. TMS or the residual solvent signals ($CDCl_3$ – 7.26 ppm, DMSO-$d_6$ – 2.50 ppm for $^1$H nuclei; DMSO-$d_6$ – 39.5 ppm, $CDCl_3$ – 77.1 ppm for $^{13}$C nuclei). High-resolution mass spectra were recorded on a Waters Xevo Qtof mass spectrometer, electrospray ionization. Elemental analysis was performed on a Perkin Elmer Series II 2400 elemental analyzer. Melting points were determined on an SMP40 apparatus. Ethyl comanate (**1**) was obtained according to a literature method.[12]

**4-Oxo-4*H*-pyran-2-carboxamide (2)**. Ethyl comanate (**1**) (2.50 g. 0.015 mol) was added to a 50-ml flask containing 20% aqueous $NH_3$ (25 ml) with cooling in a NaCl/ice bath. The obtained suspension was stirred at –10°C for 30 min. The formed precipitate was filtered off on a Buchner funnel and washed with $H_2O$ (10 ml). Yield 1.53 g (82%), colorless powder, mp 250°C (subl.). IR spectrum, ν, cm$^{-1}$: 3352, 3152, 3051, 1702, 1638, 1696. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 6.41 (1H, dd, *J* = 5.7, *J* = 2.3, H-5); 6.80 (1H, d, *J* = 2.3, H-3); 8.06 (1H, s, NHH); 8.20 (1H, d, *J* = 5.7, H-6); 8.30 (1H, s, NHH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 115.8; 117.4; 156.1; 156.5; 160.4; 178.0. Found, %: C 51.89; H 3.51; N 10.23. $C_6H_5NO_3$. Calculated, %: C 51.80; H 3.62; N 10.07.

**4-Oxo-4*H*-pyran-2-carbonitrile (3)**. $(CF_3CO)_2O$ (2.5 ml) was added to a mixture of carefully ground amide **2** (1.21 g, 8.70 mmol) and pyridine (1.73 ml) in anhydrous THF (16 ml), cooled in a NaCl/ice bath. The mixture was then stirred at –10°C for 3 h. The formed solution was diluted with $H_2O$ (30 ml), the product was extracted with $CHCl_3$ (3×10 ml). The combined extracts were concentrated under reduced pressure, and the residue was recrystallized from hexane–PhMe. Yield 0.50 g (48%), yellowish crystals, mp 90–91°C (mp 89–90°C[6]). IR spectrum, ν, cm$^{-1}$: 1705, 1621, 1599, 1502, 1483, 1474. $^1$H NMR spectrum corresponds to that described in the literature.[6] $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 6.53 (1H, dd, *J* = 6.0, *J* = 2.6, H-5); 7.32 (1H, d, *J* = 2.6, H-3); 8.26 (1H, d, *J* = 6.0, H-6). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 111.9; 118.3; 125.2; 138.1; 157.9; 175.7.

**Synthesis of enaminones 4a–f** (General method). The corresponding amine (1.82 mmol; 2.48 mmol amine for products **4a**,**b**) in cooled MeOH (1 ml) was added to a solution of 2-cyano-4-pyrone (**3**) (0.100 g, 0.826 mmol) in cold anhydrous MeOH (1 ml). The resulting reaction mixture was kept at –20°C for 7 days.

