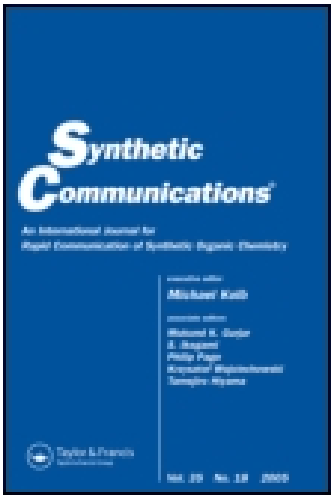

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Synthesis of Functionalized Pyrano[3,2-c]pyridines and Their Transformations to 4-Hydroxy-3[(1E)-N-hydroxyalkanimidoyl]pyridon

Farag A. El-Essawy [a], Ahmed F. Khattab [a], Magdy A. Zahran [a] & Sherif H. Gomaa [a]

[a] Faculty of Science, Chemistry Department, Monoufiya University, Shebin El-Koam, Egypt

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Synthesis of Functionalized Pyrano[3,2-*c*]pyridines and Their Transformations to 4-Hydroxy-3[(1*E*)-*N*-hydroxyalkanimidoyl]pyridones

Farag A. El-Essawy, Ahmed F. Khattab, Magdy A. Zahran, and Sherif H. Gomaa
Faculty of Science, Chemistry Department, Monoufiya University, Shebin El-Koam, Egypt

Abstract: Reaction of 4-hydroxy-6-methyl-2(1H)-pyridones **1a** and 4-hydroxy-1,6-dimethyl-2(1H)-pyridones **1b** with diethyl malonates **2a**–**e** leads to the formation of pyrano[3,2-c]pyridines **4a**–**j**. Degradation of **4a**–**i** affords the corresponding ketones **6a**–**i**. Condensation of ketones **6a**–**i** with hydroxyl amine or phenyl hydrazine hydrochloride is described.

Keywords: ethyl malonates, 4-hydroxy-2-pyridones, pyrano[3,2-c]pyridines

Pyrano[3,2-*c*]pyridine derivatives are known to possess various important biological properties such as antimicrobial, anti-angiogenic, antiviral, and cytotoxic activities.[1–3] Although a great deal of work has been published on polcyclic pyridine-containing compounds, much less is known about pyrano[3,2-*c*]pyridine systems. However, in general there has little exploitation in developing novel routes to synthesize pyrano[3,2-*c*]pyridines. Chakrasali et al. described synthesis based on the reaction of the acylketene *S*,*N*-acetals with excess of malonyl chloride.[4] Mekheimer et al.[5] and Stoyanov et al.[6] reported the cyclization of 4-hydroxy-2-pyridones with

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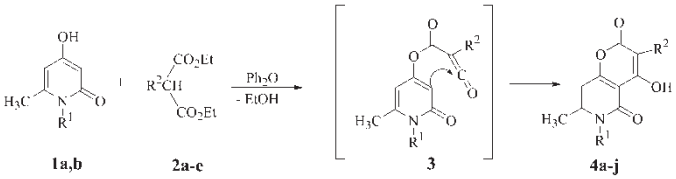
Address correspondence to Ahmed F. Khattab, Faculty of Science, Chemistry Department, Monoufiya University, Shebin El-Koam, Egypt. E-mail: khattab2000@yahoo.com

either arylmethylene cyanoacetic esters or arylmethylene malononitriles to the corresponding pyrano[3,2-*c*]pyridines. Toche et al.[7] obtained pyrano[3,2-c]pyridines using the condensation reaction of 4-hydroxy-2-pyridones with β-keto ester in the presence of ammonium acetate. Tchbanenko et al.[8] described synthesis via Diels–Alder reaction of 3-methylenepyridin-4-one with alkenes. Therefore, it seems to be possible to synthesize pyrano[3,2-*c*]pyridines in high yields by a convenient method from simple laboratory reagents. Pyrones have been obtained by the condensation of enols or phenols with 2-unsubstituted or 2-monosubstituted diethyl malonates.[9] The present study is a continuation of our previous efforts[10–14] to use malonates in the development of a new, simple, efficient, and one-step procedure for the synthesis of new heterocyclic compounds. We report here a convenient synthesis of hitherto unknown polyfunctionally substituted pyrano[3,2-*c*]pyridines and their reactions utilizing 4-hydroxy-2-pyridones **1a**,**b** and malonates as the starting materials.

