Monatshefte für Chemie 133, 643–651 (2002)

Monatshefte für Chemie
Chemical Monthly

Synthesis of 3-Diaminomethylene-2(3*H*)-furanones by Reaction of 2-Amino-4,5-dihydro-3-furancarboxamides with Amines

Kenji Yamagata*, **Fumi Okabe, Motoyoshi Yamazaki,** and **Yoshinobu Tagawa**

Faculty of Pharmaceutical Sciences, Fukuoka University, 814-0180 Fukuoka, Japan

Summary. The reaction of 2-amino-4,5-dihydro-3-furancarboxamides with morpholine in the presence of acetic acid in pyridine or under the influence of ammonium acetate gave the corresponding 3-diaminomethylene-4,5-dihydro-2(3*H*)-furanones; 4,5-dihydro-2-morpholino-3-furancarboxamides were not isolated. One of the former reacted with benzylamine to give (*E*)- and (*Z*)-3-(amino-(benzylamino)-methylene)-4,5-dihydro-4-phenyl-2(3*H*)-furanones and 2-benzylamino-4,5-dihydro-4-phenyl-3-furancarboxamide.

Keywords. Furancarboxamides; Furanones; Amines; *Michael* addition; Recyclization.

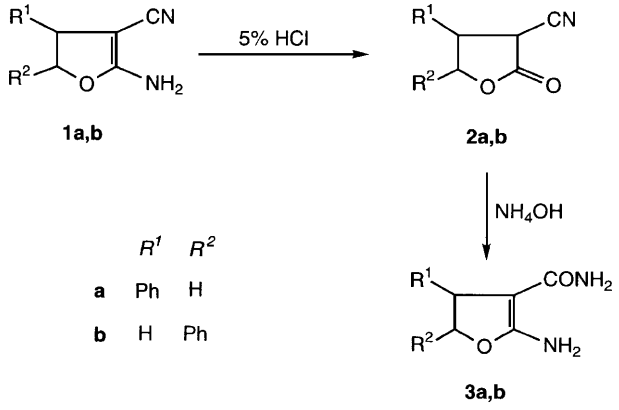
Introduction

Earlier, we have reported on the reaction of 2-amino-4,5-dihydro-3-furancarbonitriles (**1**) with amines such as morpholine, pyrrolidine, and piperidine to give 4,5-dihydro-2-morpholino-(2-pyrrolidino and 2-piperidino)-3-furancarbonitriles [1, 2]. This reaction probably occurs *via Michael* addition to the α,β-unsaturated nitrile moiety of **1** with amine to form the intermediate adduct which undergoes elimination of ammonia to give the observed products. The reaction suggests the possibility that when 2-amino-4,5-dihydro-3-furancarboxamides **3** are treated with amines, the *Michael* adduct initially formed may undergo elimination of ammonia to furnish the corresponding 2-amino-4,5-dihydro-3-furancarboxamides. Thus, we have investigated the reaction of **3** with amines.

Results and Discussion

The required tetrahydro-2-oxo-4-phenyl- and -5-phenyl-3-furancarbonitriles (**2a** and **2b**) [3, 4] were obtained by reaction of 2-amino-4,5-dihydro-4-phenyl- and -5-phenyl-3-furancarbonitriles (**1a** and **1b**) [5] with hydrochloric acid. The starting materials **3** were prepared from **2** and concentrated ammonium hydroxide according to Ref. [6] (Scheme 1).