**(*Z*)-*N*-Butyl-5-(butylamino)-3-oxopent-4-enamide (4a)**. MeOH was evaporated, the product was isolated by column chromatography, eluent EtOAc. Yield 0.137 g (69%), dark-yellow liquid. IR spectrum, ν, cm$^{-1}$: 3277, 2957, 2872, 1637, 1537, 1286, 1115, 738. $^1$H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, t, *J* = 7.1, $CH_3$); 0.96 (3H, t, *J* = 7.1, $CH_3$); 1.32–1.45 (4H, m, $2CH_2$ butyl); 1.46–1.63 (4H, m, $2CH_2$ butyl); 3.21–3.32 (4H, m, $2CH_2$ butyl); 3.25 (2H, s, $CH_2$); 5.03 (1H, d, *J* = 7.1, =CH); 6.78 (1H, dd, *J* = 13.1, *J* = 7.1, CHN); 7.48 (1H, br. s, NHC=O); 9.94 (1H, br. s, NH). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm: 13.5; 13.7; 19.5; 31.4; 38.2; 42.3; 47.7; 50.0; 92.0; 167.2; 189.8; 191.3 (1C not detected). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 13.6; 13.7; 19.6; 20.1; 31.5; 32.9; 39.1; 47.8; 49.0; 93.4; 154.4; 167.6; 193.1. Found, %: C 64.57; H 10.08; N 11.93. $C_{13}H_{24}N_2O_2$. Calculated, %: C 64.97; H 10.07; N 11.66.

**(*Z*)-*N*-Octyl-5-(octylamino)-3-oxopent-4-enamide (4b)**. The precipitated crystals were filtered off and washed with cold EtOH. Yield 0.233 g (80%), gray crystals, mp 73–74°C. IR spectrum, ν, cm$^{-1}$: 2920, 2849, 1658, 1618, 1549, 1282, 1218, 959, 872. $^1$H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.81–1.79 (26H, m, $CH_3$ octyl, $CH_2$ octyl); 3.08–3.36 (10H, m, $CH_2$ octyl, $CH_2$); 5.03 (1H, d, *J* = 7.1, =CH); 6.76 (1H, dd, *J* = 13.1, *J* = 7.1, =CHN); 7.48 (1H, br. s, NHC=O); 9.92 (1H, br. s, NH). $^{13}$C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 14.0 (2C); 22.5; 22.6; 26.5; 26.9; 29.1 (2C); 29.2 (2C); 29.4 (2C); 30.9; 31.7; 31.8; 93.4; 154.4; 167.6; 193.2 (2C not detected). Found, %: C 71.49; H 11.53; N 7.93. $C_{21}H_{40}N_2O_2$. Calculated, %: C 71.54; H 11.44; N 7.95.

**(*Z*)-*N*-Benzyl-5-(benzylamino)-3-oxopent-4-enamide (4c)**. MeOH was evaporated at room temperature, and the residue was recrystallized from a mixture of PhMe–hexane. Yield 0.188 g (74%), colorless crystals, mp 106–107°C (mp 113–114°C[6]). IR spectrum, ν, cm$^{-1}$: 3369, 3262, 3030, 2919, 1649, 1629, 1562, 1249, 951, 771. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 3.14 (2H, s, $CH_2$); 4.27 (2H, d, *J* = 5.8, $CH_2$Ph); 4.41 (2H, d, *J* = 5.8, $CH_2$Ph); 5.04 (1H, d, *J* = 7.4, =CH); 7.07 (1H, dd, *J* = 13.1, *J* = 7.4, =CHN); 7.17–7.43 (10H, m, H Ph); 8.42 (1H, t, *J* = 5.8, NHC=O); 9.88 (1H, dt, *J* = 13.1, *J* = 5.8, NH). $^1$H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.33 (2H, s, $CH_2$); 4.39 (2H, d, *J* = 6.1, $CH_2$Ph); 4.46 (2H, d, *J* = 5.8, $CH_2$Ph); 5.10 (1H, d, *J* = 7.3, =CH); 6.83 (1H, dd, *J* = 13.0, *J* = 7.3, =CHN); 7.21–7.38 (10H, m, H Ph); 7.85 (1H, br. s, NHC=O); 9.88 (1H, br. s, NH). $^{13}$C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 43.3; 47.7; 52.8; 94.2; 127.2; 127.6; 127.9; 128.5; 128.9; 137.1; 138.4; 154.2; 167.5; 193.4 (1C not detected). Found, %: C 74.20; H 6.45; N 9.29. $C_{19}H_{20}N_2O_2$. Calculated, %: C 74.00; H 6.54; N 9.08.