RESULTS AND DISCUSSION

The general method for the preparation of 4-hydroxy-7-methyl-3-(unsubstituted)substituted-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones **4a–e** is outlined in Scheme 1 by condensation of 4-hydroxy-6-methyl-2(1*H*)-pyridone **1a** with diethyl malonates **2a–e** in diphenyl ether at 200–250°C. Beside 4-hydroxy-6-methyl-2(1*H*)-pyridone **1a**, its *N*-methyl derivative **1b** was also successfully employed in the reaction to afford 4-hydroxy-6,7-dimethyl-3-(unsubstituted)-substituted-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones **4f–j**. This propably formed via the formation of ketene intermediate **3** as described earlier.[15] The ketene mechanism is also supported by observations obtained during the reaction where, at temperatures less than 200°C, the first mole of alcohol is observed to be liberated when the open chain ester is formed.



1a,b **2a-c** **3** **4a-j**

1a, R^1 = H
1b, R^1 = CH_3

2a, R^2 = H
2b, R^2 = CH_3
2c, R^2 = C_2H_5
2d, R^2 = C_4H_9-n
2e, R^2 = C_6H_5

4a- R^1 = H, R^2 = H
4b- R^1 = H, R^2 = CH_3
4c- R^1 = H, R^2 = C_2H_5
4d- R^1 = H, R^2 = C_4H_9-n
4e- R^1 = H, R^2 = C_6H_5

4f- R^1 = CH_3, R^2 = H
4g- R^1 = CH_3, R^2 = CH_3
4h- R^1 = CH_3, R^2 = C_2H_5
4i- R^1 = CH_3, R^2 = C_6H_5
4j- R^1 = CH_3, R^2 = C_4H_9-n

Scheme 1.

Increasing the temperature up to 250°C leads to liberation of the second mole of alcohol and forms the ketene intermediate **3**. The yield ranges between 78 and 96%, which shows that no further activation of the malonates is necessary. The only disadvantage of this reaction sequence is its high reaction temperature, which prevents its use with sensitive substrates and substituents.

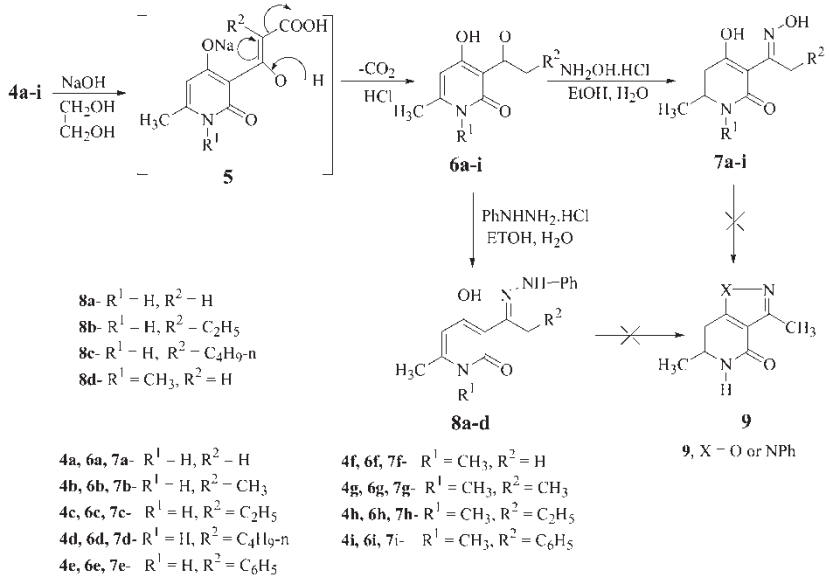
The structures of **4a–j** could be unambiguously deduced on the basis of elemental analysis and their spectral properties. The lactone carbonyl group showed strong IR absorption in the range 1701–1733 cm^{-1}. The ^1H NMR spectra of **4a–j** are in full agreement with the suggested molecular structures (Table 1).

Degradation of pyranopyridines **4a–i** to the corresponding ketones **6a–i** was performed in 1,2-ethandiol/aqueous sodium hydroxide during 2 h, instead of the 12 h necessary in aqueous sodium hydroxide solution,[16] to yield the highly pure ketones **6a–i** after acidification with conc. HCl (Scheme 2).

The formation of **6a–i** is assumed to proceed via the intermediate **5**, which is formed by carbonyllactone bond cleavage with pyrone ring

