SYNTHESES OF PYRROLO- AND FURO-1,4-DIHYDRO-PYRIDINE DERIVATIVES

Keizo Matsuo,* Masami Adachi, Tatsuko Takagi, Sachiko Ueno, Takahiko Arase, and Fumie Kuroi

Faculty of Pharmaceutical sciences, Kinki University, 3-4-1 Kowakae, Higashiosaka, Osaka 577-8502, Japan. e-mail: k-matsuo@phar.kindai.ac.jp

Abstract - Methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6\(\text{H}\)-pyrrolo[4,3-\(b\)]pyridine-3-carboxylates and methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-\(b\)]pyridine-3-carboxylate were synthesized. Attempting synthesis of methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-\(c\)]pyridine-7-carboxylates failed.

1,4-Dihydropyridine derivatives, for example, nifedipine (1) and nicardipine (2), are used clinically for the treatment of angina pectoris, cerebrovascular disorders, hypertension and so on.\(^1\) In the course of our synthetic studies on the biologically active heterocyclic compounds using tetronic acids, tetramic acids, thiotetronic acid and their analogs,\(^2\) we planned to synthesize methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6\(\text{H}\)-pyrrolo[4,3-\(b\)]pyridine-3-carboxylates (3), methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-\(b\)]pyridine-3-carboxylate (4), and methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-\(c\)]pyridine-7-carboxylates (5) expecting their biological activities (Figure 1).

\(\text{Figure 1}\)

For the synthesis of methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6\(\text{H}\)-pyrrolo[4,3-\(b\)]pyridine-3-carboxylates (3), 5,5-dimethyltetramic acid (6)\(^3\) was used for the synthon. 3-Arylmethylene-5,5-
dimethyltetramic acids (7a–c) were derived from 6 by treatment with the corresponding aryl aldehydes in the presence of conc. hydrochloric acid without solvents. When 5,5-dimethyl-3-phenylmethylene tetramic acid (7a) was treated with methyl acetoacetate in the presence of triethylamine in methanol at refluxing temperature, the Micheal adduct (8a) was obtained in 96% yield. Its 1H-NMR spectrum showed that 8a was a mixture of diastereoisomers. When 8a was allowed to react with ammonium acetate in methanol at room temperature, the alcohol (9a) was isolated in 43% yield. Elemental analysis and MS spectral data supported the molecular formula of C18H22N2O4. In IR spectrum, the \( \text{\text\'C=O} \), \( \text{\text\'N=O} \)-unsaturated ester and the five membered ring lactam appeared at 1670 cm\(^{-1}\). The 1H-NMR spectrum showed the benzylc methine proton signal at \( \delta \) 4.98. For the following dehydration reaction, the alcohol (9a) was first heated with p-toluene sulfonic acid in benzene, but the isolated product in 41% yield was the undesired pyridine derivative (10). Therefore, the same reaction was repeated using a catalytic amount of p-toluene sulfonic acid. On this reaction, the desired dihydropyridine derivative (3a) was isolated in 39% yield. The structure of 3a was fully characterized by IR, 1H-NMR and MS spectral data. Other dihydropyridine derivatives (3b, R=2-Cl and 3c, R=3-NO\(_2\)) were also prepared by similar reaction procedures to that used for 3a in moderate yields (Scheme 1). In the preparation of 9c, the intermediate (8c) was not isolated and used directly for the next reaction.

![Scheme 1](image)

For the preparation of methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-b]pyridine-3-carboxylate (4), 3-benzylidene-2-oxo-4-butanolide (11) was treated first with methyl acetoacetate in methanol in the presence of triethylamine at reflux temperature to afford the Michael adduct (12) in 90% yield. The adduct (12) was then reacted with ammonium acetate in methanol at room temperature overnight to obtain the hydroxy ester (13) in 54% yield. When 13 was dehydrated by treatment with catalytic amount of p-TsOH in benzene, the desired furodihydropyridine derivative (4) was obtained in
93% yield accompanied with the furopyridine derivative (14) (4%) as a by-product (Scheme 2).

For the synthesis of methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-c]pyridine-7-carboxylates (5a, R=H or 5b, R=Cl), 2-aryloxy-4,4-dimethyl-2-buten-4-olides (15) was used as the starting material. When 2-benzoyl-4,4-dimethyl-2-buten-4-olide (15a) was treated with methyl acetoacetate in the presence of triethylamine in methanol at room temperature, the Michael adduct (16) and the alcohol (17) were isolated in 36 and 38% yields, respectively.

