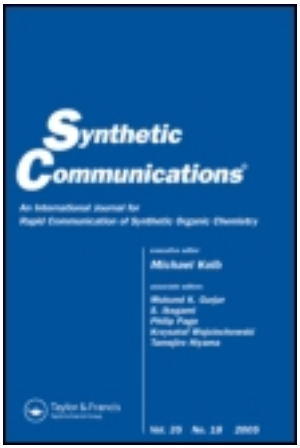

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Synthesis of 2,3-Disubstituted 4-Pyridone From a β-Aminocarboxylate Derivative and Acetoacetate

Adam Sobczak [a b] & Wiesław Z. Antkowiak [a]

[a] Faculty of Chemistry, Adam Mickiewicz University, Poznań, Poland

[b] Department of Chemistry, August Cieszkowski Agricultural University, ul. Wojska Polskiego 75, Poznan, 60-625, Poland

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Synthesis of 2,3-Disubstituted 4-Pyridone From a β-Aminocarboxylate Derivative and Acetoacetate

Adam Sobczak[‡] **and Wiesław Z. Antkowiak**
Faculty of Chemistry, Adam Mickiewicz University, Poznań, Poland

Abstract: The reaction of diethyl aminomethylenemalonate with ethyl acetoacetate proceeded, when catalyzed by anhydrous hydrogen chloride, toward a respectively substituted α- instead of γ-pyridone derivative formation, contrary to the literature report. Additionally, it was found that the amine used as a starting component in this reaction showed a great tendency to autocondensation under the influence of anhydrous hydrogen chloride to yield 5-ethoxycarbonyl-2-pyridone. The most convenient method to prepare 4-pyridone 2,3-disubstituted derivative appeared to be a three-step synthesis, starting from a chain enamine formation, which was subjected to cyclization, followed by oxidation of the last intermediate. The usefulness of the stepwise synthesis was demonstrated on the 3-ethoxycarbonyl-2-methyl-4-pyridone preparation as an example.

Keywords: Aminomethylenemalonate, autocondensation, γ-pyridone, α-pyridone

Syntheses of specifically substituted pyridine derivatives, based on a condensation of simple aliphatic amine and a carbonyl compound, have attracted considerable attention, mainly because of the constant demand for new methods applicable to total syntheses of many naturally occurring or biologically active heterocycles. Our interest in such synthetic problems results from the continuing studies carried out by us on a bipyridine mushroom

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[‡]Present affiliation: Department of Chemistry, August Cieszkowski Agricultural University, ul. Wojska Polskiego 75, 60-625 Poznan, Poland.

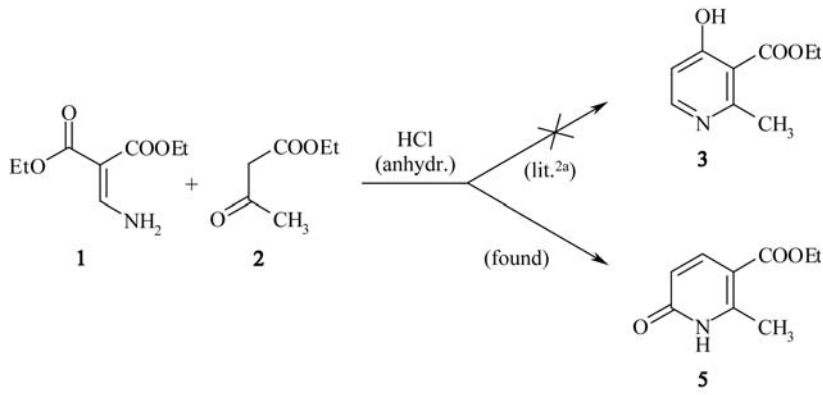
Address correspondence to Wiesław Z. Antkowiak, Faculty of Chemistry, Adam Mickiewicz University, ul. Grunwaldzka 6, 60-780, Poznań, Poland. Tel.: +48 (61) 8291-318; Fax: +48 (61) 8658-008; E-mail: wzantk@amu.edu.pl

alkaloid, orellanine,[1a–d] the molecule of which is composed of 3,4-difunctionalized 2-pyridyl N-oxide moieties.