Table 1. ^1H NMR spectral data of compounds **4a–j**

Compd.	^1H NMR (δ in ppm)
4a	2.31 (s, 3H, 7-CH_3), 5.34 (s, 1H, 3-H), 6.43 (s, 1H, 8-H), 12.75 (bs, 1H, NH), 13.23 (bs, 1H, OH)
4b	1.78 (s, 3H, 3-CH_3), 2.29 (s, 3H, 7-CH_3), 6.37 (s, 1H, 8-H), 12.60 (bs, 1H, NH), 13.20 (bs, 1H, OH)
4c	1.01 (t, 3H, $J = 7.4$ Hz, C$H_3$$CH_2$), 2.33 (q, 2H, $J_1 = 7.4$ Hz, $J_2 = 10.8$ Hz, C$H_2$$CH_3$), 2.52 (s, 3H, 7-$CH_3$), 6.40 (s, 1H, 8-H), 12.69 (bs, 1H, NH), 13.25 (bs, 1H, OH)
4d	0.90 (t, 3H, $J = 7.2$ Hz, C$H_3$$CH_2$-), 1.27–1.31 (m, 2H, -$CH_2$-), 1.33–1.42 (m, 2H, -$CH_2$-), 2.33 (t, 2H, $J = 6.3$ Hz, -C$H_2$$CH_2$-), 2.50 (s, 3H, 7-$CH_3$), 6.41 (s, 1H, 8-H), 12.68 (bs, 1H, NH), 13.26 (bs, 1H, OH)
4e	2.36 (s, 3H, 7-CH_3), 6,51 (s, 1H, 8-H), 7.28–7.47 (m, 5H, arom), 12.84 (bs, 1H, NH), 13.76 (bs, 1H, OH)
4g	1.81 (s, 3H, 3-CH_3), 2.49 (s, 3H, 7-CH_3), 3.51 (s, 3H, N-CH_3), 6.57 (s, 1H, 8-H), 13.26 (s, 1H, OH)
4h	1.01 (t, 3H, $J = 7.5$ Hz, C$H_3$$CH_2$), 2.36 (q, 2H, $J_1 = 7.5$ Hz, $J_2 = 15$ Hz, C$H_2$$CH_3$), 2.50 (s, 3H, 7-CH3), 3.51 (s, 3H, N-CH_3), 6.59 (s, 1H, 8-H), 13.33 (s, 1H, OH)
4i	2.50 (s, 3H, 7-CH_3), 3.54 (s, 3H, N-CH_3), 6.68 (s, 1H, 8-H), 7.29–7.48 (m, 5H, arom),13.81 (s, 1H, OH)
4j	0.88 (t, 3H, $J = 7.2$ Hz, C$H_3$$CH_2$-), 1.27–1.31 (m, 2H, CH2-), 1.33-1.42 (m, 2H, CH2-), 2.34 (t, 2H, $J = 7.5$ Hz, C$H_2$$CH_2$-), 2.50 (s, 3H, 7-$CH_3$), 3.51 (s, 3H, N-$CH_3$), 6.58 (s, 1H, 8-H), 13.33 (s, 1H, OH)



Scheme 2.

opening under the influence of NaOH solution, followed by a proton shift and intramolecular rearrangement with elimination of carbon dioxide to give the final product **6a–i**. Products **6a–i** are characterized from their elemental and spectral data. Condensation of ketones **6a–i** with hydroxyl amine was performed in a 1:1 ethanol/water mixture to afford the 4-hydroxy-3[(1*E*)-*N*-hydroxyalkanimidoyl]pyridones **7a–i** in 62–99% yield. Similarly, 4-hydroxy-3-[(1*E*)-*N*-phenylalkanehydrazonoyl]pyridons **8a–d** are obtained on the condensation of phenylhydrazine hydrochloride with ketones **6a**, **6c**, **6d**, and/or **6f**, respectively. The mass spectra of **7** and **8** confirmed the corresponding molecular masses. IR and ^{1}H NMR were not decisive for the elucidation of the structure configuration of compounds **7**. An absolute proof of the structure was achieved by X-ray analysis of compound **7a**. It shows that the compound **7a**, namely, 4-hydroxy-3-[(1*E*)-*N*-hydroxyethanimidoyl]-6-methylpyridin-2(1*H*)-one, exists as *E*-configuration and not as *Z*-configuration (Figure 1).

Crystallographic data for **7a**: chemical formula: $C_9H_{12}N_2O_3$, molecular weight: 196.206, temperature: 298 K, Mo Kα radiation: $\lambda = 0.71073$, crystal color: colorless, crystal system: monoclinic, unit cell parameters: a = 6.8949(4) Å, b = 13.2980 (7) Å, c = 11.5871 (8) Å, $\alpha = 90.00^\circ$, $\beta = 12$; (18) $\times 10^{1^\circ}$, $\gamma = 90.00^\circ$; space group: $P2_1/c$, cell volume: 937.76 (10) Å^3, cell formula units Z:4. Complete X-ray data for compound **7a** was deposited at the Cambridge Crystallographic Data Centre under the

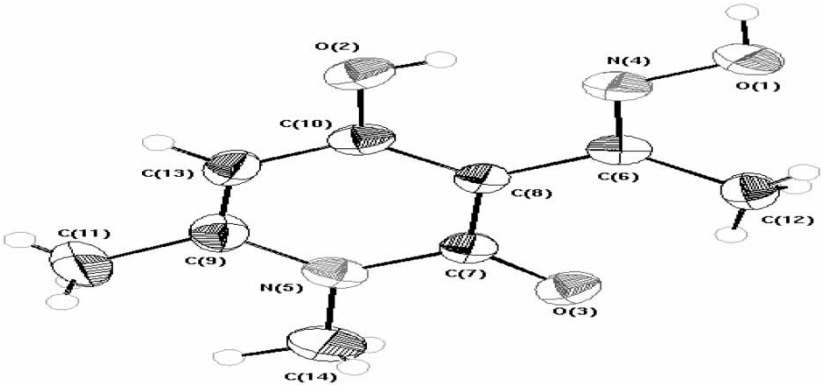


Figure 1.