* Corresponding author. E-mail: yamagata@fukuoka-u.ac.jp



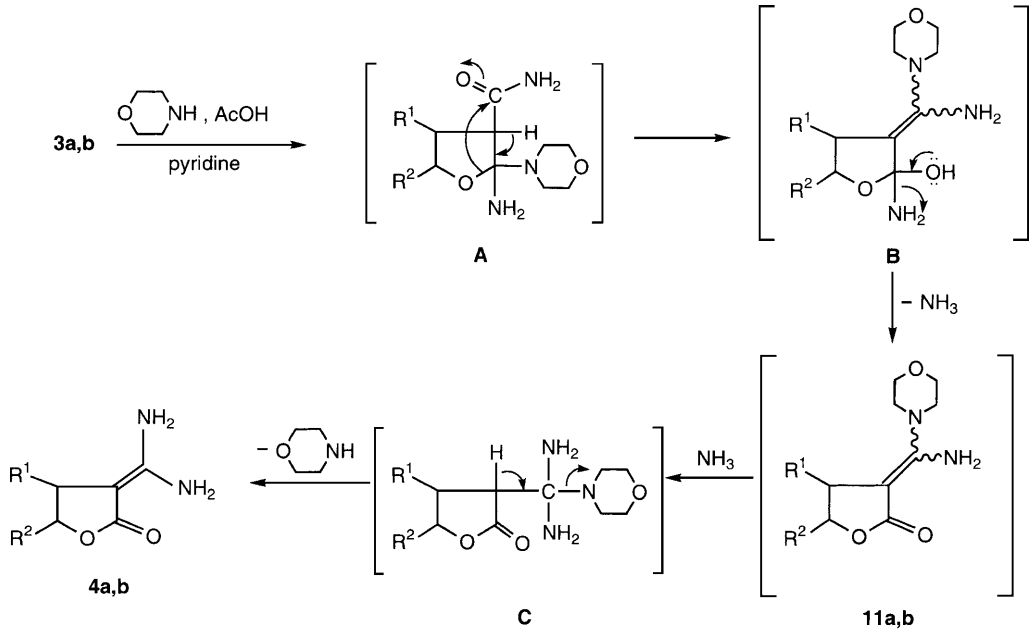
Scheme 1

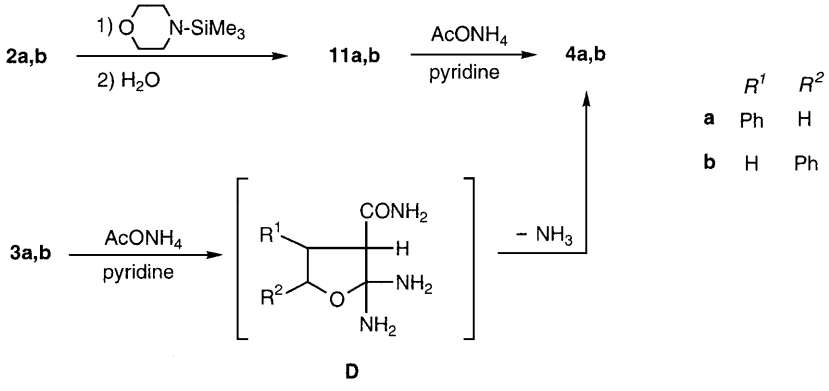
When a mixture of **3a**, morpholine, and acetic acid in pyridine was heated at 80°C, 3-diaminomethylene-4,5-dihydro-4-phenyl-2(3*H*)-furanone (**4a**) was obtained in 75% yield, and the expected 4,5-dihydro-2-morpholino-4-phenyl-3-furancarboxamide could not be isolated (Scheme 2). The structure of **4a** was deduced from satisfactory elemental analyses and spectroscopic data. The mass spectrum and the results of elemental analyses of **4a** indicate that both **4a** and **3a** have the same molecular composition $C_{11}H_{12}N_2O_2$. The IR spectrum of **4a** displays a band due to a lactone carbonyl group conjugated with an enamine group [7] at 1660 cm^{-1}. Similarly, the reaction of **3b** with morpholine afforded 3-diaminomethylene-4,5-dihydro-5-phenyl-2(3*H*)-furanone (**4b**). In order to confirm the structure of **4a**, we carried out the reaction shown in Scheme 3. The reaction of **4a** with benzoyl chloride gave 3-(amino-(benzamido)-methylene)-2(3*H*)-furanone **5**. Hydrolysis of **5** with hydrochloric acid provided N-benzoyl-3-furancarboxamide **6** which was converted into methyl 2-oxo-4-phenyl-3-furancarboxylate **7** [8] by treatment with concentrated hydrochloric acid and methanol. The structure of **7** was confirmed by direct comparison with an authentic sample which was synthesized by the following methods: methyl 2-amino-4-phenyl-3-furancarboxylate **8** was prepared from **2a** and a catalytic amount of sodium methoxide according to Ref. [9]. Hydrolysis of **8** with hydrochloric acid provided the desired compound **7**.

The formation of **4** can be explained by the mechanism shown in Scheme 2. The *Michael* addition of morpholine to **3** gives the adduct **A** which undergoes recyclization to provide **B**. **B** in turn is transformed into the intermediates **11** by elimination of ammonia. The conjugated addition of ammonia to **11** produces the adduct **C** which undergoes elimination of morpholine to yield **4**.

