Synthesis of α-Alkylidene-γ-butyrolactones *via* Ring-cleavage / Recyclization of 2-Amino-4,5-dihydro-3-furancarboxamides

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The reactions of 2-amino-4,5-dihydro-3-furancarboxamides **1a**,**b** with cyanomethylene compounds (such as alkyl cyanoacetates and malononitrile) gave the corresponding ring-opened products **2a-f**. Compounds **2a-d** reacted with methanesulfonic acid to give the corresponding α-alkylidene-γ-butyrolactones **3a-d**. On the other hand, treatment of **2e**,**f** with methanesulfonic acid yielded 3-pyridinecarbonitrile derivatives **4a**,**b**.

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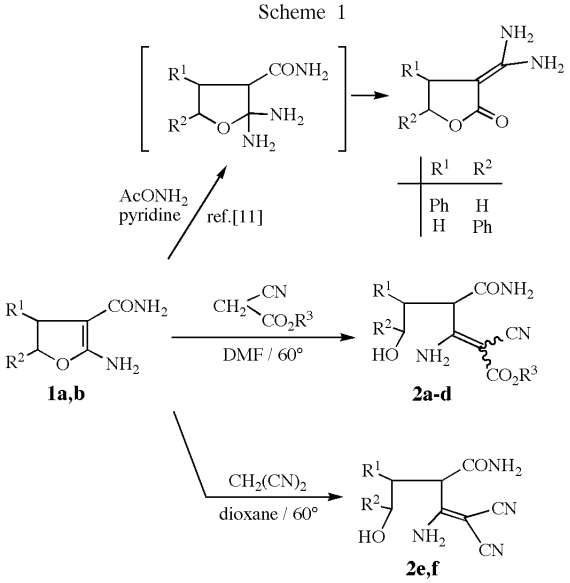
α-Methylene or α-alkylidene-γ-butyrolactones exhibit a wide range of biological activities [1], particularly cytotoxic and antitumor activity [2], fungitoxicity [3] as well as plant growth inhibition [4]. Many methods have been developed for the synthesis of such compounds [5-10]. In the previous paper, we showed that 2-amino-4,5-dihydro-3-furancarboxamides **1** react with ammonium acetate to yield 3-diaminomethylene-2(3*H*)-furanones [11] (Scheme 1). This reaction probably occurs *via* Michael addition to the α,β-unsaturated carboxamide moiety of **1** with ammonia to form the intermediate adduct, which undergoes cyclization to provide the observed products. This reaction suggests the possibility that when compounds **1** are treated with active methylene compounds, the Michael adduct initially formed may undergo cyclization to furnish the corresponding α-alkylidene-γbutyrolactones. Thus, we have investigated the reaction of **1** with active methylene compounds.

When a mixture of 2-amino-4,5-dihydro-3-furancarboxamides **1a**,**b** and methyl or ethyl cyanoacetate in *N*,*N*-dimethylformamide (DMF) was kept at 60° ring-opening products **2a-d** were obtained in moderate yields, and the expected 3-methylene-2(3*H*)-furanones could not be isolated. In a similar manner, the reaction of **1a**,**b** with malononitrile afforded an inseparable mixture showing many spots on thin-layer chromatography. When dioxane was used in place of DMF, compounds **1a**,**b** reacted with malononitrile at 60° provided **2e**,**f** in good yields. However, the reaction of **1** with active methylene compounds lacking cyano group such as dialkyl malonate and alkyl acetoacetate failed, and **1** was recovered unchanged. The pmr spectra of **2c**,**d**,**f** show two broad singlets at δ 9.1 and 8.3 for a carbamoyl group and two multiplets at δ 4.5 for a methine group of a secondary alcohol moiety. These observations indicate that **2c**,**d**,**f** exist as two diastereomers, which would probably be formed by an effect of the configuration of carbamoyl group and phenyl group. Separation of the diastereomers **2c**,**d**,**f** was attempted by column chromatography, but was not successful.