The stereochemistry of α and β-positions of the γ-lactone in 16 supposed to be cis, because, in its 1H-NMR spectrum, these two protons appeared at δ 4.85 (d, J=10.0 Hz) and 3.88 (t, J=10.0 Hz),
respectively. Expecting to obtain the dihydropyridine derivative (5a), successive treatment of the Michael adduct (16) with ammonium acetate in methanol at refluxing temperature resulted in the isolation of the pyridine derivative (18) in 27% yield. During the reaction, two spots supposed to be 5a and 18 were observed on the TLC, but TLC analysis of the worked up crude products showed disappearance of the spot supposed to be 5a. Therefore, the milder reaction conditions were employed next in the hope of isolation of 5a. Thus, the same reaction was performed at room temperature, however no reaction took place (Scheme 3).

Since the structure of the by-product (17) in the above reaction was not clear at that stage, 17 was similarly treated with ammonium acetate in methanol at refluxing temperature. The product isolated in 30% yield was the amine (19), whose structure was confirmed by X-Ray crystallographic analysis. When 17 was reacted with p-TsOH in benzene, α,β-unsaturated ketoester (20) was obtained in 47% yield. These results indicate the structure of the by-product to be 17.

![Scheme 4](image)

When 2-(2-chlorobenzoyl)-4,4-dimethyl-2-buten-4-olide (15b) was treated with methyl acetoacetate in the presence of triethylamine and successively with ammonium acetate, the alcohol (21) was obtained in 20% yield. The cis stereochemistry of the ring junction of 21 was attributed to the coupling constant (10 Hz) between those two methine protons. Dehydration reaction of 21 with p-TsOH in benzene at refluxing temperature in the hope of the isolation of the dihydropyridine derivative gave again the pyridine derivative (22) in 57% yield and 5b was not isolated (Scheme 4).

In conclusion, methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6H-pyrrolo[4,3-b]pyridine-3-carboxylates (3a-c) and methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-b]pyridine-3-carboxylate (4) were synthesized. Attempting synthesis of methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-c]pyridine-7-carboxylates (5a, b) failed and the product was the furopyridine derivatives (18, 22).
EXPERIMENTAL
Melting points were determined using a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrophotometer. $^1$H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as the internal standard. High-resolution MS spectra (HRMS) were measured with a JEOL JMS-HX100 instrument at 70 eV.

Methyl 2-[1-(4,4-dimethyl-3-oxo-4-butanelactum-2-yl)-1-phenyl]methyl-3-oxobutanoate (8a)
Triethylamine (0.25 mL, 1.79 mmol) was added to a solution of methyl acetoacetate (0.546 g, 4.70 mmol) in MeOH (5 mL) and the solution was stirred for 10 min. To this solution was added dropwise a solution of 7a (1.004 g, 4.66 mmol) in MeOH (12 mL), and the whole was heated under reflux for 5 h. After cooling the reaction mixture, the precipitates formed were collected by filtration and crystallized from MeOH to give 8a (1.489 g, 96%). mp 147-152 $^\circ$C. IR (Nujol): 3350, 1710, 1660, 1590, 1240, 1010 cm$^{-1}$. $^1$H-NMR (DMSO-$_d_6$) $\delta$: 1.13, 1.18 (each 3H, s, CH$_3$), 2.17 (3H, s, CH$_3$), 3.64 (3H, s, OCH$_3$), 4.47 (1H, d, $J$=12.0 Hz, CH), 4.99 (1H, d, $J$=12.0 Hz, CH), 7.2 (7H, m, ArH, OH, NH). HRMS ($m/z$) Calcd for C$_{18}$H$_{21}$NO$_5$: 331.1420. Found: 331.1423.