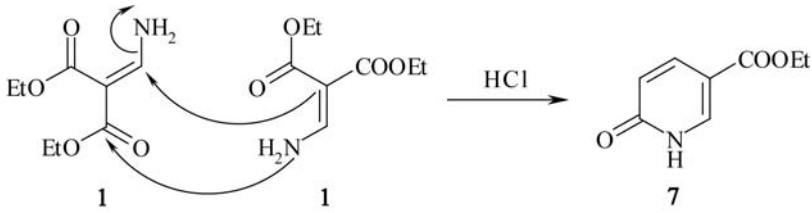
According to the literature report,[2a,b] such a synthesis of the pyridine derivative can be achieved by a condensation of diethyl aminomethylenemalonate (**1**) with ethyl acetoacetate (**2**). When sodium metal is used as an initiating agent, 3,5-diethoxycarbonyl-4-methyl-2-pyridone was obtained, but the reaction catalyzed by anhydrous hydrogen chloride yielded a derivative of an isomeric pyridone, 3-ethoxycarbonyl-2-methyl-4-pyridone (**3**).[2a] The structure of the last product would correspond to the one expected on the basis of the starting component structures and of their generally known chemical properties.

Our attempts to accomplish a condensation of **1**, or, in a separate experiment, ethyl aminomethyleneacetoacetate (**4**), with **2** dissolved in a small amount of ether in the presence of anhydrous hydrogen chloride actually yielded pyridone derivatives that turned out to be identical in both cases. However, the detailed analysis of the product's spectral properties and their comparison with the corresponding literature data[3a,b] showed the product structure to be 3-ethoxycarbonyl-2-methyl-6-pyridone (**5**), an α- instead of the expected γ-pyridone derivative. Such a conclusion was additionally proved by comparison of the product with an authentic sample, which had been obtained by an intramolecular cyclization of diethyl α-acetylglutarate in the presence of ammonium acetate, followed by an aromatization of the annulated intermediate, 3-ethoxycarbonyl-2-methyl-4,5-dihydro-6-pyridone (**6**).[4] When lead tetraacetate was used as an oxidizing agent, the final product **5** was additionally accompanied by two minor derivatives, one of the product and one of its dihydro ancestor, both acetoxylated at the α methyl group (Scheme 1).

In experiments in which reagents other than **2** were used (e.g., diethyl malonate, diethyl ketipinate, 2,4,5,7-octanetetraone), no condensation,



Scheme 1.

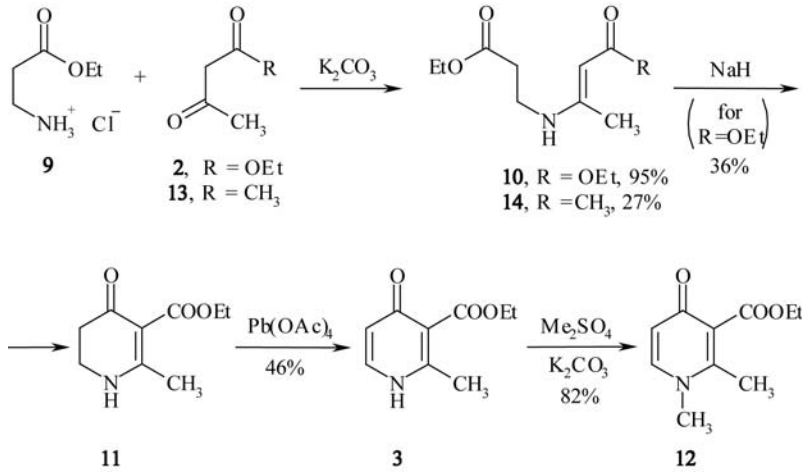


Scheme 2.

initiated by hydrogen chloride, with **1** was observed. Instead, when the reaction mixture was kept at room temperature for a few days, 5-ethoxycarbonyl-2-pyridone (ethyl 6-hydroxynicotinate, **7**) was obtained as a result of the condensation of two molecules of **1**. The tendency of **1** to undergo an autocondensation when treated with anhydrous HCl was confirmed in a separate experiment (Scheme 2).