reference number CCDC 292267; copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

All attempts to perform cyclization of either **7a** or **8a** to isoxazolopyridine derivative **9** (X = O) or pyrazolopyridine derivative **9** (X = NPh) through isomerization of *E*-configuration of **7** to *Z*-configuration and then intramolecular cyclization failed. Either no reaction took place or, under drastic conditions, decomposition of starting material was observed.

EXPERIMENTAL

Melting points were determined on a Buchi melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Germini-2000 (300 MHz) instrument and registered in DMSO-d6, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were measured on a Kratos 50 tc spectrometer. Microanalysis was performed in the microanalysis laboratory at Cairo University. X-ray calculations were performed using maXus (Bruker Nonius, Delft and MaxScience) at the National Research Center, Dokki, Cairo, Egypt. Common reagent-grade chemicals were either commercially available and were used without further purification or were prepared by standard literature procedure. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2-mm silica gel 60 F-254 (Merck) plates using UV light (254 and 360 nm) for detection. Preparation, analysis, and spectral data for compounds **4f** and **6f** have been reported earlier.[11]

General Procedure for Preparation of 4-Hydroxy-7-methyl-3-(unsubstituted)substituted-2*H* -pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones (4a–e)

A mixture of 4-hydroxy-6-methyl-2(1*H*)-pyridone **1a** (10 mmol) and the appropriate ethyl malonate (10 mmol) in diphenyl ether (5 ml) was heated at reflux in a distillation apparatus equipped with a 20-cm Vigreux column. Over 2–3 h, the liberated ethanol was distilled until no more ethanol was formed. Then the reaction mixture was allowed to cool to room temperature and treated with diethylether; the obtained precipitate was filtered off, washed with petroleum ether, dried and recrystallized from the appropriate solvent. Experimental data: Table 2; spectroscopic data: Table 1.

General Procedure for the Preparation of 4-Hydroxy-6,7-dimethyl-3-(unsubstituted)substituted-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones (4f–j)

A mixture of 4-hydroxy-1,6-dimethyl-2(1*H*)-pyridone **1b** (10 mmol) and the appropriate ethyl malonate (10 mmol) in diphenylether (5 ml) was heated at reflux in a distillation apparatus equipped with a 20-cm Vigreux column for 2–3 h. Then the reaction mixture was worked up as described previously for preparation of **4a–e** to afford **4f–j**. Experimental and infrared data: Table 2; ^{1}H NMR data: Table 1.

General Procedure for the preparation Of Compounds (6a–i)

A suspension of **4a–i** (30 mmol) in 150 ml of ethylene glycol was treated with a solution of 12 g (30 mmol) of sodium hydroxide in 15 ml of water. The mixture was heated to a gentle boil for 2 h. Then it was poured into 200 ml of ice/water, and the obtained solution was acidified with concentrated hydrochloric acid (pH = 4) to precipitate the product. It was filtered off after standing at 4°C for about 12 h, washed with water, dried, and recrystallized from ethanol to give the products as colorless crystals.

Data

3-Acetyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**6a**)

Mp 243–245°C, (yield 68%); IR: 3409 (NH), 3110 (OH), 1685 (CO), 1620 (CON); ^{1}H NMR (DMSO): 2.17 (s, 3H, CH_3), 2.57 (s, 3H, 6-CH_3), 5.81 (s, 1H, 5-H), 11.45 (bs, 1H, NH), 14.24 (s, 1H, OH). Anal. calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.46; H, 5.41; N, 8.34.

