Rhodium(II) Acetate-Catalyzed Reaction of 2-Amino-4,5-dihydro-3-furancarbonitriles with Dialkyl Diazomalonates

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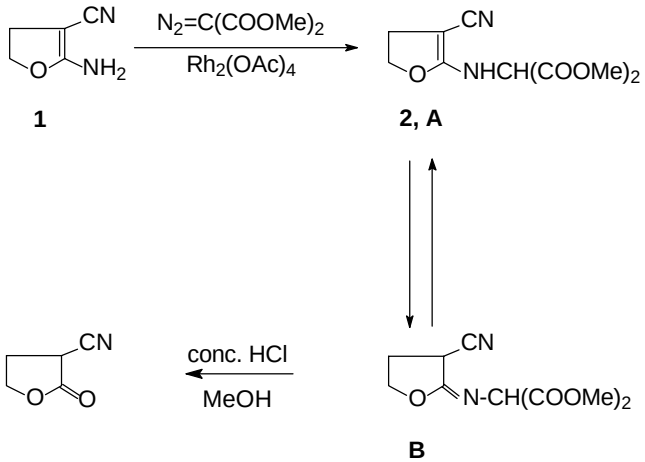
Abstract. 2-Amino-4,5-dihydro-3-furancarbonitriles **3** react with dialkyl diazomalonates in the presence of rhodium(II) acetate to yield dialkyl (5-amino-4-cyano-2,3-dihydro-3-furanyl)propanedioates **4**. Dehydrogenation of **4** with DDQ provided dialkyl (5-amino-4-cyano-3-furanyl)propanedioates **5**.

In the preceding paper, we showed that 2-amino-4,5-dihydro-3-furancarbonitriles react with α-diazo-β-keto esters such as ethyl diazoacetoacetate and ethyl diazobenzoylacetate in the presence of rhodium(II) acetate to form ethyl 2*H*-pyran-2-carboxylate [1]. In continuation of this study, we examined the reactions of 2-amino-4,5-dihydro-3-furancarbonitriles (**1** and **3**) with dimethyl diazomalonate [2] and diethyl diazomalonate [3].

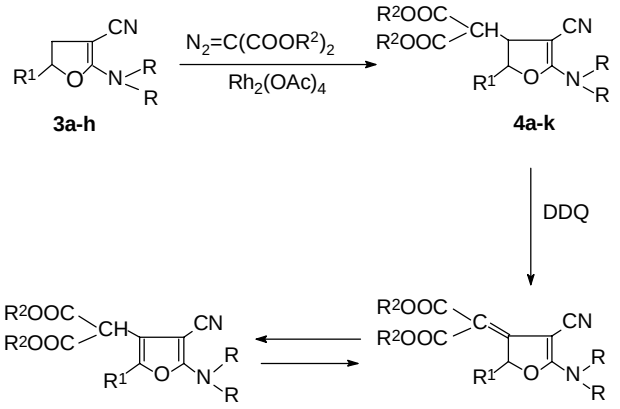
When a mixture of 2-amino-4,5-dihydro-3-furancarbonitrile **1** [4], dimethyl diazomalonate, and a catalytic amount of rhodium(II) acetate in 1,2-dichloroethane was refluxed for 1 h, an N–H insertion product, dimethyl [(3-cyano-4,5-dihydro-2-furanyl)amino]propanedioate (**2**) was obtained in 75% yield, and the expected dimethyl 2*H*-pyran-2,2-dicarboxylate could not be isolated. In order to confirm the structure of **2**, hydrolysis of **2** with hydrochloric acid led to tetrahydro-2-oxo-3-furancarbonitrile which was identical with an authentic sample [5]. The ^{1}H NMR spectrum of **2** in deuteriochloroform indicates that **2** consists of approximately a 3:2 tautomeric mixture of the enamine **A** and the imine **B** forms (Scheme 1).



Scheme 1

Subsequently, to prevent the N–H insertion reaction, we investigated the reaction of 4,5-dihydro-2-pyrrolidino-, as well as of 2-piperidino- and 2-morpholino-3-furancarbonitriles **3a**–**h** [6, 7] with dialkyl diazomalonates, and found an unexpected reaction.