**(*Z*)-3-Oxo-*N*-phenyl-5-(phenylamino)pent-4-enamide (4d)**. The precipitated crystals were filtered off and washed with cold EtOH. Yield 0.153 g (66%), yellow crystals, mp 138–139°C. IR spectrum, ν, cm$^{-1}$: 3263, 3058, 3034, 1674, 1648, 1597, 1544, 1475, 1268, 987, 887, 837, 802. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 3.46 (2H, s, $CH_2$); 5.42 (1H, d, *J* = 7.9, =CH); 7.00–7.09 (2H, m, H Ph); 7.22–7.38 (6H, m, H Ph); 7.60 (2H, d, *J* = 7.9, H-2,6 Ph); 7.73 (1H, dd, *J* = 12.5, *J* = 7.9, =CHN); 10.12 (1H, s, NHC=O); 11.42 (1H, d, *J* = 12.5, NH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 49.2; 96.5; 115.5; 119.0; 122.2; 123.2; 128.7; 129.5; 139.2; 140.9; 144.5; 166.2; 190.8. Found, %: C 72.85; H 5.61; N 9.99. $C_{17}H_{16}N_2O_2$. Calculated, %: C 72.84; H 5.75; N 9.99.

**(*Z*)-3-Oxo-*N*-(*o*-tolyl)-5-(*o*-tolylamino)pent-4-enamide (4e)**. The precipitated crystals were filtered off and washed with cold EtOH. The filtrate was evaporated, and the

residue was recrystallized from a mixture of PhMe–hexane. Combined yield 0.158 g (62%), colorless crystals, mp 126–127°C. IR spectrum, ν, $cm^{-1}$: 3253, 3030, 1642, 1587, 1565, 1524, 1470, 1456, 1276, 1115, 967. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 2.39 (3H, s, $CH_3$); 2.41 (3H, s, $CH_3$); 3.60 (2H, s, $CH_2$); 5.47 (1H, d, *J* = 7.4, =CH); 7.03–7.12 (2H, m, H Ar); 7.16–7.34 (6H, m, H Ar); 7.48 (1H, dd, *J* = 12.5, *J* = 7.4, =CHN); 10.12 (1H, s, NH); 11.42 (1H, d, *J* = 12.5, NH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 17.0; 17.8; 50.3; 96.9; 113.7; 123.2; 124.4; 124.9; 125.0; 125.9; 127.3; 130.3; 130.9; 131.1; 136.2; 138.2; 145.1; 165.7; 193.9. Found, %: C 73.93; H 6.47; N 9.24. $C_{19}H_{20}N_2O_2$. Calculated, %: C 74.00; H 6.54; N 9.08.

**(*Z*)-*N*-(4-Methoxyphenyl)-5-(4-methoxyphenylamino)-3-oxopent-4-enamide (4f)**. The precipitated crystals were filtered off. The product was recrystallized from a mixture of PhMe–hexane. Yield 0.245 g (87%), yellow crystals, mp 149–151°C (mp 152–153°C[6]). IR spectrum, ν, $cm^{-1}$: 3301, 3009, 2832, 1636, 1568, 1025, 751. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 3.38 (2H, s, $CH_2$); 3.72 (3H, s, $OCH_3$); 3.73 (3H, s, $OCH_3$); 5.36 (1H, d, *J* = 7.7, =CH); 6.88 (2H, d, *J* = 8.9, H-3,5 ArNHC=C); 6.92 (2H, d, *J* = 8.9, H-3,5 ArNHC=O); 7.21 (2H, d, *J* = 8.9, H-2,6 ArNHC=C); 7.51 (2H, d, *J* = 8.9, H-2,6 ArNHC=O); 7.62 (1H, dd, *J* = 12.7, *J* = 7.7, =CH); 9.96 (1H, s, CONH); 11.46 (1H, d, *J* = 12.7, NH). Found, %: C 67.08; H 6.05; N 8.09. $C_{19}H_{20}N_2O_4$. Calculated, %: C 67.05; H 5.92; N 8.23.

