

A FACILE SYNTHESIS OF SUBSTITUTED 4-HYDROXY-2-PYRIDONES

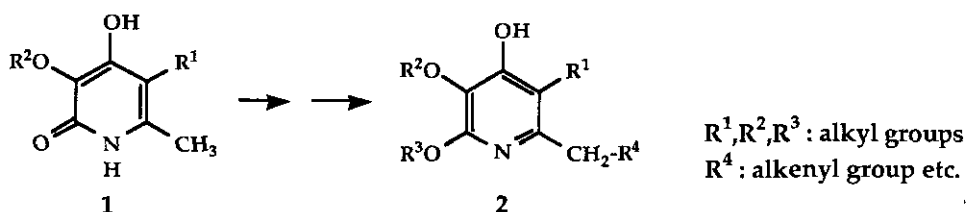
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Abstract - Substituted 4-hydroxy-2-pyridones (**1a~1d**) were easily synthesized from ethyl acetoacetate in good yields via C-alkylation, enamine formation, N-acylation, intramolecular cyclization, and debenzylation.

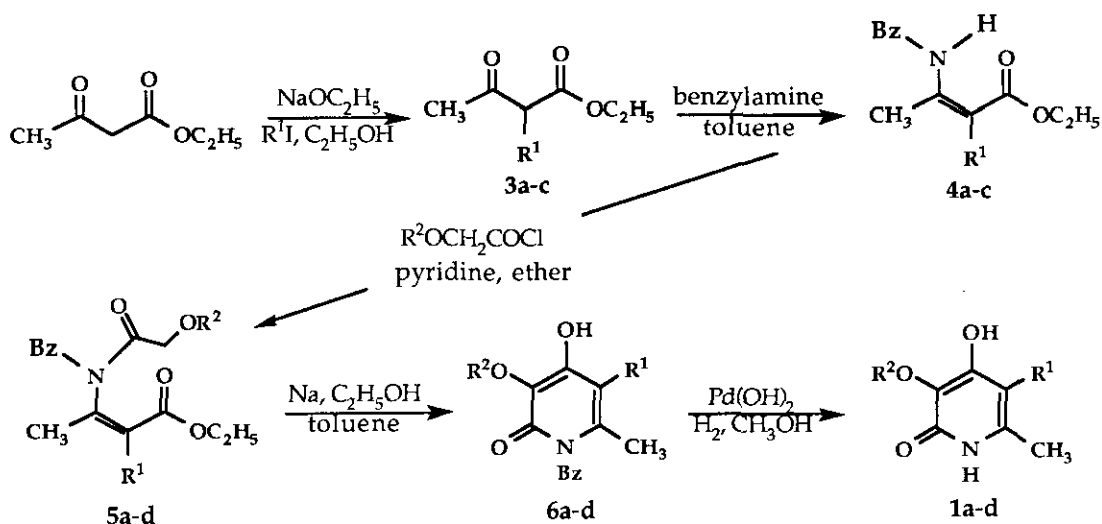
In the continuation on the search for structure-activity relationships of piericidin-like compounds (**2**), it is necessary to synthesize suitable precursors carrying various functionalities.^{2,3} Previously, we reported a route for synthesis of (**1**, R² : methyl, R¹: alkenyl) from ethyl 3-aminocrotonate, but that method gave poor over-all yields.³ Herewith, we would like to report a versatile synthetic method of 3-alkoxy-5-alkyl-4-hydroxy-6-methyl-2-pyridones (**1**), which may be useful for syntheses of piericidin-like compounds.

Ethyl 2-methylacetoacetate was easily transformed into enamine (**4**). Thus, ethyl 2-alkylaceto-



acetates were prepared from ethyl acetoacetate, following the literature procedure⁴ and ethyl 2-alkylacetoacetate was treated with benzylamine in refluxing toluene to give ethyl 3-(*N*-benzyl)amino-2-alkylcrotonates (**4**) in good yields. Theoretically, compound (**4**) can have two geometric isomers (*E* and *Z*) as in the case of 3-amino-2-methylacrylonitrile⁵ and 2-alkyl-3-aminocrotonate,³ however, ¹H-nmr spectra of these compounds clearly show the presence of only one isomer, respectively. It is postulated that the product should be the *Z*-isomer of (**4**) due to thermodynamic stability of intramolecular hydrogen-bonding between amine and carbonyl functionalities.