To achieve the desired 4-pyridone derivative preparation, we chosen a stepwise mode of synthesis with the formation, at the first step, of a linear enamine intermediate **10**, in the molecule of which the bridging nitrogen is separated from an alkoxycarbonyl group by two carbon atoms. The use in such a synthesis of a readily available **1** as a component in the reaction with **2** does not fulfil our requirements. This is because, as has already been shown by Agui et al.,[2b] this set of reagents caused 3,5-diethoxycarbonyl-2-methyl-4-pyridone (**8**) formation, a product bearing an additional substituent at C-5, originating from the substituted malonate component. Because of the difficulty in the β-aminoacrylic acid ester preparation, the synthesis was started by a condensation of ethyl 3-aminopropionate (**9**) with **2**. The resulting enamine **10** was then subjected to cyclization (both processes were carried out in basic conditions opposite those used in the case already reported), yielding 3-ethoxycarbonyl-2-methyl-5,6-dihydro-4-pyridone (**11**),[5a,b] which, when oxidized by lead tetraacetate, was transformed into **3** with a satisfactory yield. It follows from an X-ray study[6] and the spectral data analysis that the final product **3** has mainly a keto tautomer's structure instead of a hydroxypyridine's. With the aim of attaining a stabilized enol structure in the form of its methyl ether by forcing a change of the keto–enol equilibrium, **3** was treated with dimethyl sulfate in the presence of potassium carbonate. However, this procedure led to N instead of O methylation, yielding 3-ethoxycarbonyl-1,2-dimethyl-4-pyridone (**12**) exclusively (Scheme 3).

In conclusion, it has to be stated that the verification of the literature report concerning the α- instead of γ-pyridone structure of the product of **1** with **2** condensation carried out in the presence of hydrogen chloride indicates that the direction of such a synthesis does not depend on the acidic or basic reaction conditions, but on the sequence of the intermediate steps. It appeared that, besides a singular case dealing with a synthesis



Scheme 3.

carried out on a borane complex,[7a,b] the 4-pyridone derivative can only be synthesized in a stepwise manner, which is initiated by the preparation of a nitrogen-linked chain condensation product, composed of the starting amine and carbonyl derivative. The nitrogen-bridged intermediate is then subjected to cyclization. The use of **1** in this way leads to 3,5-disubstituted 4-pyridone derivative **8** formation, whereas the synthesis of the monosubstituted system, 3-ethoxycarbonyl-2-methyl-4-pyridone (**3**), requires a condensation of β-aminopropionate **9** with **2** followed by cyclization and, additionally, oxidation of the cyclic intermediate **11** to the final 4-pyridone derivative **3**.

EXPERIMENTAL

Combustion analyses were performed by using Elementar Vario EL III apparatus (samples were predried under diminished pressure of 1 mmHg within 30 min). Melting points were determined by a hot-plate method (only occasionally a Büchi 535 capillary apparatus was used) and are uncorrected. NMR spectra were recorded on a Varian Gemini 300 and a Bruker DRX-600 spectrometer using TMS (for ^{1}H and ^{13}C NMR) or nitromethane (for ^{15}N NMR) as standards. Proton and carbon assignments were based on HETCOR experiments, though occasionally double resonance, NOE and HMBC were used. UV spectra were recorded on a Jasco V-550 spectrometer, using 1-mm cell. IR spectra were measured on a FT-IR Bruker IFS 113v instrument for KBr discs. MS spectral data were obtained on an AMD 402 mass spectrometer.

TLC analyses were carried out using Merck DC–Alufolien, Kieselgel 60 WF_{254}s and AcOEt–MeOH (7:3 or 9:1, A or B, respectively) as a developing

system. Column chromatography was carried out using Merck Kieselgel 60, (230–400 mesh) as the stationary phase, and hexane, benzene, AcOEt, CH_2Cl_2, $CHCl_3$, and 5% MeOH in $CHCl_3$ were the eluting solvents.