Table 2. Experimental and infrared data of compounds **4a–j**

Compd.	Mp (°C) Solvent	Yield (%)	Mol. form. Mol.wt.	Analysis calcd./found C	H	N%	IR (KBr)
4a	265–267 AcOH	80	$C_9H_7NO_4$ 193.16	55.96/55.92	3.65/3.55	7.25/7.22	3069 (OH), 1733 (OCO), 1672 (CO)
4b	276–278 AcOH	78	$C_{10}H_9NO_4$ 207.18	57.97/57.86	4.38/4.22	6.76/6.66	3097 (OH), 1726 (OCO), 1667 (CO)
4c	266–268 AcOH	88	$C_{11}H_{11}NO_4$ 221.21	59.73/59.65	5.01/4.99	6.33/6.20	3076 (OH), 1714 (OCO), 1658 (CO)
4d	248–250 AcOH	95	$C_{13}H_{15}NO_4$ 249.26	62.64/62.43	6.07/6.04	5.62/5.43	3076 (OH), 1715 (OCO), 1661 (CO)
4e	316–318 AcOH	96	$C_{15}H_{11}NO_4$ 269.25	66.91/66.84	4.12/4.08	5.20/5.11	3059 (OH), 1716 (OCO), 1657(CO)
4g	218–221 AcOH	90	$C_{11}H_{11}NO_4$ 221.21	59.73/59.63	5.01/4.96	6.33/6.20	3095 (OH), 1702 (OCO), 1661 (CO)
4h	220–223 AcOH	94	$C_{12}H_{13}NO_4$ 235.24	61.27/61.18	5.57/5.45	5.95/5.91	3083 (OH), 1703 (OCO), 1575 (CO)
4i	240–243 AcOH	80	$C_{16}H_{13}NO_4$ 283.28	67.84/67.80	4.63/4.59	4.94/4.92	3089 (OH), 1701 (OCO), 1659 (CO)
4j	189–191 AcOH	85	$C_{14}H_{17}NO_4$ 263.29	63.87/63.83	6.51/6.49	5.32/5.26	3086 (OH), 1708 (OCO), 1663 (CO)

4-Hydroxy-6-methyl-3-propionylpyridin-2(1*H*)-one (**6b**)

Mp 231–233°C (yield 70%); IR: 3307 (NH), 3157 (OH), 1662 (CO), 1630 (CON). ^{1}H NMR (DMSO): 1.03 (t, 3H, $J = 10.8$ Hz, C*H*$_3$CH$_2$), 2.17 (s, 3H, 6-CH$_3$), 3.06 (q, 2H, $J_1 = 10.8$, $J_2 = 21.2$ Hz, CH$_2$CH$_3$), 5.80 (s, 1H, 5-H), 11.51 (bs, 1H, NH), 14.89 (s, 1H, OH). Anal. calcd. for $C_9H_{11}NO_3$: C, 54.66; H, 6.12; N, 7.73. Found: C, 54.56; H, 6.09; N, 7.64.

3-Butyryl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**6c**)

Mp 180–183°C (yield 80%); IR: 3308 (NH), 3159 (OH), 1669 (CO), 1610 (CON). ^{1}H NMR (DMSO): 0.09 (t, 3H, $J = 11.0$ Hz, CH$_3$CH$_2$), 1.52–1.62 (m, 2H, CH$_3$C*H*$_2$CH$_2$), 2.17 (s, 3H, 6-CH$_3$), 3.03 (t, 2H, $J = 10.8$ Hz, CH$_3$CH$_2$C*H*$_2$). 5.79 (s, 1H, 5-H), 11.50 (bs, 1H, NH), 15.74 (s, 1H, OH). Anal. calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.81. Found: C, 61.50; H, 6.55; N, 7.74.

3-Hexanoyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**6d**)

Mp175–177°C (yield 80%); IR: 3304 (NH), 3157 (OH), 1667 (CO), 1611 (CON). ^{1}H NMR (DMSO): 0.87 (t, 3H, $J = 10.5$ Hz, C*H*$_3$CH$_2$), 1.08–1.28 (m, 4H, 2 CH$_2$ of butyl), 1.43–1.56 (m, 2H, CH$_2$), 2.18 (s, 3H, 6-CH$_3$), 3.05 (t, 2H, $J = 10.5$ Hz, CH$_2$), 5.81 (s, 1H, 5-H), 11.50 (bs, 1H, NH), 15.76 (s, 1H, OH). Anal. calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.51; H, 7.63; N, 6.22.

4-Hydroxy-6-methyl-3-(phenylacetyl)pyridine-2(1*H*)-one (**6e**)

Mp 201–204°C (yield 69%); IR: 3057 (OH), 1662 (CO), 1615 (CON); ^{1}H NMR (DMSO): 2.19 (s, 3H, 6-CH$_3$), 4.44 (s, 2H, CH$_2$), 7.21–7.31 (m, 5H, arom), 11.57 (bs, 1H, NH), 15.42 (s, 1H, OH). Anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.10; H, 5.37; N, 5.66.

4-Hydroxy-1,6-dimethyl-3-proionylpyridin-2(1*H*)-one (**6g**)

Mp 148–151°C (yield 80%); IR: 3130 (OH), 1642 (CO), 1604 (CON); ^{1}H NMR (DMSO): 1.03 (t, 3H, $J = 9.9$ Hz, C*H*$_3$CH$_2$), 2.37 (s, 3H, 6-CH$_3$), 3.06 (q, 2H, $J_1 = 10.4$, $J_2 = 20.9$ Hz, CH$_2$CH$_3$), 3.75 (s, 1H, N-CH$_3$), 6.00 (s, 1H, 5-H), 15.43 (s, 1H, OH). Anal. calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.49; H, 6.64; N, 7.15.