The methoxyacetylation of (**4**) proceeded smoothly to give ethyl (*Z*)-3-(*N*-benzyl-*N*-methoxyacetyl)amino-2-methylcrotonate (**5a**; R=methyl) using methoxyacetyl chloride and pyridine in ether. The *N*-benzylamine (**4**) is still unstable to be applied on silica gel column chromatography, but the enamide (**5**) is stable enough for ordinary purification process. The ¹H-nmr spectra of (**5**) revealed that methylene protons of both benzyl and methoxyacetyl groups showed typical geminal couplings (*J*=14.3 and 14.5 Hz), and this suggests that enamide (**5**) should have a rigid structure due to the steric interaction amongst the three functionalities bonded to nitrogen,



	a	b	c	d
R ¹	CH ₃	C ₂ H ₅	C ₃ H ₇	CH ₃
R ²	CH ₃	CH ₃	CH ₃	C ₂ H ₅

Table 1. Conditions of Intramolecular Cyclization of Compound (5a)

entry	base	solvent	temp. (°C)	yield (%) ^a
1	LDA	THF	-78 ~ room temp.	25
2	LDA	THF	-78 ~ reflux	20
3	NaH	toluene	reflux	20
4	NaOC ₂ H ₅	ethanol	reflux	25
5	NaOC ₂ H ₅	toluene	reflux	42
6	Na	toluene	reflux	25
7	Na	toluene ^b	reflux	70

a) Isolated yields. b) Containing trace amounts of ethanol.

which provide presumably a good situation to enforce the intramolecular cyclization. And optimum conditions of the cyclization process were explored using various bases and solvents⁶ in the case of enamide (5a) (Table 1). In the cases of LDA and NaH (entries 1-3), the reaction did not proceed at low temperature (-78 °C) and the enamide (5a) was readily decomposed by those bases even at room temperature. Sodium ethoxide or metallic sodium (entries 4-6) seemed to be rather effective bases for this cyclization either in ethanol or toluene at the refluxing temperature. The best result was obtained by cyclization of (5a) under the refluxing toluene solution containing sodium and trace amounts of ethanol (entry 7).

The structure of (6a) was confirmed by spectroscopic analyses. The ¹H-nmr spectrum of (6a) showed disappearance of signals for the ethoxy and the methylene protons in the ethoxycarbonyl and the methoxyacetyl groups, respectively. The high resolution ms indicated the molecular weight and the formula of (6a) (M⁺, m/z: 259 for C₁₅H₁₇NO₃) lacking 46 mass units (C₂H₆O) from (5a). Furthermore (6a) was shown to be positive on the FeCl₃-coloring test due to the presence of the phenolic hydroxyl group in the molecule.

The removal of *N*-benzyl group from (6) was carried out by catalytic hydrogenation using palladium hydroxide on charcoal (Pearlman's catalyst)⁷ affording quantitatively the debenzylated product (1) at 100°C under 50 psi in methanol.

In conclusion, the procedure described herein is a convenient and efficient method for synthesis of substituted 4-hydroxy-2-pyridones, and further utilization of these compounds is undergoing.

EXPERIMENTAL

Solvents and reagents were dried and purified prior to use when deemed necessary. Reactions requiring an inert atmosphere were run under a stream of nitrogen. All melting points were taken with a Thomas Hoover capillary melting point apparatus and are uncorrected. $^1\text{H-Nmr}$ spectra were recorded on JEOL FX-100 and Bruker AM 300 spectrometers. Infrared spectra were taken with a Shimadzu IR-435 instrument. Low and high resolution mass spectra (ms) were recorded on Hitachi RMU-6L and RMH-2 mass spectrometers respectively.

General Synthesis of 2-alkylacetoacetates 3: The compounds were prepared according to the literature.²

Ethyl 2-methylacetoacetate 3a: 85% yield. bp 184~185 °C. Ir (neat): 2950, 1740, 1715 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 1.29 (t, $J=7.18$, 3H), 1.34 (d, $J=7.18$, 3H), 2.18 (s, 3H), 3.52 (q, $J=7.18$, 1H), 4.22 (q, $J=7.18$, 2H).

Ethyl 2-ethylacetoacetate 3b: 92% yield. bp 189~190 °C. Ir (neat): 2950, 1740, 1710 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.94 (t, $J=7.15$, 3H), 1.27 (t, $J=7.20$, 3H), 1.80 (m, 2H), 2.15 (s, 3H), 3.29 (t, $J=7.15$, 1H), 4.13 (q, $J=7.20$, 2H).