Methyl 1,4,4a,5,7-pentahydro-7a-hydroxy-2,7,7-trimethyl-5-oxo-4-phenyl-6H-pyrrolo[4,3-b]-pyridine-3-carboxylate (9a)
A solution of 8a (3.802 g, 11.47 mmol) and ammonium acetate (4.409 g, 57.19 mmol) in MeOH (150 mL) was stirred at rt overnight. The mixture was concentrated under reduced pressure to give the residue, to which was added H$_2$O. The precipitates formed were collected by filtration and crystallized from AcOEt to give 9a (1.623 g, 43%). mp 167-169 $^\circ$C. IR (Nujol): 3360, 3170, 1750, 1670, 1600, 1290, 1260, 1090 cm$^{-1}$. $^1$H-NMR (DMSO-$_d_6$) $\delta$: 1.11, 1.17 (3H, s, CH$_3$), 2.34 (3H, s, CH$_3$), 2.86 (3H, s, CH$_3$), 3.64 (3H, s, OCH$_3$), 3.35 (3H, s, OCH$_3$), 4.28 (1H, s, OH), 4.98 (1H, s, ArCH), 6.14 (1H, br s, NH), 7.15-7.25 (5H, ArH), 7.63 (1H, s, NH). Anal. Calcd for C$_{18}$H$_{22}$N$_2$O$_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.31; H, 6.68; N, 8.53. MS (m/z): 330 (M$^+$), 312, 298, 235, 215.

Methyl 1,4,4a,5,7-pentahydro-7a-hydroxy-2,7,7-trimethyl-5-oxo-4-(2-chlorophenyl)-6H-pyrrolo[4,3-b]-pyridine-3-carboxylate (9b)
Triethylamine (0.55 mL, 3.94 mmol) was added to a solution of methyl acetoacetate (2.117 g, 18.23 mmol) in MeOH (50 mL) and the solution was stirred for 10 min. To this solution was added dropwise a solution of 7b (4.571 g, 18.31 mmol) in MeOH (70 mL), and the whole was heated under reflux for 5 h. After concentration of the mixture under reduced pressure to give the residue, which was purified by SiO$_2$ column chromatography (acetone:hexane=1:2) to afford 8b (4.223 g, 63%), after crystallization from 2-propanol-hexane. This Michael adduct (8b) (4.223 g, 11.54 mmol) was dissolved in MeOH (70 mL). To this solution was added ammonium acetate (2.661 g, 34.51 mmol), and the whole was stirred at rt overnight. After concentration, H$_2$O was added to the residue to form the precipitates, which were collected by filtration and then crystallized from DMSO-H$_2$O to give 9b (2.471 g, 59%). mp 182-183 $^\circ$C. IR (Nujol): 3425, 3275, 1740, 1670, 1610, 1290, 1270, 1080 cm$^{-1}$. $^1$H-NMR (DMSO-$_d_6$) $\delta$: 1.10, 1.17.
Methyl 1,4,4a,5,7,7a-hexahydro-7a-hydroxy-2,7,7-trimethyl-5-oxo-4-(3-nitrophenyl)-6H-pyrrolo-[4,3-b]pyridine-3-carboxylate (9c)

Triethylamine (0.10 mL, 0.72 mmol) was added to a solution of methyl acetoacetate (0.225 g, 1.94 mmol) in MeOH (5 mL) and the solution was stirred for 10 min. To this solution was added dropwise a solution of 7c (0.350 g, 1.34 mmol) in MeOH (24 mL), and the whole was heated under reflux for 2 h. Concentration of the mixture under reduced pressure gave the crude 8c (0.70 g) as an oil, which was dissolved in MeOH (18 mL). To this solution was added ammonium acetate (0.505 g, 6.55 mmol), and the whole was stirred at rt for 5 h. After addition of ammonium acetate (0.207 g, 2.68 mmol), the mixture was stirred at rt overnight. After concentration, H2O was added to the residue to form the precipitates, which were collected by filtration and then crystallized from MeOH to give 9c (0.380 g, 76%). mp 189-193°C.

IR (Nujol): 3290, 1720, 1660, 1600, 1270, 1250, 1190, 1100, 1060 cm⁻¹.

1H-NMR (DMSO-d₆) δ: 1.09, 1.16 (each 3H, s, CH₃), 2.38 (3H, s, CH₃), 2.94 (1H, s, CH), 3.34 (3H, s, OCH₃), 4.35 (1H, s, OH), 5.51 (1H, s, ArCH), 6.56 (1H, s, NH), 7.51 (1H, t, J=8.0 Hz, ArH), 7.68 (1H, br d, J=8.0 Hz, ArH), 7.82 (1H, s, NH), 7.97 (1H, br d, J=8.0 Hz, ArH), 8.03 (1H, br s, ArH). HRMS (m/z) Calcd for C₁₈H₂₁N₂O₄: 364.1190. Found: 364.1198.