Subsequently, in order to obtain the α-alkylidene-γ-butyrolactones, we examined the cyclization of compounds **2a-f** with acid. The reaction of **2a-d** with methanesulfonic acid in DMF resulted in the formation of the

Scheme 1



1	R^1	R^2
a	Ph	H
b	H	Ph

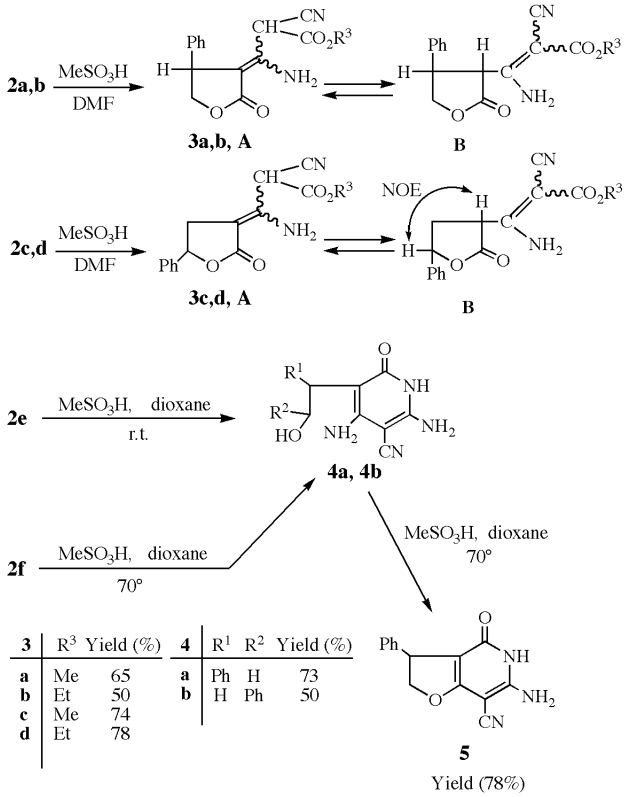
2	R^1	R^2	R^3	Yield (%)
a	Ph	H	Me	63
b	Ph	H	Et	57
c	H	Ph	Me	90
d	H	Ph	Et	96

2	R^1	R^2	Yield (%)
e	Ph	H	60
f	H	Ph	83

expected α-alkylidene-γ-butyrolactones **3a-d** in moderate to good yields. Although all compounds **2** and **3** contain two stereogenic centers, the absence of signal doubling in both pmr and cmr spectra for **2a**,**b**,**e** and **3a-d** suggests the presence of only one diastereomer (as an enantiomeric pair). The ir spectra of **3a-d** reveal a band at near 2200 cm^{-1} due to a conjugated cyano group. The pmr spectra exhibit a one-proton doublet (**3a**,**b**) or double doublet (**3c**,**d**) at δ 4.3 attributable to the α-methine proton (3-H) of the γ-lactone ring. These observations indicate that **3a-d** exist in the furan-3-yl structure **B** rather than the furanylidene structure **A**. Furthermore, in the pmr spectra of **3a**,**b** the large vicinal coupling constants (**3a**: J = 11.3 Hz; **3b**: 11.1 Hz) between the 3- and 4- methine protons in the lactone ring support a *trans* relationship of these protons. In the NOESY spectra of **3c**,**d** the presence of a NOE effect between the 3- and 5- methine protons suggests a *cis*

stereochemistry of these protons. The compounds **2a-d** and **3a-d** possessing a carbon-carbon double bond, are expected to give *E*/*Z*-isomers, but only one of the geometric isomers of these compounds could be detected in the pmr and cmr spectra. It can be assumed that steric and electronic reasons give preference to one of the isomers. However, we were not able to prove its structure unambiguously. Treatment of **2e** and **2f** with methanesulfonic acid in dioxane at 70° led to cyclization to give 3-pyridinecarbonitrile **4b** and furo[3,2-*c*]pyridine **5** in 50 and 78% yield, and the expected α-alkylidene-γ-butyrolactones could not be isolated. When a mixture of **2e** and methanesulfonic acid in dioxane was stirred at room temperature, the corresponding pyridine derivative **4a** was obtained in 73% yield. Compound **4a** was converted into **5** by treatment with methanesulfonic acid in dioxane at 70°. Compound **4b** failed to transform into furo[3,2-*c*]pyridine even after 20h heating at 70° in dioxane, and **4b** was recovered unchanged.