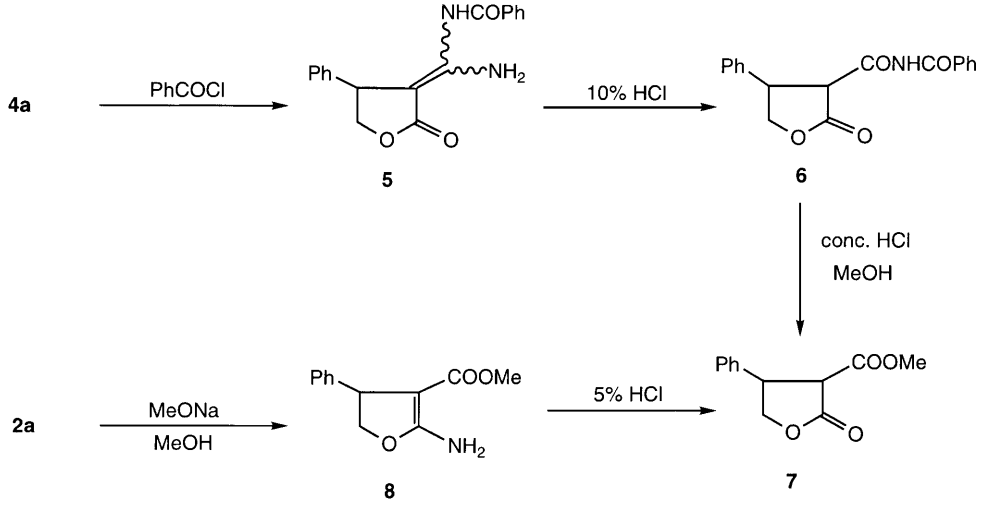
Subsequently, we examined the reaction of the intermediates **11** with ammonia in the presence of acetic acid in order to prove whether or not compounds **4** are formed. Compounds **11** were prepared by successive treatment of **2** with trimethylsilylmorpholine and water. The IR spectra of **11** showed a primary amino bands near 3300 cm^{-1}, but lacked a characteristic nitrile band. The reaction of **11** with ammonium acetate afforded **4** in good yields. In a similar manner, the reaction of **3** with ammonium acetate resulted in the formation of the same compounds **4**. Probably, this recyclization takes place through the adduct **D**.

Finally, we have examined the reaction of **3a** with benzylamine in order to explore the scope of this type of reaction. The reaction of **3a** with benzylamine

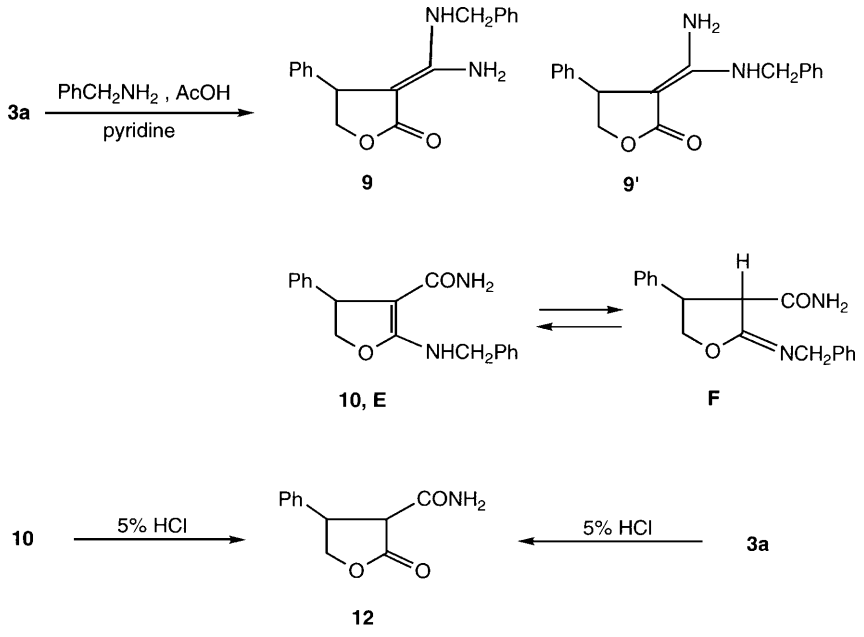




Scheme 2



Scheme 3



Scheme 4

yielded a 1:1 mixture of 3-(amino-(benzylamino)-methylene)-2(3*H*)-furanones (**9** and **9′**, 57%) and 2-benzylamino-3-furancarboxamide **10** (11%), and **4a** could not be isolated. An analogous reaction has also been observed by *Wamhoff et al*. when dealing with the reaction of ethyl 2-amino-4,5-dihydro-3-furancarboxylates and methylamine [7]. The ^{1}H NMR spectrum of **10** in deuteriochloroform indicates that **10** consists of an approximately 4:1 tautomeric mixture of the enamine (**E**) and imine (**F**) forms (Scheme 4). Separation of **9** and **9′** was attempted by column chromatography, but was not successful. When a mixture of **9**/**9′** and ammonium acetate in pyridine was heated, no reaction occurred, and **9**/**9′** were recovered unchanged. Compound **10** was easily hydrolyzed to 2-oxo-3-furancarboxamide **12** when heated with hydrochloric acid. Compound **12** was also obtained by treatment of **3a** with hydrochloric acid.

