A New and Facile Synthesis of 2-Pyridones

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So far, a number of biologically active compounds possessing 2-pyridone moiety have been known.[1] On the other hand, 5-carboxy-2-pyridone has been used as a key intermediate for the synthesis of recently developed insecticide Imidacloprid acting on the nicotinergic acetylcholine receptor.[2] There have been several reports for the synthesis of carboalkoxy-2-pyridones from alkyl coumalate.[3] However, preparations of alkyl coumalate from coumalic acid have some problems such as low yield or use of expensive coupling agent.[4] Also, the yields for the synthesis of *N*-aryl-5-carboalkoxy-2-pyridones from alkyl coumalate were poor.[3a] Other synthetic methods for carboalkoxy-2-pyridones consist of cyclization of dienamino esters prepared from enamino ester[5a] or cyclic sulfonamide.[5b] In spite of many literature procedures, use of dimethyl 4-(methoxymethylene)-2-pentenedioate for 2-pyridone synthesis has not been known.

In this note, we want to report a new and facile synthesis of 2-pyridones **4** from readily available coumalic acid **1** *via* dimethyl 4-(methoxymethylene)-2-pentenedioate **2a**/**2b** and dienamino ester intermediates **3**. Reaction of coumalic acid **1** with acetyl chloride in refluxing methanol afforded **2a**/**2b** as a mixture of geometrical isomers.

We obtained **2a** as a major compound along with minor geometrical isomer, that could be anticipated from literature.[6] This mixture of **2a**/**2b** was reacted with various amines to give dienamino esters **3**, which could be isolated or cyclized directly to produce the corresponding 5-carbomethoxy-2-pyridones **4** in high yield.

The results are summarized in Table 1.

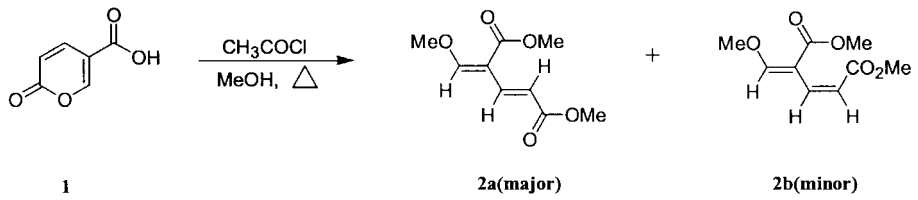
From the reaction of **2a/2b** with aqueous ammonia or benzylamine at low temperature (0 ~ -20 °C), we could isolate dienamino ester **3a** or **3c** as a single isomer. Dienamino ester **3a** was easily cyclized by refluxing in xylene under DBU catalyst to afford **4a** in 77% yields. Various *N*-substituted 2-pyridones **4b-4f** could be obtained in one-pot reaction *via in situ* generated dienamino esters from a mixture of **2a**/**2b** in 77-97% yields. We could improve the yields for *N*-aryl-2-pyridones **4d-4f**, which were difficult to obtain by conventional method employing alkyl coumalate.[3a]

In conclusion, the present method would be convenient and suitable for the synthesis of various 5-carboalkoxy-2-pyridone derivatives.

Table 1. Synthesis of dienamino ester **3** or 2-pyridones **4** from a mixture of **2a**/**2b**

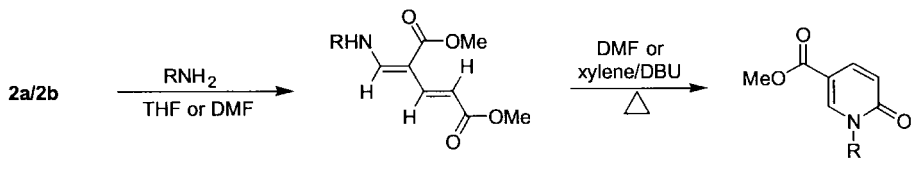
R	Product	Time (hr)	Yield (%)
H	**3a**	10 min	72
	4a	3	77[a]
n-Butyl	**4b**	5	97
Benzyl	**3c**	5 min	90
	4c	3	94
2-Pyridyl	**4d**	8	81
2-Thiazolyl	**4e**	5	77
Phenyl	**4f**	7	83

[a] Isolated yield from **3a**.