**Synthesis of 4-oxo-1,4-dihydropyridine-3-carboxamides 5a–c** (General method). Enaminone **4c**,**d**,**f** (0.325 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.078 g, 0.65 mmol) in anhydrous PhMe (1 ml) were stirred at room temperature for 24 h. The formed precipitate was filtered off and washed with hexane.

***N*,1-Dibenzyl-4-oxo-1,4-dihydropyridine-3-carboxamide (5a)**. Yield 0.083 g (80%), gray powder, mp 125–127°C (mp 129–130°C[6]). IR spectrum, ν, $cm^{-1}$: 3088, 3074, 1662, 1622, 1547, 1489, 1187, 839. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 4.51 (2H, d, *J* = 6.0, PhC<u>H</u>$_2$NH); 5.31 (2H, s, PhC<u>H</u>$_2$N); 6.47 (1H, d, *J* = 7.6, 5-CH); 7.20–7.43 (10H, m, H Ph); 7.96 (1H, dd, *J* = 7.6, *J* = 2.4, 6-CH); 8.67 (1H, d, *J* = 2.4, 2-CH); 10.65 (1H, t, *J* = 6.0, NH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 42.0; 59.0; 118.5; 120.2; 127.3; 127.8; 128.4 (2C); 129.0; 136.2; 139.3; 141.4; 144.8; 163.8; 176.5 (1C not detected). Found, %: C 75.39; H 5.69; N 8.91. $C_{20}H_{18}N_2O_2$. Calculated, %: C 75.45; H 5.70; N 8.80.

**4-Oxo-*N*,1-diphenyl-1,4-dihydropyridine-3-carboxamide (5b)**. Yield 0.082 g (87%), yellow powder, mp 134–135°C. IR spectrum, ν, $cm^{-1}$: 3098, 2961, 1686, 1629, 1598, 1544, 1488, 1294, 1230, 833. $^1$H NMR spectrum (500 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 6.69 (1H, d, *J* = 7.5, 5-CH); 7.11 (1H, t, *J* = 7.4, H-4 Ph); 7.37 (2H, t, *J* = 7.9, H-3,5 Ph); 7.56 (1H, tt, *J* = 7.4, *J* = 1.1, H-4 Ph); 7.63 (2H, t, *J* = 8.1, H-3,5 Ph); 7.67–7.73 (4H, m, H Ph); 8.27 (1H, dd, *J* = 7.5, *J* = 2.5, 6-CH); 8.71 (1H, d, *J* = 2.5, 2-CH); 12.62 (1H, s, CONH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 118.5; 119.7; 120.2; 123.3; 123.8; 128.9; 129.1; 130.1; 138.4; 141.0; 142.6; 144.0; 161.7; 176.9. Found, %: C 74.22; H 4.86; N 9.89. $C_{18}H_{14}N_2O_2$. Calculated, %: C 74.47; H 4.86; N 9.65.

***N*,1-Bis(4-methoxyphenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide (5c)**. Yield 0.084 g (74%), yellow powder, mp 201–202°C (mp 201–202°C[6]). IR spectrum, ν, $cm^{-1}$: 3074, 2902, 2835, 1677, 1608, 1552, 1504, 1236, 1018, 822. $^1$H and $^{13}$C NMR spectra correspond to those described in the literature.[6] $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 3.75 (3H, s, $OCH_3$); 3.84 (3H, s, $OCH_3$); 6.65 (1H, d, *J* = 7.4, 5-CH); 6.88 (2H, d, *J* = 8.8, H-3,5 ArNHC=O); 7.14 (2H, d, *J* = 8.9, H-3,5 ArN); 7.56–7.67 (4H, m, H Ar); 8.17 (1H, dd, *J* = 7.4, *J* = 2.4, 6-CH); 8.62 (1H, d, *J* = 2.4, 2-CH); 12.50 (1H, s, CONH).