Scheme 2



3	R^3	Yield (%)
a	Me	65
b	Et	50
c	Me	74
d	Et	78

4	R^1	R^2	Yield (%)
a	Ph	H	73
b	H	Ph	50

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-302 spectrometer or JASCO FT/IR-230 spectrometer. The pmr and cmr spectra were measured with a JEOL JNM-A500 instrument (500.00 MHz for ^{1}H, 125.65 MHz for ^{13}C) in DMSO-d_6 with TMS as internal standard. ^{13}C signal assignments were confirmed by the DEPT and ^{13}C-^{1}H COSY techniques. Mass spectra were acquired with a JEOL JMS-HX100 instrument at 70 eV. Elemental analyses were performed using a YANACO MT-6 elemental analyzer.

General Procedures for the Preparation of Ring-opening Products **2**.

Procedure A.

A mixture of **1a**,**b** (1.02 g, 5 mmoles), alkyl cyanoacetate (8 mmoles) and DMF (5 ml) was stirred at 60° for 24 hours (in the case of preparation of **2a**,**c**,**d**) or 50 hours (**2b**). The solvent was removed *in vacuo* and cold water was added to the residue. The mixture was extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with dichloromethane:acetone (4:1, v/v) as the eluent to yield **2a-d**.

Procedure B.

A suspension of **1a**,**b** (1.02 g, 5 mmoles), malononitrile (0.36 g, 5.5 mmoles) and dioxane (5 ml) was stirred at 60° for 30 hours. After removal of the solvent *in vacuo*, diethyl ether was added to the residue. The precipitate was collected, washed with diethyl ether to give **2e**,**f**.

Methyl 3-Amino-4-carbamoyl-2-cyano-6-hydroxy-5-phenyl-2-hexenoate (**2a**).

This compound was obtained as colorless prisms (0.95 g, 63%), mp 191° (dec.) (acetone-petroleum ether); ir (potassium bromide): ν 3470, 3380, 3280, 3200 (NH, OH), 2205 (C≡N), 1690, 1670 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 3.37 (ddd, J = 3.4, 7.0, 11.0 Hz, 1H, 5-H), 3.55-3.65 (m, 2H, CH_2-6), 3.69 (s, 3H, OCH_3), 3.92 (d, J = 11.0 Hz, 1H, 4-H), 4.60 (t, J = 4.3 Hz, 1H, OH), 7.20-7.30 (m, 5H, aryl), 7.05, 7.68, 8.27, 9.16 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 50.2 (C-5), 51.2 (OCH_3), 51.7 (C-4), 62.7 (C-6), 71.1 (C-2), 118.2 (C≡N), 126.6, 127.8, 128.5, 140.1 (C aryl), 167.3 (C-3), 169.0 (C=O), 170.0 (C=O); ms: m/z 304 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{17}N_3O_4$ (MW 303.3): C, 59.40; H, 5.65; N, 13.85. Found: C, 59.35; H, 5.73; N, 13.70.

Ethyl 3-Amino-4-carbamoyl-2-cyano-6-hydroxy-5-phenyl-2-hexenoate (**2b**).