3-Ethoxycarbonyl-2-methyl-4,5-dihydro-6-pyridone (6)[5]

Mp 161–162°C (AcOEt) [lit.[8] 156°C]; ^{1}H NMR ($CDCl_3$) δ: 8.59 (b, NH, 1H), 4.20 (q, J 7.1, C**H**$_2$CH$_3$, 2H), 2.66 (m, H-4, 2H), 2.48 (m, H-5, 2H), 2.31 (t, J 1.6, CH_3, 3H), 1.30 (t, J 7.1, CH_2C**H**$_3$, 3H); ^{13}C NMR ($CDCl_3$) δ: 172.43 (**C**OOEt or C-6), 167.02 (**C**OOEt or C-6), 145.42 (C-2), 104.18 (C-3), 60.08 (**C**H$_2$CH$_3$), 30.20 (C-5), 21.43 (C-4), 18.70 (CH_3), 14.41 (CH_2**C**H$_3$); Other spectroscopic data were consistent with those already reported.[4,8,9]

3-Ethoxycarbonyl-2-methyl-6-pyridone (5)

The product was obtained according to the procedure for 4-pyridone derivative **3** preparation published by Ochiai and Ito.[2a] Mp 216–218°C [lit.[3b] 222°C]; ^{13}C NMR ($CDCl_3$) δ: 165.40 (C-6), 164.71 (**C**OOEt), 152.87 (C-2), 142.77 (C-4), 116.02 (C-5), 109.01 (C-3), 60.79 (**C**H$_2$CH$_3$), 19.76 (CH_3), 14.41 (CH_2**C**H$_3$); ^{15}N NMR ($CDCl_3$) δ: −200.4; MS: 181 (84%, M^+), 166 (5%), 153 (25%), 136 (100%), 125 (12%), 108 (15%), 107 (14%), 95 (8%), 80 (20%), 53 (20%), 42 (19%).

5-Ethoxycarbonyl-2-pyridone (7)

A solution of **1** (748 mg, 4 mmol) in Et_2O (4 ml), after being saturated with anhydrous HCl, was stirred at room temperature for 3 days. Next, the volatile components were removed under diminished pressure and the oily residue, when chromatographed on silica gel (AcOEt-PhH) and recrystallized from $CHCl_3$, gave pure **7** melting at 155–156°C [lit.[3b] 150°C]; IR (KBr, cm^{-1}): 2991, 2873 (b), 2805, 2700, 1727, 1709, 1682, 1597, 1479, 1435, 1427, 1364, 1301, 1268, 1228, 1118, 1020, 846, 776, 660; ^{13}C NMR ($CDCl_3$) δ: 165.51 (C-6 or **C**OOEt), 164.07 (C-6 or **C**OOEt), 141.05 (C-4), 139.68 (C-2), 119.52 (C-5), 111.36 (C-3), 61.08 (**C**H$_2$CH$_3$), 14.22 (CH_2**C**H$_3$); MS: 167 (41%, M^+), 139 (48%), 123 (13%), 122 (100%), 111 (9%), 99 (9%), 94 (26%), 82 (5%), 67 (9%), 66 (12%).

Ethyl 3-(2-Ethoxycarbonylethylamino)-2-butenoate (10)

A mixture of β-alanine ethyl ester hydrochloride (**9**, 462 mg, 3 mmol), ethyl acetoacetate (**2**, 0.38 ml, 388 mg, 3 mmol) and anhydrous potassium