**(*Z*)-2-[(4-Bromophenyl)(piperidin-1-yl)methyl]-3-oxo-*N*-phenyl-5-(phenylamino)pent-4-enamide (6)**. Enaminone **4d** (100 mg, 0.357 mmol), *p*-bromobenzaldehyde (72.6 mg, 0.393 mmol), and piperidine (36.5 mg, 0.428 mmol) in anhydrous MeCN (2 ml) were stirred at room temperature for 2 days. The formed precipitate was filtered off. Yield 0.144 g (76%), yellow powder, mp 145–146°C. IR spectrum, ν, $cm^{-1}$: 3273, 2939, 2809, 2756, 1678, 1627, 1598, 1479, 1274, 1128, 973. $^1$H NMR spectrum (500 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 1.10–1.21 (2H, m, $CH_2$); 1.25–1.43 (4H, m, $CH_2$); 2.01–2.19 (2H, m, $CH_2$); 2.42–2.52 (2H, m, $CH_2$); 4.43 (1H, d, *J* = 11.9, CH); 4.52 (1H, d, *J* = 11.9, CH); 5.47 (1H, d, *J* = 7.7, =CH); 7.01 (1H, t, *J* = 7.3, H-4 Ph); 7.07 (1H, t, *J* = 7.4, H-4 Ph); 7.14 (2H, d, *J* = 8.3, H Ph, H Ar); 7.16 (2H, d, *J* = 8.1, H Ph, H Ar); 7.28 (2H, t, *J* = 8.0, H-3,5 Ph); 7.33 (2H, t, *J* = 7.9, H-3,5 Ph); 7.53 (2H, d, *J* = 8.3, H Ph, H Ar); 7.59 (1H, dd, *J* = 12.7, *J* = 7.7, =CH); 7.61 (2H, d, *J* = 7.8, H Ph, H Ar); 10.26 (1H, s, NH); 11.13 (1H, d, *J* = 12.7, NH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$) (selected signals), δ, ppm: 24.1; 26.1; 50.1; 60.7; 61.5; 96.7; 115.5; 119.0; 122.2; 123.7; 128.8; 129.5; 130.4; 130.5; 130.7; 134.6; 139.2; 140.8; 144.5; 166.9; 189.8. Found, %: C 65.67; H 5.86; N 8.03. $C_{29}H_{30}BrN_3O_2$. Calculated, %: C 65.41; H 5.68; N 7.89.

**(Pyrazol-3-yl)acethydrazide (7)**. Hydrazine hydrate (0.330 g, 6.60 mmol) in MeOH (1 ml) was added with stirring to a solution of 2-cyano-4-pyrone (**3**) (0.200 g, 1.65 mmol) in MeOH (1 ml) with cooling in ice bath. The reaction mixture was stirred with cooling for 1 h and at room temperature for 12 h. The precipitate was filtered off and washed with cold EtOH. Yield 0.151 g (65%), colorless powder, mp 181–182°C (mp 181–183°C[13]). IR spectrum, ν, $cm^{-1}$: 3276, 3133, 2881, 1649, 1620, 1533, 1171, 757. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 3.35 (2H, s, $CH_2$); 4.20 (2H, br. s, $NH_2$); 6.10 (1H, br. s, H-4 pyrazole); 7.24–7.65 (1H, br. s, H-5 pyrazole); 9.09 (1H, br. s, N<u>H</u>$NH_2$); 12.51 (1H, br. s, NH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: major NH-tautomer: 33.7; 103.9; 128.7; 146.0; 169.0; minor NH-tautomer: 30.8; 136.5; 168.1.