This compound was obtained as colorless prisms (0.90 g, 57%), m.p. 189° (dec.) (acetone-petroleum ether); ir (potassium bromide): ν 3410, 3340, 3300, 3200 (NH, OH), 2215 (C≡N), 1675, 1665 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 1.23 (t, J = 7.0 Hz, CH_3), 3.37 (ddd, J = 5.2, 7.7, 11.3 Hz, 1H, 5-H), 3.55-3.63 (m, 2H, 6-H), 3.92 (d, J = 11.3 Hz, 1H, 4-H), 4.10-4.21 (m, 2H, OCH_2), 4.60 (br.s, 1H, OH), 7.19-7.31 (m, 5H, aryl), 7.05, 7.67, 8.22, 9.17 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 14.2 (CH_3), 50.2 (C-5), 51.7 (C-4), 59.8 (OCH_2), 62.7 (C-6), 71.3 (C-2), 118.2 (C≡N), 126.6, 127.8, 128.5, 140.1 (C aryl), 167.3 (C-3), 168.9 (C=O), 169.8 (C=O); ms: m/z 318 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{19}N_3O_4$ (MW 317.3): C, 60.55; H, 6.04; N, 13.24. Found: C, 60.40; H, 5.93; N, 13.09.

Methyl 3-Amino-4-carbamoyl-2-cyano-6-hydroxy-6-phenyl-2-hexenoate (**2c**).

This compound (1.40 g, 90%, pale yellow oil) was obtained as an approximately 1:1 mixture of diastereomers; ir (neat): ν 3560,

3410, 3360, 3210 (NH, OH), 2206 (C≡N), 1700, 1670 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 1.85-1.89 (m, 0.5H, 5-H), 2.08 (s, 1.8H, acetone-CH_3), 2.13-2.23 (m, 1.5H, 5-H), 3.66 (s, 1.5H, OCH_3), 3.67 (s, 1.5H, OCH_3), 3.88-3.91 (m, 1H, 4-H), 4.42-4.43 (m, 0.5H, 6-H), 4.50-4.52 (m, 0.5H, 6-H), 5.38 (d, J = 4.5Hz, 0.5 H, OH), 5.40 (d, J = 4.6 Hz, 0.5H, OH), 7.21-7.34 (m, 5.5H, aryl, NH), 7.42, 7.53, 7.68, 8.26, 8.50, 9.11, 9.12 (each br.s each 0.5H, NH); cmr (DMSO-d_6): δ, ppm 30.6 (CH_3COCH_3), 40.0 (C-5), 41.4 (C-5), 46.8 (C-4), 47.5 (C-4), 51.0 (OCH_3), 51.1 (OCH_3), 69.5 (C-2), 70.1 (C-6), 70.2 (C-6), 70.7 (C-2), 117.8 (C≡N), 118.1 (C≡N), 125.5, 125.6, 126.8, 126.9, 127.9, 128.0, 145.3, 145.4 (C aryl), 167.6 (C-3), 167.7 (C-3), 170.5 (C=O), 170.6 (C=O), 170.7 (C=O), 171.0 (C=O), 206.7 (CH_3COCH_3); ms: m/z 304 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{17}N_3O_4 \bullet 0.3CH_3COCH_3$ (MW 320.7): C, 59.54; H, 5.91; N, 13.10. Found: C, 59.60; H, 5.78; N, 13.10.

Ethyl 3-Amino-4-carbamoyl-2-cyano-6-hydroxy-6-phenyl-2-hexenoate (**2d**) Semi Hydrate.