When a mixture of 2-pyrrolidino-3-furancarbonitrile **3a**, dimethyl diazomalonate, and rhodium(II) acetate in fluorobenzene was heated at 70 °C under nitrogen, an



3-5	R1	R2	NRR
a	H	Me	pyrrolidino
b	H	Me	piperidino
c	H	Me	morpholino
d	Me	Me	pyrrolidino
e	Me	Me	morpholino
f	Ph	Me	pyrrolidino
g	Ph	Me	piperidino
h	Ph	Me	morpholino

4,5	R1	R2	NRR
i	Ph	Et	pyrrolidino
j	Ph	Et	piperidino
k	Ph	Et	morpholino

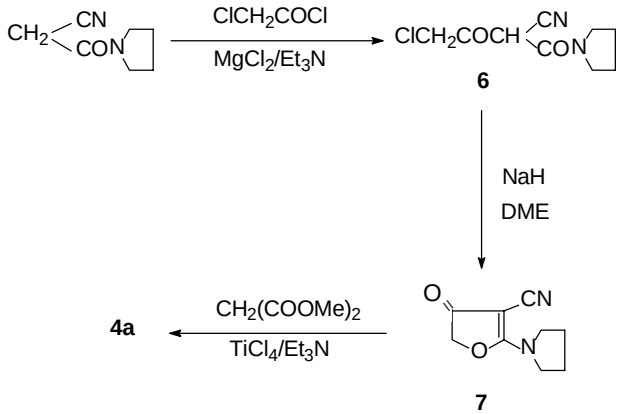
Scheme 2

  1436-9966/99/3410X-562 $ 17.50 + .50/0

allylic C–H insertion product, dimethyl (4-cyano-2,3-dihydro-5-pyrrolidino-furan-3-yl)propanedioate **4a** was obtained in 41% yield (Scheme 2).

Compound **4a** has the molecular composition $C_{14}H_{18}N_2O_5$, and its IR, ^{1}H NMR, and ^{13}C NMR spectra are consistent with the proposed structure **4a**. The analogous allylic C–H insertion was also observed by Wulfman *et al*. in their study dealing with the reactions of cyclohexenes and dimethoxycarbonylcarbenoid [8]. Compounds **3b**–**h** reacted with dimethyl diazomalonate under the same conditions to give the corresponding dimethyl furan-3-ylpropanedioates **4b**–**h** in fair yields. Similarly, the reaction of **3f**–**h** with diethyl diazomalonate afforded the corresponding diethyl 3-furanylpropanedioates **4i**–**k.** Also their structures were supported by analytical and spectral data.

In order to confirm the structure of **4a**, dehydrogenation of **4a** with DDQ led to dimethyl 3-furanylpropanedioate **5a**, which was identical with an authentic sample prepared by the following method: Chloroacetylation of 1-(cyanoacetyl)pyrrolidine [9] with chloroacetyl chloride in the presence of magnesium chloride and triethylamine gave 4-chloro-3-oxo-2-(pyrrolidinocarbonyl)butanenitrile **6** in 54% yield, and subsequent treatment with sodium hydride provided 4,5-dihydro-4-oxo-2-pyrrolidino-3-furancarbonitrile (**7**) in 66% yield. Finally, the desired **5a** was prepared by the reaction of **7** with dimethyl malonate in the presence of titanium(IV) chloride/triethylamine utilising a modification of a procedure described in the literature [10] (Scheme 3).



Scheme 3

Subsequently, aromatization of **4b**–**k** with DDQ yielded the corresponding dialkyl (furan-3-yl)propanedioates **5b**–**k**. The IR spectra of **5a**–**d** display the two bands of the conjugated ester carbonyl groups at 1 680–1 690 and 1 720–1 730 cm^{-1}. The ^{1}H NMR spectra of **5a**–**d** show a singlet at δ = 5.50–5.20 ppm (**5a**–**c**) or a quartet at δ = 6.05 ppm (**5d**) corresponding to the two protons or one proton of the 2-H of the furan ring. On the other hand, in the IR spectra of **5e**–**k**, the two bands of the non-conjugated ester carbonyl groups (1 725–1 735 and 1 740–1 760 cm^{-1}) shift to higher frequencies from 20 to 30 cm^{-1} than those of **5a**–**d**. The ^{1}H NMR spectra of **5e**–**k** reveal the signal of the malonate methine proton as a singlet at δ = 4.48–4.83 ppm, and no the signal of a methine proton (2-H) of the furan ring observed around δ = 5.50–6.50 ppm. These spectral data suggest that **5a**–**d** are the 3(2*H*)-furanylidene structure **C**, whereas those of **5e**–**k** are the furan-3-yl structure **D.**

Experimental

All melting points are uncorrected. IR spectra were recorded with a Jasco A-302 instrument. ^{1}H and ^{13}C NMR spectra were measured on a Hitachi R22 (90 MHz), Jeol JNM-GX-400 (400 MHz), and Jeol JNM-A500 (500 MHz) in $CDCl_3$, with TMS as internal standard, δ scale; coupling constants in Hz. Mass spectra were recorded with a Jeol JMS-D300, 70eV.