***N*'-Phenyl-2-(1-phenyl-1*H*-pyrazol-5-yl)acethydrazide (8)** was not isolated as an individual substance. 2-Cyano-4-pyrone (**3**) (0.100 g, 0.83 mmol) and phenylhydrazine (0.196 g, 1.82 mmol) were mixed in MeOH (1 ml) in ice

bath, and the mixture was kept at room temperature for 2 days. The formed precipitate was filtered off. Yield 0.138 g (57%), gray powder, the crude product is a mixture of regioisomers **8**:**9** = 67:33. Compound **8** in DMSO-$d_6$ solution exists as a mixture of rotamers *sin*:*anti* = 83:17. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): *sin*-**8** (83%): 3.70 (2H, s, $CH_2$); 6.42 (1H, d, *J* = 1.2, H-4); 6.59 (2H, d, *J* = 7.9, H-2,6 Ph); 6.68 (1H, t, *J* = 7.3, H-4 Ph); 7.10 (2H, t, *J* = 7.8, H-3,5 Ph); 7.52–7.56 (5H, m, H Ph); 7.62 (1H, d, *J* = 1.2, H-3); 7.74 (1H, d, *J* = 2.4, PhNHNH); 9.83 (1H, d, *J* = 2.4, PhNHNH); *anti*-**8** (17%) (selected signals): 3.73 (2H, s, $CH_2$); 6.34 (1H, d, *J* = 1.2, H-4); 7.95 (1H, s, PhNHNH); 9.19 (1H, s, PhNHNH). Found, *m*/*z*: 293.1390 $[M+H]^+$. $C_{17}H_{17}N_4O$. Calculated, *m*/*z*: 293.1402.

***N*'-Phenyl-2-(1-phenyl-1*H*-pyrazol-3-yl)acethydrazide (9)**. 2-Cyano-4-pyrone (**3**) (0.100 g, 0.83 mmol) and phenylhydrazine (0.196 g, 1.82 mmol) in PhMe (2 ml) were kept at room temperature for 2 days. The formed precipitate was filtered off. Yield 0.215 g (89%), gray powder, mp 154–155°C, the crude product is a mixture of regioisomers **8**:**9** = 15:85. After recrystallization from EtOH, compound **9** was obtainned in pure form. Yield 0.115 g (46%), yellow crystals, mp 164–165°C. IR spectrum, ν, cm$^{-1}$: 3361, 3229, 3046, 1683, 1651, 1595, 1492, 1384, 1242, 1046, 838. Compound **9** in DMSO-$d_6$ solution exists as a mixture of rotamers *sin*:*anti* = 93:7. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): *sin*-**9** (93%): 3.60 (2H, s, $CH_2$); 6.46 (1H, d, *J* = 2.6, H-4); 6.69 (1H, t, *J* = 7.3, H-4 Ph); 6.75 (2H, d, *J* = 7.7, H-2,6 Ph); 7.12 (2H, t, *J* = 7.8, H-3,5 Ph); 7.29 (1H, t, *J* = 7.4, H-4 Ph); 7.50 (2H, t, *J* = 8.0, H-3,5 Ph); 7.78 (1H, d, *J* = 2.5, PhNHNH); 7.83 (2H, d, *J* = 7.7, H-2,6 Ph); 8.43 (1H, d, *J* = 2.6, H-5); 9.89 (1H, d, *J* = 2.5, PhNHNH); *anti*-**9** (7%) (selected signals): 3.67 (2H, s, $CH_2$); 6.39 (1H, d, *J* = 2.4, H-4); 8.06 (1H, s, PhNHNH); 8.37 (1H, d, *J* = 2.4, H-5); 9.15 (1H, s, PhNHNH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 33.8; 107.8; 112.1; 117.9; 118.4; 125.9; 128.3; 128.6; 129.5; 139.6; 148.4; 149.2; 168.8. Found, %: C 69.91; H 5.63; N 19.13. $C_{17}H_{16}N_4O$. Calculated, %: C 69.85; H 5.52; N 19.17.