carbonate (1 g) in 10 ml of benzene was refluxed under the Dean–Stark trap for 3 h. The reaction mixture, when cooled and diluted with AcOEt and CH_2Cl_2, was filtered, and the obtained solution was concentrated under diminished pressure, yielding pure enamine **10** (652 mg, 95%). Yellow oil. Rf 0.8 (B). HRMS for $C_{11}H_{19}NO_4$ $[M]^+$: calcd. 229.13141, found 229.13061. IR (KBr film, cm^{-1}): 3287, 2981, 2935, 2905, 1733, 1652, 1608, 1503, 1444, 1376, 1342, 1295, 1251, 1174, 1114, 1052, 1029, 785; ^{1}H NMR ($CDCl_3$) δ: 8.66 (broad, NH, 1H), 4.47 (s, =CH, 1H), 4.18 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 4.09 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 3.52 (q, *J* 6.6, NHC**H**$_2$CH$_2$CO, 2H), 2.56 (t, *J* 6.6, NHCH$_2$C**H**$_2$CO, 2H), 1.95 (s, CH$_3$, 3H), 1.27 (t, *J* 7.1, CH$_2$C**H**$_3$, 3H), 1.24 (t, *J* 7.1, CH$_2$C**H**$_3$, 3H); ^{13}C NMR ($CDCl_3$) δ: 171.29 (**C**OOEt), 170.46 (**C**OOEt), 161.20 (C-3), 83.02 (C-2), 60.81 (**C**H$_2$CH$_3$), 58.31 (**C**H$_2$CH$_3$) 38.55 (NH**C**H$_2$CH$_2$CO), 35.45 (NHCH$_2$**C**H$_2$CO), 19.23 (CH$_3$), 14.56 (CH$_2$**C**H$_3$), 14.09 (CH$_2$**C**H$_3$); MS: 229 (43%, M^+), 200 (2%), 184 (60%), 157 (44%), 156 (50%), 154 (12%), 142 (39%), 138 (21%), 136 (7%), 128 (7%), 110 (99%), 101 (30%), 96 (100%), 84 (60%), 82 (29%), 73 (28%), 70 (20%), 68 (38%), 55 (35%).

2-(2-Ethoxycarbonylethylamino)-2-penten-4-one (14)

The compound **14** was prepared from β-alanine ethyl ester hydrochloride (**9**, 4.62 g, 30 mmol) and acetylacetone (**13**, 3.0 g, 30 mmol) in the presence of K_2CO_3 by using a procedure similar to that described in the preparation of the enamine butenoate derivative **10**. The crude product (3.86 g, 65%) was subjected to a short-path distillation (80–160°C, 1 mm Hg), yielding 1.59 g (27%) of a yellow liquid. Rf 0.6 (B, a bright yellow spot at λ 366 nm). ^{1}H NMR ($CDCl_3$) δ: 10.85 (b, NH, 1H), 4.98 (s, =CH, 1H), 4.17 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 3.55 (q, *J* 6.6, NHC**H**$_2$CH$_2$CO, 2H), 2.59 (t, *J* 6.6, NHCH$_2$C**H**$_2$CO, 2H), 2.00 (s, CH$_3$, 3H), 1.96 (s, CH$_3$, 3H), 1.27 (t, *J* 7.1, CH$_2$C**H**$_3$, 3H); MS: 199 (100%, M^+), 184 (83%), 182 (31%), 170 (2%), 156 (19%), 154 (14%), 142 (6%), 138 (29%), 126 (51%), 112 (85%), 110 (32%), 108 (24%), 101 (24%), 97 (30%), 96 (51%), 94 (9%), 84 (30%), 82 (12%), 73 (12%), 70 (9%), 68 (13%), 55 (22%), 43 (57%), 42 (43%).

3-Ethoxycarbonyl-2-methyl-5,6-dihydro-4-pyridone (11)

A solution of ethyl 3-(2-ethoxycarbonylethylamino)-2-butenoate (**10**, 13.74 g, 60 mmol) in 350 ml of benzene was supplied with sodium hydride (4 g of a 50% dispersion in oil, 83 mmol; before use, the reagent was washed with benzene) and the resulting yellow suspension, when stirred, was kept at reflux for 3 h. Next, after the mixture had been cooled to room temperature, the reaction was quenched with water (160 ml) and the organic solvent was removed in vacuum. The obtained alkaline, aqueous solution was treated