This compound (1.57 g, 96%, pale yellow oil) was obtained as an approximately 1:1 mixture of diastereomers; ir (neat): ν 3560, 3430, 3370, 3220, 3170 (NH, OH), 2210 (C≡N), 1700, 1670 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 1.21 (t, J = 7.1 Hz, 1.5H, CH_3), 1.22 (t, J = 7.0 Hz, 1.5H, CH_3), 1.84-1.90 (m, 0.5H, 5-H), 2.09-2.23 (m, 1.5H, 5-H), 3.90 (dd, J = 5.5, 9.3 Hz, 1H, 4-H), 4.10-4.16 (m, 2H, OCH_2), 4.40-4.43 (m, 0.5H, 6-H), 4.49-4.53 (m, 0.5H, 6-H), 5.38 (d, J = 4.5Hz, 0.5 H, OH), 5.40 (d, J = 4.5 Hz, 0.5H, OH), 7.21-7.33 (m, 5.5H, aryl, NH), 7.42, 7.52, 7.66, 8.23, 8.47, 9.12, 9.22 (each br.s, each 0.5H, NH); cmr (DMSO-d_6): δ, ppm 14.2 (CH_3), 14.3 (CH_3), 40.0 (C-5), 41.4 (C-5), 46.8 (C-4), 47.5 (C-4), 59.5 (OCH_2), 59.6 (OCH_2), 69.8 (C-2), 70.0 (C-6), 70.1 (C-6), 70.9 (C-2), 117.8 (C≡N), 118.1 (C≡N), 125.5, 125.6, 126.8, 126.9, 127.9, 128.0, 145.3, 145.4 (C aryl), 167.3 (C-3), 167.4 (C-3), 170.5 (C=O), 170.6 (C=O), 170.7 (C=O), 170.9 (C=O); ms: m/z 318 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{19}N_3O_4 \bullet 0.5H_2O$ (MW 326.3): C, 58.89; H, 6.18; N, 12.88. Found: C, 58.85; H6.20; N, 13.04.

2-(1-Amino-2,2-dicyanoethenyl)-4-hydroxy-3-phenylbutanamide (**2e**).

This compound was obtained as colorless columns (0.81 g, 60%), mp 184°(dec.) (acetone); ir (potassium bromide): ν 3480, 3320, 3190 (NH, OH), 2210, 2200 (C≡N), 1705 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 3.38-3.43 (m, 1H, 3-H), 3.54-3.60 (m, 2H, 4-H), 3.87 (d, J = 11.3 Hz, 1H, 2-H), 4.71 (t, J = 4.6 Hz, 1H, OH), 7.19-7.30 (m, 5H, aryl), 7.07, 7.64, 8.08, 8.62 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 49.4 (C-3), 49.9 (C-2'), 51.0 (C-2), 62.8 (C-4), 115.2 (C≡N), 116.2 (C≡N), 126.6, 127.8, 128.5, 139.8 (C aryl), 169.1 (C-1'), 170.8 (C=O); ms: m/z 271 $[M+H]^+$.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$ (MW 270.3): C, 62.21; H, 5.22; N, 20.73. Found: C, 62.18; H, 5.30; N, 20.61.

2-(1-Amino-2,2-dicyanoethenyl)-4-hydroxy-4-phenylbutanamide (**2f**).

This compound (1.12 g, 83%, colorless needles) was obtained as an approximately 1:1 mixture of diastromers; mp 171° (dec.) (acetone-petroleum ether); ir (potassium bromide): ν 3560, 3360, 3200 (NH, OH), 2210, 2200 (C≡N), 1690 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 1.86-1.92 (m, 0.5H, 3-H), 2.07-2.10 (m, 0.5H, 3-H), 2.22-2.27 (m, 1H, 3-H), 3.76 (dd, J = 5.5, 8.8 Hz, 0.5H, 2-H), 3.85 (dd, J = 4.9, 10.0 Hz, 0.5H, 2-H), 4.38-4.40 (m, 0.5H, 4-H), 4.48-4.52 (m, 0.5H, 4-H), 5.40 (d, J = 4.6 Hz, 0.5H, OH), 5.46 (d, J = 4.6 Hz, 0.5H, OH), 7.21-7.34 (m, 5.5H, aryl, NH), 7.40, 7.54, 7.64, 8.11, 8.37, 8.48, 8.52 (each br.s, each 0.5H, NH); cmr (DMSO-d_6): δ, ppm 39.5 (C-3), 40.7 (C-3), 46.3 (C-2), 46.8 (C-2), 48.6 (C-2'), 49.7 (C-2'), 69.7 (C-4), 70.2 (C-4), 115.3, 115.4, 116.2, 116.4 (C≡N), 125.5, 125.6, 126.8, 126.9, 127.9, 128.0, 145.1, 145.4 (C aryl), 169.9, 170.1 (C-1'), 172.1, 172.6 (C=O); ms: m/z 270 $[M+H]^+$.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$ (MW 270.3): C, 62.21; H, 5.22; N, 20.73. Found: C, 62.07; H, 5.34; N, 20.61.