**4-Oxo-4*H*-pyran-2-carboxylic acid amidoxime (10)**. KOH (0.200 g, 3.57 mmol) and $NH_2OH·HCl$ (0.270 g, 3.89 mmol) were stirred in MeOH (4 ml) for 10 min, the formed precipitate of KCl was filtered. The filtrate was added from the dropping funnel to a cooled solution of 2-cyano-4-pyrone (**3**) (0.400 g, 3.30 mmol) in MeOH (4 ml). The reaction mixture was stirred with cooling for further 2 h, the resulting product was filtered off. Yield 0.367 g (72%), gray powder, mp 235–237°C. IR spectrum, ν, cm$^{-1}$: 3399, 3151, 1680, 1606, 1253, 906, 796. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 5.77 (2H, s, $NH_2$); 6.26 (1H, dd, *J* = 5.8, *J* = 2.5, 5-CH); 6.63 (1H, d, *J* = 2.5, 3-CH); 8.04 (1H, d, *J* = 5.8, 6-CH); 10.33 (1H, s, OH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 112.4; 116.9; 145.3; 156.1; 157.6; 177.5. Found, %: C 46.37; H 3.80; N 17.93. $C_6H_6N_2O_3$. Calculated, %: C 46.76; H 3.92; N 18.18.

**2-[5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl]-4*H*-pyran-4-one (11)**. Amidoxime **10** (0.100 g, 0.649 mmol), $(CF_3CO)_2O$ (0.400 g, 1.95 mmol), pyridine (0.150 g, 1.95 mmol) in anhydrous $CH_2Cl_2$ (2 ml) were stirred in ice bath for 1 h, then the mixture was kept at room temperature overnight. The solvent was evaporated under reduced pressure, and $H_2O$ was added to the residue. The precipitate was filtered off and recrystallized from a mixture of PhMe–hexane. Yield 0.062 g (41%), gray crystals, mp 123–125°C. IR spectrum, ν, cm$^{-1}$: 3081, 1723, 1655, 1312, 1180, 1149, 847. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 6.47 (1H, dd, *J* = 5.9, *J* = 2.6, 5-CH); 7.05 (1H, d, *J* = 2.6, 3-CH); 8.30 (1H, d, *J* = 5.9, 6-CH). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 115.4 (q, *J* = 273.4, $CF_3$); 117.8; 118.0; 151.1; 157.1 (q, *J* = 18.1, C-2); 163.3; 165.6 (q, *J* = 44.5, $\underline{C}CF_3$); 176.6. Found, %: C 41.43; H 1.47; N 11.70. $C_8H_3F_3N_2O_3$. Calculated, %: C 41.40; H 1.30; N 12.07.

**2-(Tetrazol-5-yl)-4*H*-pyran-4-one (12)**. 2-Cyano-4-pyrone (**3**) (0.400 g, 3.30 mmol), $NH_4Cl$ (0.265 g, 4.95 mmol), $NaN_3$ (0.322 g, 4.95 mmol), and THF–$H_2O$, 1:1 (8 ml) were heated under reflux for 1.5 h (until phase separation disappears). Then, THF was evaporated, and the residue was treated with 4 M aqueous HCl to pH 1. The precipitate from $H_2O$ was filtered off and washed with $H_2O$. Yield 0.352 g (65%), colorless powder, mp 215–216°C (decomp.). IR spectrum, ν, cm$^{-1}$: 3084, 1654, 1618, 1420, 932. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 6.23 (1H, dd, *J* = 5.8, *J* = 2.6, 5-CH); 6.77 (1H, d, *J* = 2.6, 3-CH); 8.12 (1H, d, *J* = 5.8, 6-CH). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm: 115.5; 117.5; 152.2; 152.6; 156.7; 176.9. Found, %: C 43.70; H 2.25; N 34.21. $C_6H_4N_4O_2$. Calculated, %: C 43.91; H 2.46; N 34.14.