Ethyl 2-propylacetoacetate 3c: 77% yield. bp 194~195 °C. Ir (neat): 2950, 1720, 1710 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.81~1.95 (m, 10H), 2.18 (s, 3H), 3.32 (t, $J=7.15$, 1H), 4.13 (q, $J=7.20$, 2H).

General Synthesis of 2-alkyl-3-benzylaminocrotonate 4: A mixture of **3** (0.1 mol) and benzylamine (10.7 g, 0.1 mol) in toluene (200 ml) was stirred under reflux for 3 h with a Dean-Stark trap and a reflux condenser. The cooled mixture was evaporated to give the residue (about 100% of crude product) which was used in the next step without further purification.

Ethyl 3-benzylamino-2-methylcrotonate 4a: colorless oil. Ir (neat): 3230, 2950, 1640, 1600 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 1.24 (t, $J=7.20$, 3H), 1.77 (s, 3H), 1.89 (s, 3H), 4.10 (q, $J=7.20$, 2H), 4.35 (d, $J=6.10$, 2H), 7.19 (m, 5H). Ms m/z (rel. int.): 233 (M^+ , 10), 186 (5).

Ethyl 3-benzylamino-2-ethylcrotonate 4b: colorless oil. Ir (neat): 3230, 2950, 1640, 1600 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.94 (t, $J=7.20$, 3H), 1.23 (t, $J=7.20$, 3H), 1.91 (s, 3H), 2.23 (q, $J=7.20$, 2H), 4.08 (q, $J=7.20$, 2H), 4.31 (d, $J=6.10$, 2H), 7.20 (m, 5H).

Ethyl 3-benzylamino-2-propylcrotonate 4c: colorless oil. Ir (neat): 3220, 2950, 1640 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.82~2.28 [13H, m {1.87 (s, 3H) involved}], 4.08 (q, $J=7.20$, 2H), 4.31 (d, $J=6.10$, 2H), 7.20 (m, 5H).

General Synthesis of ethyl 2-alkyl-3-(N-benzyl)alkoxyacetamidocrotonate 5: To a stirred solution of ethyl 2-alkyl-3-benzylaminocrotonate (**4**, 50 mmol) and pyridine (4 ml) in chloroform (250 ml) at 0 °C was added, under nitrogen, a solution of alkoxyacetyl chloride (55 mmol) in chloroform (40 ml) and then it was allowed to warm to room temperature. The mixture was washed with water (2x300 ml), saturated NaHCO₃, and dried over MgSO₄. After evaporation of the solvent, the residue was chromatographed on silica gel with ethyl acetate-hexane (1:4) to give (**5**) as oil.

Ethyl 3-(N-benzyl)methoxyacetamido-2-methylcrotonate 5a: 88% yield. colorless oil. Ir (neat): 3050, 2950, 1710, 1680 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.20 (t, J= 7.15 Hz, 3H), 1.74 (s, 3H), 1.89 (s, 3H), 3.43 (s, 3H), 3.96 (d, J= 14.45 Hz, 1H), 3.97 (q, J= 7.15 Hz, 2H), 4.13 (d, J= 14.45 Hz, 1H), 4.33 (d, J= 14.32 Hz, 1H), 4.93 (d, J= 14.32 Hz, 1H), 7.24~7.31 (m, 5H). Ms m/z (rel. int.): 305 (M⁺, 20), 259 (10), 211 (95), 110 (20), 91 (100). Hrms: Found: 305.3761, Calcd for C₁₇H₂₃NO₄: 305.3772.

Ethyl 3-(N-benzyl)methoxyacetamido-2-ethylcrotonate 5b: 85% yield. colorless oil. Ir (neat): 3050, 2950, 1720, 1680 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.00 (t, J= 7.51 Hz, 3H), 1.21 (t, J= 7.07 Hz, 3H), 1.72 (s, 3H), 2.24~2.32 (m, 2H), 3.45 (s, 3H), 3.98 (d, J= 14.48 Hz, 1H), 4.12 (q, J= 7.07 Hz, 2H), 4.16 (d, J= 14.48 Hz, 1H), 4.30 (d, J= 14.30 Hz, 1H), 4.96 (d, J= 14.30 Hz, 1H), 7.25~7.32 (m, 5H). Ms m/z (rel. int.): 319 (M⁺, 3), 247 (100), 186 (10), 125 (5), 91 (10). Hrms: Found: 319.4033. Calcd for C₁₈H₂₅NO₄: 319.4042.