General Procedure for the Preparation of γ-Lactone **3**.

A mixture of **2a-d** (2 mmoles), methanesulfonic acid (0.23 g, 2.4 mmoles) and DMF (2 ml) was stirred at 70° for 5 hours. The solvent was removed *in vacuo* and cold water was added to the residue. The mixture was extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with dichloromethane as eluent to give **3a-d**.

Methyl *trans*-3-Amino-2-cyano-3-(tetrahydro-2-oxo-4-phenylfuran-3-yl)propenoate (**3a**).

This compound was obtained as colorless needles (0.37 g, 65%), mp 188-189° (acetone-petroleum ether); ir (potassium bromide): ν 3380, 3280, 3220 (NH, OH), 2210 (C≡N), 1780, 1690 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 3.64 (s, 3H, OCH_3), 4.23 (ddd, J = 8.3, 10.5, 11.3 Hz, 1H, 4'-H), 4.40 (d, J = 11.3 Hz, 1H, 3'-H), 4.41 (dd, J = 8.3, 10.5 Hz, 1H, 5'-H), 4.68 (t, J = 8.3 Hz, 1H, 5'-H), 7.30-7.44 (m, 5H, aryl), 9.03, 9.17 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 47.1 (C-4'), 51.2 (CH_3), 52.2 (C-3'), 71.5 (C-5'), 71.7 (C-2), 117.7 (C≡N), 127.6, 127.9, 128.7, 135.7 (C aryl), 166.9 (C-3), 167.0 (C=O), 172.0 (C=O); ms: m/z 287 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$ (MW 286.3): C, 62.93; H, 4.93; N, 9.79. Found: C, 62.79; H, 4.95; N, 9.77.\

Ethyl *trans*-3-Amino-2-cyano-3-(tetrahydro-2-oxo-4-phenylfuran-3-yl)propenoate (**3b**).

This compound was obtained as colorless needles (0.30 g, 50%), mp 186-187° (acetone-petroleum ether); ir (potassium bromide): ν 3350, 3280, 3210 (NH), 2210 (C≡N), 1780, 1685 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 1.18 (t, J = 7.0 Hz, 3H, CH_3), 4.06-4.16 (m, 2H, OCH_2), 4.23 (ddd, J = 8.2, 10.5, 11.1 Hz, 1H, 4'-H), 4.39 (dd, J = 8.2, 10.5 Hz, 1H, 5'-H), 4.40 (d, J =11.1 Hz, 1H, 3'-H), 4.68 (t, J = 8.2 Hz, 1H, 5'-H), 7.30-7.45 (m, 5H, aryl), 9.01, 9.18 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 14.1 (CH_3), 47.0 (C-4'), 52.1 (C-3'), 59.9 (OCH_2), 71.5 (C-5'), 72.0 (C-2), 117.7 (C≡N), 127.6, 127.9, 128.7, 135.7 (C aryl), 166.6 (C-3), 167.0 (C=O), 172.1 (C=O); ms: m/z 301 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$ (MW 300.3): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.73; H, 5.34; N, 9.30.

Methyl *cis*-3-Amino-2-cyano-3-(tetrahydro-2-oxo-5-phenylfuran-3-yl)propenoate (**3c**).

This compound was obtained as colorless prisms (0.42 g, 74%), mp 188-190° (acetone-petroleum ether); ir (potassium bromide): ν 3400, 3280, 3240 (NH, OH), 2210 (C≡N), 1760, 1750, 1690 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 2.50-2.55 (m, 1H, 4'-H), 2.90-2.96 (m, 1H, 4'-H), 3.69 (s, 3H, OCH_3), 4.29 (dd, J = 8.3, 12.6 Hz, 1H, 3'-H), 5.65 (dd, J = 5.2, 11.0 Hz, 1H, 5'-H),

7.35-7.61 (m, 5H, aryl), 9.07, 9.25 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 36.5 (C-4'), 47.5 (C-3'), 51.2 (CH_3), 70.7 (C-2), 79.7 (C-5'), 118.0 (C≡N), 126.7, 128.3, 128.7, 137.7 (C aryl), 167.2 (C-3), 167.6 (C=O), 172.0 (C=O); ms: m/z 287 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$ (MW 286.3): C, 62.93; H, 4.93; N, 9.79. Found: C, 62.89; H, 4.99; N, 9.61.