Experimental

All melting points are uncorrected. IR spectra were taken with a Jasco A-302 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on Jeol JNM-A500 instrument (500.00 MHz for ^{1}H, 125.65 MHz for ^{13}C) with *TMS* as internal standard; ^{13}C signal assignments were confirmed by the DEPT technique. Mass spectra were recorded with a Jeol JMS-HX110 equipment at 70 eV. Elemental analyses were performed using a MT-6 elemental analyzer (Yanaco); the data were found to be within 0.3% of the calculated values.

Tetrahydro-2-oxo-3-furancarbonitriles (**2**); *general procedure*

A mixture of 18.60 g (100 mmol) **1** and 150 cm^{3} 5% HCl was stirred at room temperature for 1 h. The precipitate was collected by filtration, washed with H_2O, and dried to give **2**.

Tetrahydro-2-oxo-4-phenyl-3-furancarbonitrile (**2a**; $C_{11}H_9NO_2$)

Yield: 16.82 g (90%); colorless needles; m.p.: 94–95°C (acetone/petroleum ether) (Ref. [3]: m.p.: 126–128°C); IR (KBr): $\nu = 2250$ (C≡N), 1790 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.80 (d, $J =$ 11.6 Hz, 0.8H, 3-H), 4.01 (ddd, $J = 4.0/6.4/8.6$ Hz, 0.2H, 4-H), 4.06 (d, $J = 8.6$ Hz, 0.2H, 3-H), 4.08 (ddd, $J = 8.0/10.4/11.6$ Hz, 0.8H, 4-H), 4.34 (dd, $J = 9.5/10.4$ Hz, 0.8H, 5-H), 4.66 (dd, $J = 4.0/$ 9.7 Hz, 0.2H, 5-H), 4.72 (dd, $J = 6.4/9.7$ Hz, 0.2H, 5-H), 4.75 (dd, $J = 8.0/9.5$ Hz, 0.8H, 5-H), 7.28–7.50 (m, 5H, aryl) ppm; MS (FAB): m/z (%) = 188 (62) [$M^+ + H$].

Tetrahydro-2-oxo-5-phenyl-3-furancarbonitrile (**2b**; $C_{11}H_9NO_2$)

Yield: 16.31 g (87%); colorless needles; m.p.: 134–136°C (acetone/petroleum ether) (Ref. [3]: m.p.: 113–115°C); IR (KBr): $\nu = 2270$ (C≡N), 1770 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ): 2.55–2.70 (m, 1H, 4-H), 3.00–3.10 (m, 1H, 4-H), 4.62 (dd, $J = 7.9/9.8$ Hz, 0.2H, 3-H), 4.71 (dd, $J = 8.2/12.5$ Hz, 0.8H, 3-H), 5.55 (dd, $J = 5.5/10.7$ Hz, 0.8H, 5-H), 5.83 (dd, $J = 5.2/8.0$ Hz, 0.2H, 5-H), 7.40–7.50 (m, 5H, aryl) ppm; MS (FAB): m/z (%) = 188 (37) [$M^+ + 1$].

2-Amino-4,5-dihydro-3-furancarboxamides (**3**); *general procedure*

A mixture of 3.74 g (20 mmol) **2** and 20 cm^3 concentrated ammonium hydroxide was stirred at room temperature for 1 h. The reaction mixture was cooled and diluted with H_2O. The resulting precipitate was collected by filtration, washed with H_2O, and dried to give **3**.

2-Amino-4,5-dihydro-4-phenyl-3-furancarboxamide (**3a**; $C_{11}H_{12}N_2O_2$)

Yield: 3.89 g (95%); colorless columns; m.p.: 177–178°C (acetone); IR (KBr): $\nu = 3480$, 3450, 3285, 3190 (NH), 1655 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ): 4.04 (dd, $J = 4.5/8.0$ Hz, 1H, 5-H), 4.22 (dd, $J = 4.5/8.0$ Hz, 1H, 4-H), 4.61 (t, $J = 8.0$ Hz, 1H, 5-H), 5.60 (s, 2H, NH_2), 6.96 (s, 2H, NH_2), 7.19–7.24 (m, 3H, aryl), 7.28–7.31 (m, 2H, aryl) ppm; ^{13}C NMR (*DMSO*-d_6, δ): 45.0 (C-4), 77.0 (C-3), 79.0 (C-5), 126.4, 127.0, 128.3, 145.2 (C aryl), 166.5 (C-2), 168.7 (C=O) ppm; MS (EI): m/z (%) = 204 (52) [M^+].