Ethyl 3-(N-benzyl)methoxyacetamido-2-propylcrotonate 5c: 85% yield. colorless oil. Ir (neat): 3050, 2950, 1720, 1640 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 0.93 (t, J= 7.35 Hz, 3H), 1.21 (t, J= 7.12 Hz, 3H), 1.44 (m, 2H), 1.71 (s, 3H), 2.25 (m, 2H), 3.45 (s, 3H), 3.99 (d, J= 14.38 Hz, 1H), 4.00 (q, J= 7.12 Hz, 2H), 4.18 (d, J= 14.38 Hz, 1H), 4.28 (d, J= 14.30 Hz, 1H), 4.98 (d, J= 14.30 Hz, 1H), 7.25~7.32 (m, 5H). Ms m/z (rel. int.): 333 (M⁺, 2), 260 (100), 138 (20), 91 (30). Hrms: Found: 333.4327. Calcd for C₁₉H₂₇NO₄: 333.4313.

Ethyl 3-(N-benzyl)ethoxyacetamido-2-methylcrotonate 5d: 80% yield. colorless oil. Ir (neat): 2950, 1710, 1660 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.19 (t, J= 7.16 Hz, 3H), 1.24 (t, J= 7.05 Hz, 3H), 1.76 (s, 3H), 1.88 (s, 3H), 3.55 (q, J= 7.02 Hz, 1H), 3.63 (q, J= 7.02 Hz, 1H), 3.96 (q, J= 7.12 Hz, 2H), 4.03 (d, J= 14.44 Hz, 1H), 4.16 (d, J= 14.44 Hz, 1H), 4.34 (d, J= 14.32 Hz, 1H), 4.90 (d, J= 14.32 Hz, 1H), 7.22~7.31 (m, 5H). Ms m/z (rel. int.): 319 (M⁺, 10), 274 (20), 247 (100), 232 (50), 186 (35), 110 (95), 91 (90). Hrms: Found: 319.4041. Calcd for C₁₈H₂₅NO₄: 319.4042.

General Synthesis of 3-alkoxy-5-alkyl-N-benzyl-4-hydroxy-6-methyl-2-pyridone 6: To a stirred solution of dry toluene (200 ml), ethanol (0.3 ml), and sodium metal pieces (1.15 g, 50 mg atoms),

under nitrogen, was slowly added ethyl 2-alkyl-(*N*-benzyl)alkoxyacetamidocrotonate (**5**, 50 mmol) in toluene (50 ml) under reflux, and the reaction mixture was left for 2 h. The cooled solution was neutralized by careful addition of 5% HCl-ethanol. After removal of solvent, the residue was triturated in ethyl acetate and filtered. The resultant organic mixture was evaporated, and chromatographed on silica gel with ethyl acetate-hexane (1:2) to give (**6**).

N-Benzyl-5,6-dimethyl-4-hydroxy-3-methoxy-2-pyridone **6a**: 70% yield. mp 140~142 °C (ethyl acetate-hexane). Ir (KBr): 3400, 2900, 1640 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 2.03 (s, 3H), 2.16 (s, 3H), 3.99 (s, 3H), 5.88 (s, 2H), 7.24 (m, 5H). Ms m/z (rel. int.): 259 (M^+ , 70), 244 (13), 182 (8), 168 (22), 140 (14), 91 (100). Hrms: Found: 259.3089. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3$: 259.3076.

N-Benzyl-5-ethyl-4-hydroxy-3-methoxy-6-methyl-2-pyridone **6b**: 65% yield. mp 206~208 °C (ethyl acetate-hexane). Ir (KBr): 3400, 2900, 1630 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 1.03 (t, $J = 7.42$ Hz, 3H), 2.18 (s, 3H), 2.29 (q, $J = 7.42$ Hz, 2H), 3.88 (s, 3H), 5.33 (s, 2H), 7.13 (m, 5H). Ms m/z (rel. int.): 273 (M^+ , 55), 258 (10), 197 (5), 182 (5), 140 (5), 91 (100). Hrms: Found: 273.3356. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: 273.3347.