Ethyl *cis*-3-Amino-2-cyano-3-(tetrahydro-2-oxo-5-phenylfuran-3-yl)propenoate (**3d**).

This compound was obtained as colorless needles (0.47 g, 78%), mp 182-184° (acetone-petroleum ether); ir (potassium bromide): ν 3380, 3280, 3220 (NH), 2200 (C≡N), 1755, 1675 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 1.23 (t, J = 7.0 Hz, 3H, CH_3), 2.50-2.57 (m, 1H, 4'-H), 2.90-2.97 (m, 1H, 4'-H), 4.16 (q, J = 7.0 Hz, 2H, OCH_2), 4.29 (dd, J = 8.1, 12.6 Hz, 1H, 3'-H), 5.65 (dd, J = 5.5, 11.0 Hz, 1H, 5'-H), 7.36-7.61 (m, 5H, aryl), 9.04, 9.26 (each br.s, each 1H, NH); cmr (DMSO-d_6): δ, ppm 14.2 (CH_3), 36.5 (C-4'), 47.5 (C-3'), 59.8 (OCH_2), 70.9 (C-2), 79.7 (C-5'), 118.0 (C≡N), 126.7, 128.4, 128.7, 137.8 (C aryl), 166.9 (C-3), 167.6 (C=O), 172.0 (C=O); ms: m/z 301 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$ (MW 300.3): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.94; H, 5.38; N, 9.21.

General Procedure for the Preparation of 3-Pyridinecarbonitriles **4**.

A mixture of **2e**,**f** (0.54 g, 2 mmoles), methanesulfonic acid (0.23 g, 2.4 mmoles) and dioxane (2 ml) was stirred at room temperature (in the case of the preparation of **4a**) or 70°(**4b**) for 5 hours (**4a**) or 2 hours (**4b**). The solvent was removed *in vacuo* and cold water was added to the residue. The resulting precipitate was collected by filtration, washed with water and dried to yield **4a**,**b**.

2,4-Diamino-1,6-dihydro-5-(2-hydroxy-1-phenylethyl)-6-oxo-3-pyridinecarbonitrile (**4a**) Semi Hydrate.

This compound was obtained as colorless prisms (0.38 g, 73%), m.p. 238° (dec.) (methanol); ir (potassium bromide): ν 3360, 3230 (NH, OH), 2220 (C≡N), 1660 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 3.90-4.20 (m, 3H, 1'-H, 2'-H), 5.38 (s, 1H, OH), 6.05 (s, 2H, NH_2), 6.09 (s, 2H, NH_2), 7.15-7.33 (m, 5H, aryl), 9.97 (s, 1H, NH); cmr (DMSO-d_6): δ, ppm 40.5 (C-1'), 62.0 (C-2'), 69.8 (C-3), 87.6 (C-5), 118.4 (C≡N), 125.8, 127.3, 128.4, 140.5 (C aryl), 151.6 (C-4), 160.0 (C-2), 160.9 (C-6); ms: m/z 271 $[M+H]^+$.

Anal. Calcd. for $C_{14}H_{14}N_4O_2 \bullet 0.5H_20$ (MW 279.3): C, 60.21, H, 5.41; N, 20.06. Found: C, 60.26; H, 5.25; N, 19.87.

2,4-Diamino-1,6-dihydro-5-(2-hydroxy-2-phenylethyl)-6-oxo-3-pyridinecarbonitrile (**4b**).