3-Butyryl-4-hydroxy-1,6-dimethylpyridin-2(1*H*)-one (**6h**)

Mp 163–165°C (yield 99%); IR: 3231 (OH), 1643 (CO), 1619 (CON); ^{1}H NMR (DMSO): 0.90 (t, 3H, $J = 10.8$ Hz, C*H*$_3$CH$_2$), 1.50–1.60 (m, 2H,

$CH_2CH_2CH_3$), 2.35 (s, 3H, 6-CH_3), 3.02 (t, 2H, $J = 10.8$ Hz, $CH_2CH_2CH_3$), 3.35 (s, 3H, N-CH_3), 5.96 (s, 1H, 5-H), 15.47 (s, 1H, OH). Anal. calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.11; H, 7.19; N, 6.64.

4-Hydroxy-1,6-dimethyl-3-(phenylacetyl)pyridine-2(1*H*)-one (**6i**)

Mp 150–153°C (yield 82%); IR: 3059 (OH), 1652 (CO), 1667 (CON); ^{1}H NMR (DMSO): 2.38 (s, 3H, 6-CH_3), 3.41 (s, 3H, N-CH_3), 4.45 (s, 2H, CH_2), 7.19–7.32 (m, 5H, arom), 15.17 (s, 1H, OH). Anal. calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.98; H, 5.76; N, 5.37.

General Procedure for the Preparation of 4-Hydroxy-3-[(1*E*)-*N*-hydroxyalkanimidoyl]-pyridones (7a–i)

A mixture of compound **4a–i** (5 mmol), hydroxyl amine hydrochloride (0.7 g, 5 mmol), and sodium bicarbonate (0.84 g, 10 mmol) in 40 ml of ethanol/water (3:1) was heated under reflux with stirring for 4 h. The solvent was evaporated in vacuo, and the residue was triturated with cold water. The precipitated solid product was collected by filtration, washed with water, dried, and recrystallized from an ethanol/water mixture (5:1) to afford the product as colorless crystals.

Data

4-Hydroxy-3-[(1*E*)-*N*-hydroxyethanimidoyl]-6-methylpyridin-2(1*H*)-one (**7a**)

Mp 153–155°C (yield 50%); IR: 3383 (NH), 3165 (OH), 1647 (CO); ^{1}H NMR (DMSO): 2.16 (s, 3H, 6-CH_3), 2.29 (s, 3H, CH_3), 5.72 (s, 1H, 5-H), 11.08 (bs, 1H, NH), 11.13 (bs, 1H, N-OH), 12.94 (bs, 1H, OH). MS (EI): m/z (%) 183 (M^+, 1), 182 (M^+, 26), 165 (100), 138 (33). Anal. calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.70; H, 5.48; N, 15.24.

4-Hydroxy-3-[(1*E*)-*N*-hydroxypropanimidoyl]-6-methylpyridin-2(1*H*)-one (**7b**)

Mp 192–194°C (yield 65%); IR: 3312 (NH), 3159 (OH), 1634 (CO); ^{1}H NMR (DMSO): 1.03 (t, 3H, $J = 11.1$ Hz, CH_3CH_2), 2.10 (s, 3H, 6-CH_3), 2.89 (q, 2H, $J_1 = 11.1$, $J_2 = 22.2$, CH_2CH_3), 5.71 (s, 1H, 5-H), 11.04 (bs, 1H, N-OH), 13.32 (bs, 1H, OH). MS (EI) m/z (%) 197 ($M^+ + 1$, 18), 196 (M^+, 12), 179 (100), 151 (19), 134 (12). Anal. calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.06; H, 6.12; N, 14.24.

4-Hydroxy-3-[(1*E*)-*N*-hydroxybutanimidoyl]-6-methylpyridin-2(1*H*)-one (**7c**)

Mp 178–180°C (yield 44%); IR: 3310 (NH), 3159 (OH), 1636 (CO); ^{1}H NMR (DMSO): 0.88 (t, 3H, $J = 10.5$ Hz, CH_3CH_2), 1.48–1.51 (m, 2H, $CH_2CH_2CH_3$), 2.11 (s, 3H, 6-CH_3), 2.90 (t, 2H, $J = 11.0$ Hz, -$CH_2CH_2CH_3$), 5.72 (s, 1H, 5-H), 11.06 (bs, 1H, NH), 11.08 (bs, 1H, N-OH), 13.12 (bs, 1H, OH). MS (EI) m/z (%) 211 ($M^+ + 1$, 5), 210 (M^+, 16), 193 (100), 176 (53), 151 (49). Anal. calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.10; H, 6.68; N, 13.29.