with 15% hydrochloric acid (25 ml), then washed with Et_2O (3 × 100 ml), followed with making it alkaline again by means of $NaHCO_3$ and taking up the product into methylene chloride (3 × 100 ml). After being dried over Na_2SO_4, the CH_2Cl_2 solution was concentrated to a pale yellow solid residue (3.97 g, 36%, melting at 115–121°C), which was recrystallized from AcOEt/hexane, yielding almost colorless crystals of mp 126–127°C. Rf 0.15 (B), 0.5 (A). Anal. calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; found: C, 58.96; H, 7.20; N, 7.59. HRMS: for $[M]^+$, $C_9H_{13}NO_3$, calcd. 183.08954, found 183.09004; for $[M\text{-}C_2H_5O]^+$, $C_7H_8NO_2$, calcd. 138.05550, found 138.05568; IR (KBr, cm^{-1}): 3248, 3092, 2977, 2902, 1705, 1671, 1618, 1607, 1570, 1527, 1445, 1418, 1384, 1337, 1314, 1291, 1230, 1214, 1169, 1111, 1085, 1054, 1027, 958, 886, 740, 537; UV (MeOH): 244 nm (ε 8000), 301 nm (ε 12600); ^{1}H NMR ($CDCl_3$) δ: 7.27 (b, NH, 1H), 4.22 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 3.58 (td, *J* 7.7, 3.0, H-6, 2H), 2.47 (t, *J* 7.7, H-5, 2H), 2.32 (s, CH_3, 3H), 1.31 (t, *J* 7.1, CH_2C**H**$_3$, 3H); ^{1}H NMR (DMSO) δ: 8.48 (b, NH, 1H), 4.03 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 3.40 (td, *J* 7.7, 2.7, H-6, 2H), 2.22 (t, *J* 7.7, H-5, 2H), 2.12 (s, CH_3, 3H), 1.17 (t, *J* 7.1, CH_2C**H**$_3$, 3H); ^{13}C NMR ($CDCl_3$) δ: 188.66 (C-4), 167.27 (C-2), 166.78 (**C**OOEt), 103.03 (C-3), 59.79 (**C**H$_2$CH$_3$), 40.44 (C-6), 35.51 (C-5), 21.68 (CH_3), 14.33 (CH_2**C**H$_3$); ^{15}N NMR ($CDCl_3$) δ: −269.2; MS: 183 (31%, M^+), 154 (1%), 138 (100%), 126 (2%), 111 (62%), 96 (4%), 94 (3%), 86 (13%), 84 (37%), 82 (20%), 80 (10%), 67 (42%), 55 (33%).

3-Ethoxycarbonyl-2-methyl-4-pyridone (3)

A mixture of 3-ethoxycarbonyl-2-methyl-5,6-dihydro-4-pyridone (**11**, 183 mg, 1 mmol) and lead tetraacetate (1.33 g, 3 mmol) in 2 ml of acetic acid was stirred under reflux for 4 h. Next, the solvent was removed under diminished pressure and the dark yellow, oily residue was digested with a 10% solution of EtOH in CH_2Cl_2 (50 ml). The resulting suspension was filtered through a layer of silica gel (2 g), and the filtrate was concentrated, yielding a colorless solid. The crude product was chromatographied on a silica gel (1 g) column and the solid (84 mg, 46%) eluted by a 10% solution of MeOH in CH_2Cl_2, when recrystallized from AcOEt, gave needles of mp 148–149°C. Rf 0.1 (B), 0.35 (A). HRMS for $[M]^+$, $C_9H_{11}NO_3$, calcd. 181.07390, found 181.07480; IR (KBr, cm^{-1}): 3253, 3052, 2983, 2941, 2754 (b), 1722, 1633, 1617, 1535, 1512, 1397, 1299, 1220, 1106, 1096, 1041, 852, 604, 537; UV (MeOH): 256 nm (ε 12300); ^{1}H NMR (DMSO) δ: 11.56 (b, NH, 1H), 7.59 (d, *J* 7.1, H-6, 1H), 6.07 (d, *J* 7.1, H-5, 1H), 4.19 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 2.18 (s, CH_3, 3H), 1.24 (t, *J* 7.1, CH_2C**H**$_3$, 3H); ^{1}H NMR ($CDCl_3$, 25°C) δ: 12.91 (b, NH, 1H), 7.64 (b, H-6, 1H), 6.40 (d, *J* 6.6, H-5, 1H), 4.30 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 2.46 (s, CH_3, 3H), 1.33 (t, *J* 7.1, CH_2C**H**$_3$, 3H); ^{1}H NMR ($CDCl_3$, −50°C) δ: 13.60 (b, NH, 1H), 7.67 (t, *J* 6.3, H-6, 1H), 6.43 (d, *J* 6.9, H-5, 1H), 4.30 (q, *J* 7.1, C**H**$_2$CH$_3$, 2H), 2.45 (s, CH_3, 3H),