2-Amino-4,5-dihydro-5-phenyl-3-furancarboxamide (**3b**; $C_{11}H_{12}N_2O_2$)

Yield: 3.29 g (81%); colorless prisms; m.p.: 134–135°C (acetone); IR (KBr): $\nu = 3480$, 3445 (sh), 3280, 3160 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ): 2.63 (dd, $J = 7.1/12.5$ Hz, 1H, 4-H), 3.18 (dd, $J = 9.8/12.5$ Hz, 1H, 4-H), 5.56 (dd, $J = 7.1/9.8$ Hz, 1H, 5-H), 6.01 (s, 2H, NH_2), 6.82 (s, 2H, NH_2), 7.32–7.39 (m, 5H, aryl) ppm; ^{13}C NMR (*DMSO*-d_6, δ): 36.2 (C-4), 72.8 (C-3), 80.9 (C-5), 125.4, 127.8, 128.4, 141.9 (C aryl), 164.8 (C-2), 169.0 (C=O) ppm; MS (FAB): m/z (%) = 205 (100) [$M^+ + H$].

3-Diaminomethylene-4,5-dihydro-2(3H)-furanones (**4**); *general procedure*

Procedure A: To an ice-cooled and stirred solution of 4.08 g (20 mmol) **3** and 1.92 g (22 mmol) morpholine in 15 cm^3 pyridine, 1.32 g (22 mmol) acetic acid were added. The mixture was stirred at 80°C for 3 h. The solvent was removed, and 50 cm^3 H_2O were added to the residue. The precipitate was collected, washed with H_2O, and dried. Yields: **4a** (3.04 g, 75%) and **4b** (1.22 g, 30%).

Procedure B: A mixture of 1.37 g (5 mmol) **11** and 0.42 g (5.5 mmol) ammonium acetate in 5 cm^3 pyridine was stirred at 60°C for 3 h. The solvent was removed, and 20 cm^3 H_2O were added to the residue. The precipitate was collected, washed with H_2O, and dried. Yields: **4a** (0.92 g, 90%) and **4b** (0.60 g, 59%).

Procedure C: A mixture of 2.04 g (10 mmol) **3** and 0.85 g (11 mmol) ammonium acetate in 10 cm^3 pyridine was stirred at 80°C for 3 h. The solvent was removed, and 50 cm^3 H_2O were added to the residue. The precipitate was collected, washed with H_2O, and dried. Yields: **4a** (1.74 g, 85%) and **4b** (1.20 g, 59%).

3-Diaminomethylene-4,5-dihydro-4-phenyl-2(3H)-furanone (**4a**; $C_{11}H_{12}N_2O_2$)

Colorless columns; m.p.: 207–208°C (acetone); IR (KBr): $\nu = 3490$, 3430, 3225, 3155 (NH), 1660 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ): 3.79 (dd, $J = 3.0/8.9$ Hz, 1H, 4-H), 4.14 (dd, $J = 2.8/8.9$ Hz, 1H, 5-H), 4.38 (t, $J = 8.9$ Hz, 1H, 5-H), 5.57 (s, 2H, NH_2), 6.63 (s, 2H, NH_2), 7.18–7.30 (m, 5H, aryl) ppm; ^{13}C NMR (*DMSO*-d_6, δ): 42.6 (C-4), 70.6 (C-3), 71.8 (C-5), 126.2, 126.7, 128.2, 145.7 (C aryl), 158.3 (=$C(NH_2)_2$), 173.0 (C-2) ppm; MS (EI): m/z (%) = 204 (88) [M^+].

3-Diaminomethylene-4,5-dihydro-5-phenyl-2(3H)-furanone (**4b**; $C_{11}H_{12}N_2O_2$)

Colorless prisms; m.p.: 176–177°C (acetone); IR (KBr): $\nu = 3510$, 3450, 3350, 3200 (NH), 1665 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ): 2.50 (dd, $J = 6.4/12.5$ Hz, 1H, 4-H), 3.11 (dd, $J = 9.5/12.5$ Hz, 1H, 4-H), 5.30 (dd, $J = 6.4/9.5$ Hz, 1H, 5-H), 5.91 (s, 2H, NH_2), 6.50 (s, 2H, NH_2), 7.27–7.38 (m, 5H, aryl) ppm; ^{13}C NMR (*DMSO*-d_6, δ): 34.2 (C-4), 64.8 (C-3), 75.0 (C-5), 125.2, 127.3, 128.3, 143.5 (C aryl), 157.8 (=$C(NH_2)_2$), 172.3 (C-2) ppm; MS (FAB): m/z (%) = 205 (100) [$M^+ + H$].