1 **2a(major)** **2b(minor)**

Scheme 1



3 **4**

Scheme 2

Experimental Section

General. Most starting materials were used without further purification. ^{1}H NMR, ^{13}C NMR were measured by Varian Gemini-200 MHz spectrometer. Chemical shifts were expressed in ppm downfield from TMS used as internal standard. IR spectra were obtained by Digilab FTS-165 FT-IR spectrometer. Melting point was measured by Thomas hoover capillary melting point apparatus. All chromatographic separations were performed on Merck silica gel 60 (70-230 mesh). Mass data were obtained by Micromass AutoSpec mass-spectrometer (EI, 70 eV 200 °C).

Preparation of dimethyl 4-(methoxymethylene)-2-pentenedioate (2a/2b). Acetyl chloride (2.83 mL, 21.41 mmol) was dropwise added to a coumalic acid (3.00 g, 21.41 mmol) in MeOH (30 mL) over 10 min at 0 °C. The reaction mixture was refluxed for 10 hr in oil bath, cooled to room temperature followed by concentration. The reaction mixture was diluted with ethyl acetate and washed by brine (30 mL) and extracted with ethyl acetate (3 × 30 mL), filtered through $MgSO_4$. The filtrate was concentrated *in vacuo* to afford crude product which was purified by column chromatography (SiO_2, EtOAc : *n*-Hexane = 1 : 5) to give a mixture of **2a** and **2b** (4.00 g) as a yellow solid.

Yield 93% (a ratio of **2a** to **2b** = 7.3 : 1), mp 56-57 °C (recrystallized with ether/*n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$): **2a** δ 3.65-3.88 (m, 6H), 4.03 (s, 3H), 6.61 (d, J = 16.28 Hz, 1H), 7.58 (d, J = 16.28 Hz, 1H), 7.62 (s, 1H); **2b** δ 3.65-3.88 (m, 6H), 3.91 (s, 3H), 6.45 (d, J = 9.82 Hz, 1H), 7.79 (dd, J_1 = 9.82 Hz, J_2 = 2.54 Hz, 1H), 8.29-8.31 (m, 1H); IR (KBr) 1721 cm^{-1}; MS: m/z 200 (M^+).

General procedure for the preparation of enamino ester (3a, 3c). Amine was added to a mixture of **2a**/**2b** in THF (5 mL) at low temperature (0 ~ -20 °C). After 10 min, the reaction mixture was diluted with ethyl acetate (10 mL), washed by brine (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude solid product which was purified by column chromatography and recrystallization in ether/*n*-hexane system.

Preparation of dimethyl (2E,4Z)-4-aminomethylene-2-pentenedioate (3a). Yield 72%, white solid, mp 138 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.81 (s, 3H), 5.50-5.80 (br, 1H), 6.10 (d, J = 15.87 Hz, 1H), 7.30 (d, J = 15.87 Hz, 1H), 8.30-8.60 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 50.904, 51.162, 56.882, 97.027, 109.294, 111.516, 143.339, 154.536, 169.155; IR (KBr) 1694 cm^{-1}; MS: m/z 185 (M^+).

Preparation of dimethyl (2E,4Z)-4-[(benzylamino)-methylene]-2-pentenedioate (3c). Yield 90%, white solid, mp 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.72(s, 3H), 3.78 (s, 3H), 4.48 (d, J = 5.90 Hz, 1H), 6.10 (d, J = 15.67 Hz, 1H), 7.20-7.48 (m, 7H), 9.00-9.30 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 50.927, 51.087, 52.960, 95.305, 108.111, 127.311, 128.168, 129.018, 136.687, 143.211, 157.010, 169.170, 169.496; IR (KBr) 1709, 1655 cm^{-1}; MS: m/z 275 (M^+).

General procedure for the preparation of 5-pyridones (4a~4f). Enamino ester **3a** (1.00 mmol) in xylene (5 mL) under DBU (0.05 mmol) catalyst (for **4a**) or enamino ester solution which was *in situ* generated by the reaction of amine (1.10 mmol) with a mixture of **2a**/**2b** (1.00 mmol) in DMF (5 mL) (for **4b~4f**) was refluxed to the end of cyclization. Then the mixture was cooled to room temperature, diluted with diethyl ether and washed with brine (20 mL). The reaction mixture was extracted with diethyl ether (3 × 20 mL), and filtered through $MgSO_4$. The filtrate was concentrated *in vacuo* to afford solid product which was purified by column chromatography and recrystallization in ether/*n*-hexane system.