1.35 (t, *J* 7.1, CH_2CH_3, 3H); ^{13}C NMR ($CDCl_3$, −50°C) *δ*: 176.43 (C-4), 166.67 (**C**OOEt), 148.79 (C-2), 138.18 (C-6), 121.83 (C-3), 116.43 (C-5), 61.47 (CH_2CH_3), 17.94 (CH_3), 13.97 (CH_2CH_3); ^{1}H NMR ($CDCl_3$ + AcOH) *δ*: 11.94 (b, NH, 1H), 7.67 (d, *J* 7.1, H-6, 1H), 6.46 (d, *J* 7.1, H-5, 1H), 4.29 (q, *J* 7.1, CH_2CH_3, 2H), 2.47 (s, CH_3, 3H), 1.33 (t, *J* 7.1, CH_2CH_3, 3H); ^{1}H NMR (CD_3CN) *δ*: 10.64 (b, NH, 1H), 7.51 (d, *J* 7.1, H-6, 1H), 6.23 (d, *J* 7.1, H-5, 1H), 4.25 (q, *J* 7.1, CH_2CH_3, 2H), 2.28 (s, CH_3, 3H), 1.28 (t, *J* 7.1, CH_2CH_3, 3H); ^{1}H NMR (TFA) *δ*: 8.37 (d, *J* 6.9, H-6, 1H), 7.38 (d, *J* 7.1, H-5, 1H), 4.72 (q, *J* 7.1, CH_2CH_3, 2H), 3.10 (s, CH_3, 3H), 1.58 (t, *J* 7.1, CH_2CH_3, 3H); MS: 181 (50%, M^+), 166 (1%), 153 (1%), 135 (100%), 107 (47%), 94 (3%), 79 (17%), 67 (9%), 53 (23%), 42 (9%).

3-Ethoxycarbonyl-1,2-dimethyl-4-pyridone (12)

A stirred suspension of 3-ethoxycarbonyl-2-methyl-4-pyridone (**3**, 181 mg, 1 mmol) and anhydrous potassium carbonate (265 mg, 1.9 mmol) in 3 ml of acetone was treated dropwise with dimethyl sulfate (0.25 g, 0.19 ml, 2 mmol) and the stirring at room temperature was continued overnight. To complete the reaction (according to TLC), the mixture was then kept at 60°C for a further 1.5 h. Next, the solvent was removed under diminished pressure, and the crude product was isolated by extraction with CH_2Cl_2 of the residue dissolved in water. Purification on a silica gel (4 g) column gave, from an AcOEt fraction, a colorless solid (160 mg, 82%), which, when recrystallized from PhH/CH_2Cl_2 (2:1) mixture, melted at 161.5–162°C. Rf 0.3 (A). HRMS for $[M]^+$, $C_{10}H_{13}NO_3$, calcd. 195.08954, found 195.08809; IR (KBr, cm^{-1}): 2990, 2964, 2927, 1719, 1644, 1576, 1534, 1492, 1311, 1280, 1227, 1193, 1150, 1081, 1059, 1021, 842, 787, 563, 471; ^{1}H NMR ($CDCl_3$) *δ*: 7.25 (d, *J* 7.5, H-6, 1H), 6.32 (d, *J* 7.5, H-5, 1H), 4.38 (q, *J* 7.1, CH_2CH_3, 2H), 3.58 (s, NCH_3, 3H), 2.30 (s, CH_3, 3H), 1.36 (t, *J* 7.1, OCH_2CH_3, 3H); ^{13}C NMR ($CDCl_3$) *δ*: 175.25 (C-4), 167.14 (**C**OOEt), 146.32 (C-2), 141.62 (C-6), 125.46 (C-3), 118.18 (C-5), 61.49 (CH_2CH_3), 41.24 (NCH_3), 17.31 (CH_3), 14.16 (OCH_2CH_3); MS: 195 (M^+, 8%), 151 (15%), 150 (37%), 138 (7%), 124 (8%), 123 (100%), 122 (18%), 95 (5%), 94 (11%), 84 (3%), 82 (6%), 67 (19%).

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