Methyl 5,7-dihydro-2,7,7-trimethyl-5-oxo-4-phenyl-6H-pyrrolo[4,3-b]pyridine-3-carboxylate (10)
p-TsOH · H₂O (0.431 g, 2.72 mmol) was added to a solution of 9a (0.30 g, 0.908 mmol) in C₆H₆ (20 mL) and the reaction mixture was heated under reflux for 2 h, during the reaction, water formed was removed continuously. After cooling, the reaction mixture was concentrated under reduced pressure to give the residue, which was dissolved in CHCl₃. The solution was washed with saturated NaHCO₃ aqueous solution, H₂O, and brine, respectively and then dried over Na₂SO₄. Removal of the solvent gave the residue, which was crystallized from CHCl₃-hexane to afford 10 (0.115 g, 41%). mp 217-220°C.

IR (Nujol): 3210, 1710, 1690, 1590, 1370, 1270, 1160, 1100 cm⁻¹.

1H-NMR (CDCl₃) δ: 1.58 (6H, s, 2x CH₃), 2.68 (3H, s, CH₃), 3.57 (3H, s, OCH₃), 6.31 (1H, s, NH), 7.36-7.25 (5H, m, ArH), 7.29 (1H, s, CONH), 8.99 (1H, br s, NH). Anal. Calcd for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.72; H, 5.87; N, 9.04.

Methyl 1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-4-phenyl-6H-pyrrolo[4,3-b]pyridine-3-carboxylate (3a)
p-TsOH · H₂O (80 mg, 0.42 mmol) was added to a solution of 9a (0.256 g, 0.775 mmol) in C₆H₆ (90 mL) and the reaction mixture was heated under reflux for 1 h, during the reaction, water formed was removed continuously. After cooling the reaction mixture, the precipitates formed were collected by filtration. Recrystallization of the precipitates from 2-propanol-hexane gave 95 mg (39%) of 3a. mp 198-201°C.

IR (Nujol): 3300, 1710, 1660, 1610, 1220, 1090 cm⁻¹.

1H-NMR (DMSO-d₆) δ: 1.29 and 1.31 (each 3H, s, CH₃), 2.32 (3H, s, CH₃), 3.47 (3H, s, OCH₃), 4.66 (1H, s, ArCH), 7.05-7.25 (5H, m, ArH), 7.29 (1H, s, CONH), 8.99 (1H, br s, NH). HRMS (m/z) Calcd for C₁₈H₂₄N₂O₃: 312.1474. Found: 312.1492.
Methyl 1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-4-(2-chlorophenyl)-6H-pyrrolo[4,3-b]pyridine-3-carboxylate (3b)

3b (0.565 g, 66%) was obtained from 9b (0.90 g, 2.47 mmol) and p-TsOH • H2O (94 mg, 0.493 mmol) by the same procedure used for 3a. mp 285-289 °(MeOH-hexane). IR (Nujol): 3200, 1700, 1660, 1640, 1270, 1210, 1170, 1080, 1040 cm⁻¹. ¹H-NMR (DMSO-d₆): δ: 1.28 and 1.32 (each 3H, s, CH₃), 2.30 (3H, s, CH₃), 3.41 (3H, s, OCH₃), 5.11 (1H, s, ArCH), 7.10 (1H, s, NH), 7.17-7.26 (4H, m, ArH), 9.02 (1H, s, NH). Anal. Calcd for C₁₈H₁₉N₂O₃Cl: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.32; H, 5.58; N, 7.99

Methyl 1,4,5,7-tetrahydro-2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxo-6H-pyrrolo[4,3-b]pyridine-3-carboxylate (3c)

3c (54 mg, 52%) was obtained from 9c (0.110 g, 0.293 mmol) and p-TsOH • H₂O (11 mg, 0.058 mmol) by the same procedure used for 3a. mp 173-176 °(MeOH). IR (Nujol): 3280, 1710, 1680, 1640, 1610, 1340, 1220, 1190, 1090, 1030 cm⁻¹. ¹H-NMR (DMSO-d₆): δ: 1.30 and 1.32 (each 3H, s, CH₃), 2.33 (3H, s, CH₃), 3.48 (3H, s, OCH₃), 4.83(1H, s, ArCH), 7.42 (1H, s, NH) , 7.50-8.02 (4H, m, ArH), 9.20 (1H, s, NH). HRMS (m/z) Calcd for C₁₈H₁₉N₃O₅: 357.1325. Found: 357.1317.