Methyl 6-oxo-1,6-dihydro-3-pyridinecarboxylate (4a). Yield 77%, white solid, mp 164-165 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.58 (d, J = 9.56 Hz, 1H), 8.00 (dd, J_1 = 11.62 Hz, J_2 = 1.82 Hz, 1H), 8.21 (d, J = 2.44 Hz, 1H), 12.90-13.20 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.141, 111.046, 119.588, 139.759, 140.988, 164.520, 165.475; IR (KBr) 1707, 1656 cm^{-1}; MS: m/z 153 (M^+).

Methyl 1-butyl-6-oxo-1,6-dihydro-3-pyridinecarboxylate (4b). Yield 97%, brown oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, J = 7.50 Hz, 3H), 1.41 (m, 2H), 1.79 (m, 2H), 3.86 (s, 3H), 3.97 (t, J = 7.12 Hz, 2H), 6.50 (d, J = 9.56 Hz, 1H), 7.82 (dd J_1 = 9.56 Hz, J_2 = 2.52 Hz, 1H), 8.19 (dd, J_1 = 1.84 Hz, J_2 = 0.62 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.520, 19.703, 31.158, 50.184, 51.913, 109.400, 119.656, 138.189, 142.740, 162.297, 164.664; IR (KBr) 1721, 1665 cm^{-1}; MS: m/z 209 (M^+).

Methyl 1-benzyl-6-oxo-1,6-dihydro-3-pyridinecarboxylate (4c). Yield 94%, white solid, mp 90-91 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.83 (s, 3H), 5.16 (s, 2H), 6.59 (d, J = 9.56 Hz, 1H), 7.23-7.45 (m, 5H), 7.85 (dd, J_1 = 12.00 Hz, J_2 = 2.40 Hz, 1H), 8.19 (d, J = 2.65 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.989, 52.603, 109.961, 119.990, 128.175, 128.365, 129.017, 135.511, 138.507, 142.642, 162.441, 164.633; IR (KBr) 1713, 1660 cm^{-1}; MS: m/z 243 (M^+).

Methyl 6-oxo-1-(2-pyridinyl)-1,6-dihydro-3-pyridinecarboxylate (4d). Yield 81%, white solid, mp 156-157 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.66 (d, J = 9.56 Hz, 1H), 7.30-7.50 (m, 1H), 7.80-8.00 (m, 3H), 8.60 (d, J = 4.88 Hz, 1H), 8.74 (d, J = 2.24 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.126, 103.915, 110.394, 121.006, 121.287, 123.752, 137.931, 139.076, 141.678, 149.165, 161.849, 197.981; IR (KBr) 1721, 1686 cm^{-1}; MS: m/z 230 (M^+).

Methyl 6-oxo-1-(1,3-thiazol-2-yl)-1,6-dihydro-3-pyridinecarboxylate (4e). Yield 77%, white solid, mp 159-160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.94 (s, 3H), 6.79 (d, J = 9.56 Hz, 1H), 7.38 (d, J = 3.45 Hz, 1H), 7.75 (d, J = 3.46 Hz, 1H), 8.00 (dd, J_1 = 12.00 Hz, J_2 = 2.40 Hz, 1H), 9.61-9.64 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.429, 112.424, 119.444, 120.604, 136.884, 138.090, 138.621, 150.963, 171.969, 198.004; IR (KBr) 1715, 1685 cm^{-1}; MS: m/z 236 (M^+).

Methyl 6-oxo-1-phenyl-1,6-dihydro-3-pyridinecarboxylate (4f). Yield 83%, white solid, mp 100-101 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.64 (d, J = 9.77 Hz, 1H),

7.35-7.60 (m, 5H), 7.90 (dd, J_1 = 12.20 Hz, J_2 = 2.42 Hz, 1H), 8.22 (d, J = 2.65 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.095, 103.877, 109.809, 120.597, 126.362, 129.047, 129.480, 138.833, 143.279, 161.202, 162.457; IR (KBr) 1720, 1674 cm^{-1}; MS: m/z 229 (M^+).

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