This compound was obtained as colorless prisms (0.27 g, 50%), m.p. 267° (dec.) (methanol); ir (potassium bromide): ν 3460, 3350, 3240 (NH, OH), 2220 (C≡N), 1655 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 2.49-2.54 (m, 2H, 1'-H), 4.61-4.64 (m, 2H, 2'-H), 5.52 (br.s, 1H, OH), 5.88 (s, 2H, NH_2), 6.10 (s, 2H, NH_2), 7.21-7.44 (m, 5H, aryl), 9.90 (s, 1H, NH); cmr (DMSO-d_6): δ, ppm 33.0 (C-1'), 69.6 (C-3), 71.9 (C-2'), 83.6 (C-5), 118.6 (C≡N), 126.0, 126.7, 127.6, 145.2(C aryl), 151.9 (C-4), 160.2 (C-2), 160.9 (C-6); ms: m/z 271 $[M+H]^+$.

Anal . Calcd. for $C_{14}H_{14}N_4O_2$ (MW 270.3): C, 62.21, H, 5.22; N, 20.73. Found: C, 62.11; H, 5.34; N, 20.64.

6-Amino-2,3,4,5-tetrahydro-4-oxo-3-phenyl-furo[3,2-*c*]pyridine-7-carbonitrile (**5**).

A mixture of **2e** (0.54 g, 2 mmoles) or **4a** (0.56 g, 2 mmoles), methanesulfonic acid (0.23 g, 2.4 mmoles) and dioxane (2 ml) was stirred at 70° for 2 hours. The solvent was removed *in vacuo* and cold water was added to the residue. The resulting precipitate was collected by filtration, washed with water and dried to give **5** [from **2e**: 0.40 g (78%), from **4a**: 0.40 g (78%)], mp 255-256° (methanol); ir (potassium bromide): ν 3480, 3360, 3240 (NH), 2235 (C≡N), 1660 cm^{-1} (C=O); pmr (DMSO-d_6): δ, ppm 4.41 (dd, J = 3.2, 9.0 Hz, 1H, 3-H), 4.55 (dd, J = 3.2, 9.0 Hz, 1H, 2-H), 4.96 (t, J = 9.0 Hz, 1H, 2-H), 6.56 (s, 2H, NH_2), 7.14-7.36 (m, 5H, aryl), 11.97 (s, 1H, NH); cmr (DMSO-d_6): δ, ppm 42.9 (C-3), 71.5 (C-7), 80.7 (C-2), 89.7 (=C), 117.3 (C≡N), 126.9, 127.0, 128.5, 142.0 (C aryl), 157.2 (O-C=), 162.5 (C-6), 163.3 (C-4); ms: m/z 254 $[M+H]^+$.

Anal . Calcd. for $C_{14}H_{11}N_3O_2$ (MW 253.3): C, 66.39, H, 4.38; N, 16.59. Found: C, 66.12; H, 4.57; N, 16.55.

REFERENCES AND NOTES

[1] H. M. R. Hoffmann and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, **24**, 94 (1985).

[2] S. M. Kupchan, M. A. Eakin and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).

[3] C. R. Hutchinson, *J. Org. Chem.*, **39**, 1854 (1974).

[4] Y. Iino, A. Tanaka and K. Yamashita, *Agric. Biol. Chem.*, **36**, 2505 (1972).

[5] R. Ballini, G. Bosia and D. Livi, *Synthesis*, 1519 (2001).

[6] F. T. Luo, M. W. Wang and Y. S. Lin, *Heterocycles,* **43**, 2725 (1996).

[7] J. Ji and X. Lu, *Tetrahedron*, **50**, 9067 (1994).

[8] X. Lu, Z. Wang and J. Ji, *Tetrahedron Lett.*, 613 (1994).

[9] N. Petragnani, M. C. Ferraz and G. V. J. Silva, *Synthesis,* 157 (1986).

[10] P. A. Grieco, *Synthesis,* 67 (1975).

[11] K. Yamagata, F. Okabe, M. Yamazaki and Y. Tagawa, *Monatsch. Chem.*, **133**, 643 (2002).