3-(2-Methoxycarbonyl-3-oxo-1-phenylbutyl)-2-oxo-4-butanolide (12)

To a solution of methyl acetoacetate (1.83 g, 15.76 mmol) and triethylamine (0.8 mL, 5.74 mmol) in MeOH (40 mL) was added drop wise a solution of 11 (2.0 g, 10.63 mmol) in MeOH (60 mL), and the whole was heated under reflux for 4.5 h. After cooling the reaction mixture, the precipitates formed were collected by filtration to give 12 (2.90 g, 90%). mp 137-138.5 °(2-propanol-hexane) . IR (Nujol): 3420, 1740, 1680, 1250, 1150, 1130, 1090, 1040, 1000 cm⁻¹. ¹H-NMR (DMSO-d₆): δ: 1.98 (3H, s, CH₃), 3.63 (3H, s, OCH₃), 4.40-4.80 (4H, m, ArCH, OCH₂, COCHCO), 7.27 (5H, m, ArH), 9.80 (1H, br s, OH). HRMS (m/z) Calcd for C₁₆H₁₆O₆: 304.0947. Found: 304.0921.

Methyl 1,4,4a,5,7,7a-hexahydro-7a-hydroxy-2-methyl-7-oxo-4-phenylfuro[3,4-b]pyridine-3-carboxylate (13)

A solution of 12 (0.20 g, 0.66 mmol) and ammonium acetate (0.26 g, 3.37 mmol) in MeOH (10 mL) was added drop wise a solution of 11 (2.0 g, 10.63 mmol) in MeOH (60 mL), and the whole was heated under reflux for 4.5 h. After cooling the reaction mixture, the precipitates formed were collected by filtration to give 13 (0.107 g, 54%), which was crystallized from AcOEt. mp 185-188.5 °. IR (Nujol): 3350, 1760, 1675, 1590, 1290, 1220, 1120, 1100, 1000 cm⁻¹. ¹H-NMR (DMSO-d₆): δ: 2.34 (3H, s CH₃), 2.95 (1H, m OCH₂CH), 3.39 (3H, s, OCH₃), 3.75 (1H, dd, J=10.0, 8.0 Hz, OCH₂CH), 3.91 (1H, br s, ArCH), 4.44 (1H, t, J=8.0 Hz, OCH₂CH), 5.95 (1H, br s, OH), 7.21 (5H, m, ArH), 7.33 (1H, br s, NH). HRMS (m/z) Calcd for C₁₆H₁₇NO₅: 303.1107. Found: 303.1086.

Methyl 1,4,4a,5,7,7a-hexahydro-7a-hydroxy-2-methyl-7-oxo-4-phenylfuro[3,4-b]pyridine-3-carboxylate (13) and Methyl 5,7-dihydro-3-methyl-7-oxo-4-phenylfuro[3,4-b]pyridine-3-carboxylate (4) and Methyl 5,7-dihydro-3-methyl-7-oxo-4-phenylfuro[3,4-b]pyridine-3-carboxylate (14)

p-TsOH • H₂O (0.010 g, 0.05 mmol) was added to a solution of 13 (0.30 g, 0.99 mmol) in C₆H₆ (120 mL) and the reaction mixture was heated under reflux for 5 min, during the reaction, water formed was
removed continuously. After cooling, the reaction mixture was washed with saturated NaHCO₃ aqueous solution, H₂O, and brine, respectively and then dried over Na₂SO₄. Removal of the solvent gave the residue, which was crystallized from C₆H₆ to afford 4 (0.252 g). The filtrate was concentrated under reduced pressure and the residue was purified by SiO₂ PTLC (C₆H₆:AcOEt=4:1) to give 4 (11 mg, total 0.263 g, 93%) and 14 (10 mg, 4%). 4: mp 198-200° (C₆H₆). IR (Nujol): 3300, 1740, 1710, 1640, 1590, 1500, 1260, 1100 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.42 (3H, s, CH₃), 3.55 (3H, s, OCH₃), 4.51, 4.68 (each 1H, dd, J=16.5, 1.8 Hz, OCH₂C), 4.94 (1H, br s, ArCH), 7.15-7.37 (5H, m, ArH). Anal. Calcd for C₁₆H₁₅NO₄: C, 67.36; H, 5.30; N, 4.91. Found:  C, 67.33; H, 5.36; N, 4.83. 14: mp 200-203° (C₆H₆). IR (CHCl₃): 1782, 1734, 1595, 1456, 1355, 1289, 1218, 1212, 1174, 1101, 1030 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.76 (3H, s, CH₃), 3.67 (3H, s, OCH₃), 5.27 (2H, s, OCH₂), 7.18-7.35 (5H, m, ArH). HRMS (m/z) Calcd for C₁₆H₁₃NO₄: 283.0845. Found: 283.0856.