N-Benzyl-4-hydroxy-3-methoxy-6-methyl-5-propyl-2-pyridone **6c**: 65% yield. mp 195~198 °C (ethyl acetate-hexane). Ir (KBr): 3400, 2900, 1620 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.89 (t, $J = 7.00$ Hz, 3H), 1.67~1.75 (m, 2H), 2.17 (s, 3H), 2.32 (t, $J = 7.22$ Hz, 2H), 3.85 (s, 3H), 5.30 (s, 2H), 7.18 (m, 5H). Ms m/z (rel. int.): 287 (M^+ , 37), 272 (35), 196 (15), 182 (20), 168 (5), 150 (10), 91 (100). Hrms: Found: 287.3605. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_3$: 287.3618.

N-Benzyl-5,6-dimethyl-3-ethoxy-4-hydroxy-2-pyridone **6d**: 61% yield. mp 140~142 °C (ethyl acetate-hexane). Ir (KBr): 3400, 2900, 1620 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 1.32 (t, $J = 7.50$ Hz, 3H), 2.00 (s, 3H), 2.16 (s, 3H), 4.30 (q, $J = 7.50$ Hz, 2H), 5.32 (s, 2H), 7.17 (m, 5H). Ms m/z (rel. int.): 273 (M^+ , 90), 244 (15), 164 (5), 126 (5), 91 (100). Hrms: Found: 273.3360. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: 273.3347.

General Synthesis of 3-alkoxy-5-alkyl-4-hydroxy-6-methyl-2-pyridone **1**: A mixture of of 3-alkoxy-5-alkyl-*N*-benzyl-4-hydroxy-6-methyl-2-pyridone (**6**, 10 mmol), palladium hydroxide on carbon (Pearlman's catalyst, 20%, 0.2 g) and ethanol (125 ml) was hydrogenated for 5 h at 50 psi and at 100 °C (Parr apparatus). The reaction mixture was filtered through a Celite bed and the solvent was evaporated to give (**1**) as white solid.

5,6-Dimethyl-4-hydroxy-3-methoxy-2-pyridone **1a**: 95% yield. mp 263~265 °C (ethyl acetate). Ir (KBr): 3400, 2950, 1610 cm^{-1} . $^1\text{H-Nmr}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$) δ : 1.95 (s, 3H), 2.15 (s, 3H), 3.88 (s, 3H). Ms

m/z (rel. int.): 169 (M^+ , 90), 151 (22), 126 (58). Hrms: Found: 169.1805. Calcd for $C_8H_{11}NO_3$: 169.1818.

5-Ethyl-4-hydroxy-3-methoxy-6-methyl-2-pyridone 1b: 92% yield. mp 193~195 °C (ethyl acetate). Ir (KBr): 3400, 2950, 1620 cm^{-1} . 1H -Nmr ($CDCl_3$ -DMSO- d_6) δ : 1.09 (t, J= 7.50 Hz, 3H), 2.24~2.43 [m, 5H {2.41 (s, 3H) involved}], 3.77 (s, 3H). Ms m/z (rel. int.): 183 (M^+ , 100), 168 (30), 140 (97). Hrms: Found: 183.2103. Calcd for $C_9H_{13}NO_3$: 183.2089.

4-Hydroxy-3-methoxy-6-methyl-5-propyl-2-pyridone 1c: 90% yield. mp 178~181 °C (ethyl acetate). Ir (KBr): 3400, 2950, 1650 cm^{-1} . 1H -Nmr ($CDCl_3$ -DMSO- d_6) δ : 0.80 (t, J= 7.10 Hz, 3H), 1.74~2.00 (4H, m), 2.11 (s, 3H), 3.74 (s, 3H). Ms m/z (rel. int.): 197 (M^+ , 100), 182 (15), 168 (22). Hrms: Found: 197.2371. Calcd for $C_{10}H_{15}NO_3$: 197.2360.

5,6-Dimethyl-3-ethoxy-4-hydroxy-2-pyridone 1d: 93% yield. mp 230~233 °C (ethyl acetate). Ir (KBr): 3400, 2950, 1650 cm^{-1} . 1H -Nmr ($CDCl_3$ -DMSO- d_6) δ : 1.27 (t, J= 7.45 Hz, 3H), 1.90 (s, 3H), 2.15 (s, 3H), 3.92 (q, J= 7.45 Hz, 2H). Ms m/z (rel. int.): 183 (M^+ , 72), 168 (33), 155 (100). Hrms: Found: 183.2095. Calcd for $C_9H_{13}NO_3$: 183.2089.

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