3-(Amino-(benzamido)-methylene)-4,5-dihydro-4-phenyl-2(3H)-furanone
(**5**; $C_{18}H_{16}N_2O_3$)

To an ice-cooled and stirred suspension of 2.04 g (10 mmol) **4a** in 10 cm^3 pyridine, 1.55 g (11 mmol) benzoyl chloride were added. The mixture was heated at 50°C for 1 h. The solvent was removed, and 50 cm^3 H_2O were added to the residue. The precipitate was collected, washed with H_2O, and dried.

Yield: 2.62 g (85%); pale yellow needles; m.p.: 174–175°C (acetone); IR (KBr): $\nu = 3480$, 3340 (NH), 1775, 1630 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 4.10 (dd, $J = 6.1/9.5$ Hz, 1H, 4-H), 4.31 (dd, $J = 6.1/9.5$ Hz, 1H, 5-H), 4.71 (t, $J = 9.5$ Hz, 1H, 5-H), 5.00–6.70 (br, 2H, NH_2), 7.40–7.60 (m, 8H, aryl), 8.01–8.03 (m, 2H, aryl), 12.46 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, δ): 43.7 (C-4), 73.7 (C-5), 78.3 (C-3), 127.3, 127.7, 128.0, 129.0, 129.5, 132.5, 133.1, 141.2 (C aryl), 153.0 (=$C(NH_2)$NH), 167.7, 174.9 (C=O) ppm; MS (FAB): m/z (%) = 309 (100) [$M^+ + H$].

N-Benzoyltetrahydro-2-oxo-4-phenyl-3-furancarboxamide (**6**; $C_{18}H_{15}NO_4$)

To a stirred suspension of 1.54 g (5 mmol) **5** in 10 cm^3 acetone, 10 cm^3 10% HCl were added. The mixture was stirred at room temperature for 15 h, cooled, and poured onto 30 cm^3 H_2O. The precipitate was collected, washed with H_2O, and dried.

Yield: 1.44 g (93%); colorless needles; m.p.: 179–180°C (acetone/petroleum ether); IR (KBr): $\nu = 3360$ (NH), 1770, 1750, 1695 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 4.36 (t, $J = 9.8$ Hz, 1H, 5-H), 4.41 (dt, $J = 8.6/10.1$ Hz, 1H, 4-H), 4.64 (d, $J = 10.1$ Hz, 1H, 3-H), 4.75 (t, $J = 8.6$ Hz, 1H, 5-H), 7.30–7.60 (m, 8H, aryl), 7.85–7.90 (m, 2H, aryl), 9.61 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, δ): 43.3 (C-4), 54.1 (C-3), 72.8 (C-5) 127.4, 127.8, 128.1, 129.0, 129.2, 132.4, 133.5, 137.3 (C aryl), 164.8, 165.6, 172.7 (C=O) ppm; MS (FAB): m/z (%) = 310 (59) [$M^+ + H$].

Methyl tetrahydro-2-oxo-4-phenyl-3-furancarboxylate (**7**; $C_{12}H_{12}O_4$)

Procedure A: A mixture of 1.55 g (5 mmol) **6** and 10 cm^3 concentrated HCl in 10 cm^3 MeOH was refluxed for 6 h. The solvent was removed, and 30 cm^3 cold H_2O were added to the residue. The

mixture was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2 as the eluent to give **7** (0.71 g, 65%).

Procedure B: A suspension of 1.10 g (5 mmol) **8** and 10 cm^3 5% HCl was stirred at room temperature for 0.5 h. The oily product was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2 as the eluent to give **7** (0.97 g, 88%).

Colorless prisms; m.p.: 60–61°C (Et_2O/petroleum ether); IR (KBr): $\nu = 1788$, 1732 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 3.73 (d, $J = 10.1$ Hz, 1H, 3-H), 3.80 (s, 3H, CH_3), 4.19–4.25 (m, 1H, 4-H), 4.28 (t, $J = 8.8$ Hz, 1H, 5-H), 4.72 (dd, $J = 8.0/8.8$ Hz, 1H, 5-H), 7.25–7.39 (m, 5H, aryl) ppm; MS (FAB): m/z (%) = 221 (100) [$M^+ + H$].

Methyl 2-amino-4,5-dihydro-4-phenyl-3-furancarboxylate (**8**; $C_{12}H_{13}NO_3$)

A mixture of 5.61 g (30 mmol) **2a** and 0.16 g (3 mmol) MeONa in 20 cm^3 MeOH was heated at 60°C for 7 h. The mixture was cooled, and 0.16 g (3 mmol) acetic acid were added. The solvent was removed, and 50 cm^3 H_2O were added to the residue. The mixture was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on alumina with CH_2Cl_2 as the eluent to give **8**.