2-Benzoyl-3-(1-methoxycarbonyl-2-oxopropyl)-4-methyl-4-pentanolide (16) and Methyl 1,3,3a,4,5,6,7,7a-octahydro-4-hydroxy-1,1-dimethyl-4-phenylisobenzofuran-7-carboxylate (17)

To a solution of methyl acetoacetate (0.787 g, 6.78 mmol) and triethylamine (0.4 mL, 2.87 mmol) in MeOH (10 mL) was added dropwise a solution of 15a (1.008 g, 4.66 mmol) in MeOH (18 mL), and the whole was stirred at rt for 5 h. The precipitates formed were collected by filtration to give 17 (0.589 g, 38%). After concentration of the filtrate, the residue was crystallized from 2-propanol to give 16 (0.554 g, 36%). 16: mp 114-120°. IR (Nujol): 1755, 1730, 1715, 1675, 1595, 1580 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.38, 1.58 (each 3H, s, CH₃), 2.14 (3H, s, COCH₃), 3.54 (1H, d, J=10.0 Hz, CHCO₂CH₃), 3.77 (3H, s, CO₂CH₃), 3.88 (1H, t, J=10.0 Hz, CHC(CH₃)₂), 4.85 (1H, d, J=10.0 Hz, CHCOPh), 7.46-8.05 (5H, m, ArH). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 65.10; H, 6.09. 17: mp 210-212°. IR (Nujol): 3400, 1765, 1750, 1710 cm⁻¹. ¹H-NMR (DMSO-ⅉ₆) δ: 1.33, 1.38 (each 3H, s, CH₃), 3.73 (3H, s, OCH₃), 5.96 (1H, br s, OH), 7.20-7.61 (5H, m, ArH). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 64.92; H, 6.06.

Methyl 1,3-dihydro-1,1,6-trimethyl-3-oxo-4-phenylfuro[3,4-c]pyridine-7-carboxylate (18)

A solution of 16 (0.425 g, 1.28 mmol) and ammonium acetate (0.558 g, 7.24 mmol) in MeOH (17 mL) was stirred at rt for 6 h, and then heated under reflux for 2 h. The mixture was concentrated under reduced pressure to give the residue, to which was added H₂O. The mixture was extracted with CHCl₃ and the extracts were washed with brine and dried over Na₂SO₄. Removal of the solvent afforded an yellow oil (0.422 g), 0.141 g of which was purified by SiO₂ column chromatography (ether:hexane=3:2) to give 18 (36 mg, 27%) as colorless crystals. mp 127-130° (ether). IR (CHCl₃): 1760, 1725, 1585, 1275, 1235, 1205, 1160, 1120, 1070, 1015 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.74 (6H, s, 2 x CH₃), 2.76 (3H, s, CH₃), 4.02 (3H, s, OCH₃), 7.46-7.94 (5H, m, ArH). Anal. Calcd for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.36; H, 5.55; N, 4.40.

Methyl 6-amino-1,3,3a,7a-tetrahydro-1,1-dimethyl-3-oxo-4-phenylisobenzofuran-7-carboxylate (19)

A mixture of 17 (0.374 g, 1.13 mmol) and ammonium acetate (0.500 g, 6.49 mmol) in MeOH (20 mL) was heated under reflux for 3 h. After addition of further ammonium acetate (0.250 g, 3.24 mmol), the
Mixture was heated under reflux for further 2 h. The mixture was concentrated under reduced pressure to give the residue, to which was added H₂O to form the precipitates. Purification of the products by SiO₂ column chromatography (CHCl₃) gave 19 (0.108 g, 30%) as yellow crystals. mp 183-185°C. IR (Nujol): 3450, 3330, 1755, 1665, 1605, 1535, 1280, 1235, 1190, 1095 cm⁻¹. ¹H-NMR (CDCl₃): δ: 1.29, 1.505 (each 3H, s, CH₃), 3.75 (3H, s, OCH₃), 3.82 (1H, d, J=11.5 Hz, (CH₃)₂CCH), 4.15 (1H, dd, J=11.5, 2.5 Hz, COCH), 5.99 (1H, d, J=2.5 Hz, =CH), 7.33-7.47 (5H, m, ArH). HRMS (m/z) Calcd for C₁₈H₁₉NO₄: 313.1314. Found: 313.1333.