4-Hydroxy-3-[(1*E*)-*N*-hydroxyhexanimidoyl]-6-methylpyridin-2(1*H*)-one (**7d**)

Mp 160–163°C (yield 53%); IR: 3408 (NH), 3161 (OH), 1631 (CO); ^{1}H NMR (DMSO): 0.84 (t, 3H, $J = 11.1$ Hz, CH_3CH_2), 1.03–1.10 (m, 4H, 2 CH_2 of butyl), 1.31–1.40 (m, 2H, CH_2 of butyl), 2.10 (s, 3H, 6-CH_3), 2.91 (t, 2H, $J = 10.5$ Hz, CH_2CH_2), 5.72 (s, 1H, 5-H), 11.22 (bs, 1H, NH), 11.35 (bs, 1H, N-OH), 13.75 (bs, 1H, OH). MS (EI) m/z (%) 239 ($M^+ + 1$, 3), 238 (M^+, 12), 221 (100), 204 (26), 165 (37). Anal. calcd. for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.45; H, 7.58; N, 11.73.

4-Hydroxy-3-[(1*E*)-*N*-hydroxy-2-phenylethanimidoyl]-6-methylpyridin-2(1*H*)-one (**7e**)

Mp 190–193°C (yield 92%); IR: 3384 (NH), 3160 (OH), 1655 (CO); ^{1}H NMR (DMSO): 2.08 (s, 3H, 6-CH_3), 4.45 (s, 2H, CH_2), 5.70 (s, 1H, 5-H), 7.12–7.21 (m, 5H, arom), 11.11 (bs, 1H, NH), 11.21 (bs, 1H, N-OH), 12.99 (bs, 1H, OH). MS (EI) m/z (%) 259 (M^+, 5), 258 (M^+, 17), 241 (76), 91 (100). Anal. calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.09; H, 5.40; N, 10.79.

4-Hydroxy-3-[(1*E*)-*N*-hydroxyethanimidoyl]-1,6-dimethylpyridin-2(1*H*)-one (**7f**)

Mp 200–203°C (yield 62%); IR: 3165 (OH), 1652 (CO); ^{1}H NMR (DMSO): 2.23 (s, 3H, 6-CH_3), 2.39 (s, 3H, CH_3), 3.36 (s, 3H, N-CH_3) 5.88 (s, 1H, 5-H), 11.05 (bs, 1H, N-OH), 12.65 (bs, 1H, OH). MS (EI) m/z (%) 196 (M^+, 32), 179 (100), 152 (38), 98 (25). Anal. calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.06; H, 6.14; N, 14.25.

4-Hydroxy-3-[(1*E*)-*N*-hydroxypropanimidoyl]-1,6-dimethylpyridin-2(1*H*)-one (**7g**)

Mp 166–170°C (yield 60%); IR: 3141 (OH), 1639 (CO); ^{1}H NMR (DMSO): 1.00 (t, 3H, $J = 7.8$ Hz, CH_3CH$_2$), 2.26 (s, 3H, 6-CH$_3$), 2.79 (q, 2H, $J_1 = 5.7$, $J_2 = 16.5$ Hz, CH$_2$CH$_3$), 3.30 (s, 3H, N-CH$_3$), 5.84 (s, 1H, 5-H), 10.94 (bs, 1H, N-OH), 12.53 (bs, 1H, OH). MS (EI) m/z (%) 211 ($M^+ + 1$, 3), 210 (M^+, 13), 193 (100), 176 (17), 166 (18), 165 (20). Anal. calcd. for $C_{10}H_{14}N_2O_3$ (210.23): C, 57.13; H, 6.71; N, 13.33. Found: C, 57.11; H, 6.69; N, 13.30.

4-Hydroxy-3-[(1*E*)-*N*- hydroxybutanimidoyl]-1,6-dimethylpyridin-2(1*H*)-one (**7h**)

Mp 185–188°C (yield 60%); IR: 3269 (OH), 1641 (CO); ^{1}H NMR (DMSO): 0.84 (t, 3H, $J = 7.2$ Hz, CH_3CH2), 1.36–1.51 (m, 2H, CH$_2$), 2.28 (s, 3H, 6-CH$_3$), 2.81 (t, 2H, $J = 9.6$ Hz, CH_2CH$_2$), 3.36 (s, 3H, N-CH$_3$), 5.86 (s, 1H, 5-H), 10.92 (bs, 1H, N-OH), 12.59 (bs, 1H, OH). MS (EI) m/z (%) 225 ($M^+ + 1$, 14), 224 (M^+, 9), 207 (100), 190 (40), 165 (21). Anal. calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.88; H, 7.17; N, 12.46.