**2-(5-Methyl-1,3,4-oxadiazol-2-yl)-4*H*-pyran-4-one (13)**. Tetrazolylpyrone **12** (0.300 g, 1.73 mmol) in $Ac_2O$ (12 ml) was heated under reflux for 24 h. After that, the solvent was evaporated in an evaporating dish at room temperature, and the residue was recrystallized from a PhMe–hexane mixture. Yield 0.204 g (66%), colorless crystals, mp 164–165°C. IR spectrum, ν, cm$^{-1}$: 3076, 3049, 1655, 1625, 1343, 1217, 909. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 2.65 (3H, s, $CH_3$); 6.42 (1H, dd, *J* = 5.9, *J* = 2.5, H-5); 6.93 (1H, d, *J* = 2.5, H-3); 8.26 (1H, d, *J* = 5.9, H-6). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm: 10.6; 115.9; 117.6; 149.6; 156.8; 158.1; 165.6; 176.6. Found, *m*/*z*: 179.0457 $[M+H]^+$. $C_6H_8N_3O_2$. Calculated, *m*/*z*: 179.0457.

**4-Hydroxypicolinic acid amidoxime (14)**. Amidoxime **10** (0.100 g, 0.65 mmol) and 20% aqueous $NH_3$ (2 ml) were stirred for 4 days. The solvent was evaporated in an evaporating dish at room temperature, the solid residue was washed with PhMe and dried at 120°C. Yield 0.087 g (88%), beige powder, mp 235–236°C. IR spectrum, ν, cm$^{-1}$: 3253, 3034, 2784, 1655, 1594, 1386, 1218, 966, 863. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 5.78 (2H, s, $NH_2$); 6.73 (1H, br. s, H-5); 7.19 (1H, br. s, H-3); 8.17 (1H, br. s, H-6); 9.83 (1H, br. s, OH); 10.18–11.05 (1H, br. s, OH). $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 106.4; 112.6; 149.4; 151.4; 164.2 (1C not detected). Found, *m*/*z*: 154.0621 $[M+H]^+$. $C_6H_8N_3O_2$. Calculated, *m*/*z*: 154.0617.

**4-Hydroxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine (15)**. Pyrone **13** (0.070 g, 0.39 mmol) in 15% $NH_3$/EtOH (2 ml) was stirred at 0°C for 1 h, then the stirring was continued for 4 days. The starting pyrone dissolved over time. The excess solvent was evaporated in an evaporating dish at room temperature, the solid residue was washed with PhMe and dried at 120°C. Yield 0.052 g (75%), gray crystals, mp 190–191°C. IR spectrum, ν, $cm^{-1}$: 3312, 2851, 1677, 1634, 1524, 1196, 1095, 992, 869, 815. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 2.60 (3H, s, $CH_3$); 6.85 (1H, dd, *J* = 5.6, *J* = 2.3, H-5); 7.44 (1H, d, *J* = 2.3, H-3); 8.31 (1H, d, *J* = 5.6, H-6); OH proton not detected. $^{13}$C NMR spectrum (126 MHz, DMSO-$d_6$), δ, ppm: 10.6; 110.4; 114.0; 144.0; 151.1; 163.6; 164.6; 165.5. Found, *m*/*z*: 178.0622 $[M+H]^+$. $C_8H_8N_3O_2$. Calculated, *m*/*z*: 178.0617.

**2-(1*H*-Tetrazol-5-yl)-4-hydroxypyridine (16)**. Tetrazolylpyrone **12** (0.100 g, 0.58 mmol) in 20% aqueous $NH_3$ (2 ml) was kept for 4 day. Ammonia was evaporated under reduced pressure, 4 M aqueous HCl (4 ml) was added to the residue, the formed precipitate was filtered off and dried at 120°C. Yield 0.068 g (68%), colorless crystals, mp >318°C. IR spectrum, ν, $cm^{-1}$: 3096, 2897, 1618, 1463, 1315, 1230, 865. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (*J*, Hz): 7.18 (1H, dd, *J* = 6.1, *J* = 2.3, H-5); 7.81 (1H, d, *J* = 2.3, H-3); 8.46 (1H, d, *J* = 6.1, H-6); 8.50 (2H, br. s, OH, NH). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm: 110.1; 113.6; 114.6; 149.4; 154.9; 166.7. Found, %: C 44.17; H 3.21; N 42.83. $C_6H_5N_5O$. Calculated, %: C 44.17; H 3.09; N 42.93.

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