Methyl 1,3,3a,6,7,7a-hexahydro-1,1-dimethyl-3,6-dioxo-4-phenylisobenzofuran-7-carboxylate (20)
p-TsOH·H₂O (1.436 g, 7.55 mmol) was added to a solution of 17 (1.932 g, 5.81 mmol) in C₆H₆ (250 mL) and the reaction mixture was heated under reflux for 7 h, during the reaction, water formed was removed continuously. After cooling, the reaction mixture was washed with saturated NaHCO₃ aqueous solution, H₂O, and brine, respectively. The organic layer was dried over Na₂SO₄ and then concentrated under reduced pressure to give the brown oil, which was crystallized from AcOEt-hexane to afford 20 (0.861 g, 47%) as colorless crystals. mp 115-120°C. IR (Nujol): 1765, 1740, 1660, 1610, 1260, 1155, 1120, 1010 cm⁻¹. ¹H-NMR (CDCl₃): δ: 1.39, 1.60 (each 3H, s, CH₃), 3.54 (1H, dd, J=11.5, 7.0 Hz, CHC(CH₃)₂), 3.61 (1H, d, J=11.5 Hz, COCHCO), 3.86 (3H, s, OCH₃), 4.47 (1H, dd, J=7.0, 1.0 Hz, ArCCH), 6.54 (1H, d, J=1.0 Hz, C=CH), 7.40-7.66 (5H, m, ArH). Anal. Calcd for C₁₈H₁₈O₅: C, 68.78; H, 5.77; N. Found: C, 68.72; H, 5.72.

Methyl 4-(2-chlorophenyl)-1,3,3a,4,5,7a-hexahydro-4-hydroxy-1,1,6-trimethyl-3-oxofuro[3,4-c]-pyridine-7-carboxylate (21)
To a mixture of methyl acetoacetate (0.412 g, 3.55 mmol) and triethylamine (0.2 mL, 1.44 mmol) in MeOH (15 mL) was added dropwise a solution of 15b (0.540 g, 2.15 mmol) in MeOH (10 mL), and the whole was stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure to give an yellow oil (1.489 g), which was dissolved in MeOH (27 mL). Ammonium acetate (0.870 g, 11.3 mmol) was added to the mixture and the whole was heated under reflux for 3.5 h. After concentration under reduced pressure, the residue was dissolved in CHCl₃. The mixture was washed with H₂O and brine, and then dried over Na₂SO₄. Removal of the solvent gave an yellow oil (0.801 g), which was purified by SiO₂ column chromatography (CHCl₃) to afford 21 (0.156 g, 20%). mp 127-129.5°C. (C₆H₅O). IR (Nujol): 3400, 3300, 1745, 1690 cm⁻¹. ¹H-NMR (CDCl₃): δ: 1.35, 1.55 (each 3H, s, CH₃), 2.35 (3H, s, =CCH₃), 3.63 (3H, s, OCH₃), 3.43 (1H, d, J=10.0 Hz, (CH₃)₂CCH), 4.15 (1H, d, J=10.0 Hz, COCH), 5.15, 5.78 (each 1H, br s, NH, OH), 7.22-7.48 (4H, m, ArH). MS (m/z): 365, 310, 278, 261, 250, 132. HRMS (m/z) Calcd for C₁₈H₁₈O₅Cl: 365.1030. Found: 365.1159.
SiO₂ TLC (ether:hexane=3:1) to give 22 (15 mg, 57%) as colorless crystals. mp 118-123 °C (C₆H₆). IR (Nujol): 1770, 1720, 1575, 1265, 1210, 1070, 1055, 1020 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.74 (6H, s, 2 x CH₃), 2.77 (3H, s, CH₃), 4.04 (3H, s, OCH₃), 7.35-7.54 (4H, m, ArH). HRMS (m/z) Calcd for C₁₈H₁₆NO₄ (M⁺-Cl): 310.1079. Found: 310.1071.

REFERENCES