Yield: 5.48 g (83%); colorless prisms; m.p.: 150–151°C (CH_2Cl_2/petroleum ether); IR (KBr): $\nu = 3470$, 3250 (NH), 1660 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 3.50 (s, 3H, CH_3), 4.54 (dd, $J = 3.9/8.1$ Hz, 1H, 4-H), 4.29 (dd, $J = 3.9/8.1$ Hz, 1H, 5-H), 4.70 (t, $J = 8.1$ Hz, 1H, 5-H), 5.75 (s, 2H, NH_2), 7.15–7.30 (m, 5H, aryl) ppm; MS (FAB): m/z (%) = 220 (100) [$M^+ + H$].

Reaction of **3a** *with benzylamine*

To an ice-cooled and stirred solution of 2.04 g (10 mmol) **3a** and 1.18 g (11 mmol) benzylamine in 10 cm^3 pyridine, 0.66 g (11 mmol) acetic acid were added. The mixture was stirred at 60°C for 3 h. The solvent was removed, and 30 cm^3 H_2O were added to the residue. The mixture was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on alumina with CH_2Cl_2:acetone = 4:1 as the eluent to give a mixture of **9**, **9′**, and **10**. Fractional recrystallization from acetone/petroleum ether gave colorless needles (**9** and **9′**, 1.67 g, 57%) and colorless columns (**10**, 0.33 g, 11%).

(E)- and (Z)-3-(Amino-(benzylamino)-methylene)-4,5-dihydro-4-phenyl-2(3H)-furanones (**9** and **9′**; $C_{18}H_{18}N_2O_2$)

M.p.: 135–137°C; IR (KBr): $\nu = 3460$, 3430, 3370, 3260 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 3.91 (br s, 1H, NH_2), 3.97 (dd, $J = 5.7/8.3$ Hz, 0.5H, 4-H), 3.99 (dd, $J = 5.2/8.3$ Hz, 0.5H, 4-H), 4.27 (dq, $J = 5.1/13.1$ Hz, 1H, benzylic H), 4.21 (dd, $J = 5.7/8.3$ Hz, 0.5H, 5-H), 4.22 (dd, $J = 5.2/8.3$ Hz, 0.5H, 5-H), 4.26 (br t, $J = 5.1$ Hz, 0.5H, NH), 4.36 (dq, $J = 6.2/15.3$ Hz, 1H, benzylic H), 4.59 (t, $J = 8.3$ Hz, 1H, 5-H), 6.14 (br s, 1H, NH_2), 7.40–7.70 (m, 10H, aryl), 8.71 (br t, $J = 6.2$ Hz, 0.5H, NH) ppm; MS (FAB): m/z (%) = 295 (100) [$M^+ + H$].

2-Benzylamino-4,5-dihydro-4-phenyl-3-furancarboxamide (**10**; $C_{18}H_{18}N_2O_2$)

M.p.: 110–112°C; IR (KBr): $\nu = 3490$, 3270, 3120 (NH), 1660 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 3.66 (d, $J = 7.3$ Hz, 0.2H, 3-H), 4.13–4.18 (m, 0.2H, 4-H), 4.17 (dd, $J = 6.1/8.9$ Hz, 0.8H, 4-H), 4.26 (dd, $J = 7.2/8.9$ Hz, 0.2H, 5-H), 4.31 (dd, $J = 6.1/9.5$ Hz, 0.8H, 5-H), 4.36 (br s, 1.6H, NH_2), 4.49 (d, $J = 6.7$ Hz, 1.6H, benzylic H), 4.55 (q, $J = 13.7$ Hz, 0.4H, benzylic H), 4.64 (dd, $J = 8.0/8.9$ Hz,

0.2H, 5-H), 4.75 (dd, $J = 8.9/9.5$ Hz, 0.8H, 5-H), 5.44 (br s, 0.2H, NH_2), 7.26–7.36 (m, 10H, aryl), 7.77 (br s, 0.2H, NH_2), 8.15 (br s, 0.8H, NH) ppm; MS (FAB): m/z (%) = 295 (100) $[M^+ + H]$.

Tetrahydro-2-oxo-4-phenyl-3-furancarboxamide (**12**; $C_{11}H_{11}NO_3$)

Procedure A: A mixture of 0.59 g (2 mmol) **10** and 5 cm^3 5% HCl was stirred at 40°C for 2 h. The product was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2:acetone = 4:1 as the eluent to give **12** (0.23 g, 56%).

Procedure B: A mixture of 1.02 g (5 mmol) **3a** and 5 cm^3 5% HCl was stirred at room temperature for 0.5 h. The precipitate was collected, washed with H_2O, and dried to give **12** (0.74 g, 72%).