4-Hydroxy-3-[(1*E*)-*N*-hydroxy-2-phenylethanimidoyl]-1,6-dimethylpyridin-2(1*H*)-one (**7i**)

Mp 172–175°C (yield 65%); IR: 3159 (OH), 3128 (OH), 1637 (CO); ^{1}H NMR (DMSO): 2.23 (s, 3H, 6-CH$_3$), 3.41 (s, 3H, N-CH$_3$), 4.34 (s, 2H, CH$_2$), 5.85 (s, 1H, 5-H), 7.10–7.19 (m, 5H, arom), 11.21 (bs, 1H, N-OH), 12.64 (bs, 1H, OH). MS (EI) (%) 272 (M^+, 13), 255 (73), 254 (100), 256 (17), 228 (24), 226 (14). Anal. calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.14; H, 5.89; N, 10.26.

General Procedure for the Preparation of 4-Hydroxy-3-[(1*E*)-*N*-phenylalkanehydrazonoyl]-pyridones (8a–d)

A mixture of ketone **6a** or **6c** or **6d** and/or **6f** (5 mmol), phenyl hydrazine hydrochloride (10 mmol), and sodium bicarbonate (10 mmol), in 40 ml of ethanol/water (3:1) was heated under reflux with stirring for 4 h. The reaction mixture was added to cold water with stirring; the colorless precipitated solid product was collected by filtration, washed with water, dried, and recrystallized from ethanol to afford the products as colorless crystals.

Data

4-Hydroxy-6-methyl-3-[(1*E*)-*N*-phenylethanehydrazonoyl]pyridine-2(1*H*)-one (**8a**).

Mp 212–215°C (yield 66%). IR: 3320, (NH), 3250 (OH), 1624 (CO); ^{1}H NMR (DMSO): 2.14 (s, 3H, 6-CH_3), 2.58 (s, 3H, CH_3), 5.74 (s, 1H, 5-H), 6.81–7.28 (m, 5H, arom), 9.15 (s, 1H, N*H*-Ph), 11.06 (bs, 1H, NH), 15.12 (bs, 1H, OH). MS (EI) m/z (%) 257 (M^+, 100), 240 (49), 165 (38). Anal. calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.29; H, 5.66; N, 16.25.

4-Hydroxy-6-methyl-3-[(1*E*)-*N*-phenylbutanehydrazonoyl]pyridine-2(1*H*)-one (**8b**)

Mp 225–230°C (yield 65%); IR: 3368 (NH), 3277 (OH), 1626 (CO); ^{1}H NMR (DMSO): 0.95 (t, 3H, $J = 10.4$ Hz, C*H*$_3$CH$_2$), 1.41–1.54 (m, 2H, CH_2), 2.11 (s, 3H, 6-CH_3), 3.16 (t, 2H, $J = 11.3$ Hz, C*H*$_2$CH$_2$), 5.70 (s, 1H, 5-H), 6.65–7.29 (m, 5H, arom), 9.18 (s, 1H, N*H*-Ph), 10.98 (bs, 1H, NH), 15.25 (bs, 1H, OH). MS (EI) m/z (%) 286 ($M^+ + 1$, 11), 285 (M^+, 32), 193 (100). Anal. calcd. for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.30; H, 6.62; N, 14.68.

4-Hydroxy-6-methyl-3-[(1*E*)-*N*-phenylhexanehydrazonoyl]pyridine-2(1*H*)-one (**8c**)

Mp 200–203°C (yield 48%); IR: 3379 (NH), 3294 (OH), 1630 (CO); ^{1}H NMR (DMSO): 0.87 (t, 3H, $J = 5.1$ Hz, C*H*$_3$CH$_2$), 1.28–1.50 (m, 6H, 3CH_2 of butyl), 2.10 (s, 3H, 6-CH_3), 3.18 (t, 2H, $J = 11.3$ Hz, C*H*$_2$CH$_2$), 5.69 (s, 1H, 5-H), 6.80–7.28 (m, 5H, Ph), 9.15 (s, 1H, N*H*-Ph), 10.95 (bs, 1H, NH), 15.26 (bs, 1H, OH). MS (EI) m/z (%) 314 ($M^+ + 1$, 22), 313 (M^+, 48), 221 (100). Anal. calcd. for $C_{18}H_{23}N_3O_2$ (313.39): C, 68.98; H, 7.40; N, 13.41. Found: C, 68.88; H, 7.33; N, 13.32.

4-Hydroxy-1,6-methyl-3-[(1*E*)-*N*-phenylethanehydrazonoyl]pyridine-2(1*H*)-one (**8d**)

Mp 225–228°C (yield 55%); IR: 3436 (NH), 329 (OH), 1665 (CO); ^{1}H NMR (DMSO): 2.32 (s, 3H, 6-CH_3), 2.49 (s, 3H, N-CH_3), 5.89 (s, 1H, 5-H), 6.78–7.28 (m, 5H, arom), 9.19 (s, 1H, N*H*-Ph), 14.59 (bs, 1H, OH). MS (EI) m/z (%) 272 ($M^+ + 1$, 23), 271 (M^+, 100), 255 (21), 179 (73). Anal. calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; H, 15.49. Found: C, 66.36; H, 6.28; N, 15.45.

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