Colorless columns; m.p.: 119–121°C (acetone/petroleum ether); IR (KBr): $\nu = 3470$, 3360 (NH), 1755, 1700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 3.58 (d, $J = 8.9$ Hz, 1H, 3-H), 4.25–4.35 (m, 2H, 4-H, 5-H), 4.72 (t, $J = 8.0$ Hz, 1H, 5-H), 5.73 (br s, 1H, NH), 6.69 (br s, 1H, NH), 7.25–7.30 (m, 3H, aryl), 7.35–7.40 (m, 2H, aryl) ppm; MS (FAB): m/z (%) = 206 (100) $[M^+ + H]$.

3-(Amino-(morpholino)-methylene)-4,5-dihydro-2(3H)-furanones (**11**); *general procedure*

A solution of 3.74 g (20 mmol) **2** and 3.50 g (22 mmol) trimethylsilylmorpholine in 20 cm^3 CH_2Cl_2 was stirred at room temperature for 48 h. The mixture was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on alumina with CH_2Cl_2 as the eluent to give **11**.

3-(Amino-(morpholino)-methylene)-4,5-dihydro-4-phenyl-2(3H)-furanone (**11a**; $C_{15}H_{18}N_2O_3$)

Yield: 1.49 g (27%); colorless columns; m.p.: 134–135°C (acetone/petroleum ether); IR (KBr): $\nu = 3300$, 3220 (NH), 1630 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 3.00–3.40 (m, 8H, $4CH_2$ morpholine), 3.83 (dd, $J = 6.7/8.3$ Hz, 1H, 5-H), 4.36 (dd, $J = 6.7/8.9$ Hz, 1H, 4-H), 4.54 (dd, $J = 8.3/8.9$ Hz, 1H, 5-H), 6.32 (s, 2H, NH_2), 7.16–7.33 (m, 5H, aryl) ppm; ^{13}C NMR ($CDCl_3$, δ): 46.3 (C-4, NCH_2), 66.0 (OCH_2), 72.6 (C-5), 75.8 (C-3), 127.1, 127.3, 128.7, 142.9 (C aryl), 161.2 (=C–NH_2), 176.5 (C-2) ppm; MS (FAB): m/z (%) = 275 (100) $[M^+ + H]$.

3-(Amino-(morpholino)-methylene)-4,5-dihydro-5-phenyl-2(3H)-furanone (**11b**; $C_{15}H_{18}N_2O_3$)

Yield: 3.81 g (70%); colorless columns; m.p.: 144–146°C (acetone/petroleum ether); IR (KBr): $\nu = 3390$, 3240 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 2.77 (dd, $J = 7.0/12.9$ Hz, 1H, 4-H), 3.24 (dd, $J = 8.6/12.9$ Hz, 1H, 4-H), 3.23–3.30 (m, 4H, $2CH_2$ morpholine), 3.67–3.71 (m, 4H, $2CH_2$ morpholine), 5.36 (dd, $J = 7.0/8.6$ Hz, 1H, 5-H), 6.14 (s, 2H, NH_2), 7.30–7.40 (m, 5H, aryl) ppm; ^{13}C NMR ($CDCl_3$, δ): 37.0 (C-4), 46.8 (NCH_2), 66.6 (OCH_2), 72.8 (C-3), 77.0 (C-5), 125.4, 127.8, 128.5, 142.1 (C aryl), 160.5 (=C–NH_2), 175.6 (C-2) ppm; MS (FAB): m/z (%) = 275 (100) $[M^+ + H]$.

References

[1] Yamagata K, Takaki M, Yamazaki M (1992) Liebigs Ann Chem 1109
[2] Yamagata K, Akizuki K, Yamazaki M (1998) J Prakt Chem **340**: 51
[3] Hashem AI, Shaban ME (1981) Indian J Chem **20B**: 807
[4] Allegretti M, D'Annibale A, Trogolo C (1993) Tetrahedron **49**: 10705

[5] Matsuda T, Yamagata K, Tomioka Y, Yamazaki M (1985) Chem Pharm Bull **33**: 937
[6] a) Campaigne E, Ho J, Bradford M (1970) J Heterocycl Chem **7**: 257; b) Campaigne E, Ellis RL, Bradford M (1969) J Heterocycl Chem **6**: 159
[7] Huang Z, Wamhoff H (1984) Chem Ber **117**: 622
[8] Hussain SMMT, Ollis WD, Smith C, Stoddart JF (1975) J Chem Soc Perkin Trans 1, 1480
[9] Campaigne E, Ellis RL, Bradford M, Ho J (1969) J Med Chem **12**: 339

Received October 4, 2001. Accepted October 10, 2001