Dimethyl (3-Cyano-4,5-dihydro-2-furanyl)aminopropanedioate **2**

A mixture of **1** [4] (1.10 *g*, 10 mmol), dimethyl diazomalonate [2] (1.74 g, 11 mmol), and $Rh_2(OAc)_4$ (0.05 g) in 1,2-dichloroethane (20 ml) was refluxed for 1 h. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with CH_2Cl_2/acetone (4:1) as eluent, to afford **2**. Colorless prisms; *m.p*. 88–90 °C (CH_2Cl_2/petroleum ether). – IR (KBr): ν/cm^{-1} = 2190 (C≡N), 1 750 (C=O). – ^{1}H NMR (500 MHz): δ/ppm = 2.50–2.70 (m, 0.8H, 4-H), 2.91 (t, *J* =10, 1.2H, 4-H), 3.78 (s, 1.3H, CH_3), 3.81 (s, 1.3H, CH_3), 3.84 (s, 3.4H, CH_3), 3.92 (t, *J* = 7.5, 0.4H, 3-H), 4.35–4.52 (m, 0. 8H, 5-H), 4.44 (t, *J* = 10, 1.2H, 5-H), 5.02 (d, *J* = 8.5, 0.6H, NHC<u>H</u>), 5.04 (s, 0.4H, =N–CH), 5.54 (d, *J* = 8.5, 0.6H, N<u>H</u>CH).

$C_{10}H_{12}N_2O_5$	Calcd.:	C 50.00	H 5.04	N 11.66
(240.2)	Found:	C 50.26	H 5.01	N 11.80.

Reactions of 2-Amino-4,5-dihydro-3-furancarbonitriles 3 with Dialkyl Diazomalonates (General Procedure)

Procedure A: A mixture of **3** (10 mmol), dimethyl diazomalonate (1.74 g, 11 mmol), and $Rh_2(OAc)_4$ (0.05 g) in C_6H_5F (20 ml) was heated at 70 °C with stirring for 4 h under nitrogen. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on alumina with CH_2Cl_2 as eluent. Yield **4a** (1.20 g, 41%), **4b** (1.08 g, 35%), **4c** (1.30 g, 42%), **4d** (1.19 g, 39%), **4e** (1.16 g, 36%), **4f** (1.51 g, 41%),**4g** (1.42 g, 37%), and **4h** (1.17 g, 30%).

Procedure B: From **3** (10 mmol) and diethyl diazomalonate [3] (2.79 g, 15 mmol) as described for *Procedure A*. Yield **4i** (0.93 g, 23%), **4j** (0.90 g, 22%), and **4k** (1.19 g, 29%).

Dimethyl (4-Cyano-2,3-dihydro-5-pyrrolidino-furan-3-yl)propanedioate **4a**

From 4,5-dihydro-2-pyrrolidino-3-furancarbonitrile [6] (1.64 *g*, 10 mmol). Colorless prisms; *m.p*. 125–126 °C (diethyl ether). – ^{13}C NMR (125 MHz): 25.2, 42.9, 47.7, 49.9,

52.5, 52.7, 55.4, 73.6, 120.0, 165.0,168.0, 168.3. – MS (FAB) *m/z* (%): 295 (54) [M^+ + H].

Dimethyl (4-Cyano-2,3-dihydro-5-piperidino-furan-3-yl)propanedioate **4b**

From 4,5-dihydro-2-piperidino-3-furancarbonitrile [7] (1.78 g, 10 mmol). Colorless prisms; *m.p*. 99–100 °C (diethyl ether). – ^{13}C NMR (100 MHz): 24.0, 25.4, 43.1, 47.3, 50.5, 52.5, 52.7, 55.0, 72.5, 120.1, 166.0, 168.0, 168.2. – MS (FAB) *m/z* (%): 309 (53) [M^+ + H].

Dimethyl (4-Cyano-2,3-dihydro-5-morpholino-furan-3-yl)propanedioate **4c**

From 4,5-dihydro-2-morpholino-3-furancarbonitrile [6] (1.80 g, 10 mmol). Colorless prisms; *m.p*. 110–111 °C (diethyl ether). – ^{13}C NMR (100 MHz): 42.9, 46.1, 52.1,52.6, 54.9, 66.1, 72.9, 119.3, 166.0, 167.9, 168.1. – MS(EI) *m/z* (%): 310(7)[M^+].

Dimethyl (4-Cyano-2,3-dihydro-2-methyl-5-pyrrolidino-furan-3-yl)propanedioate **4d**

From 4,5-dihydro-5-methyl-2-pyrrolidino-3-furancarbonitrile [6] (1.78 g, 10 mmol). Colorless columns; *m.p*. 99–100 °C (diethyl ether). – ^{13}C NMR (100 MHz): 21.2, 25.2, 47.6, 48.8, 49.6, 52.4, 52.6, 55.6, 82.3, 120.8, 164.0, 168.0, 168.3.

Dimethyl (4-Cyano-2,3-dihydro-2-methyl-5-morpholino-furan-3-yl)propanedioate **4e**

From 4,5-dihydro-5-methyl-2-morpholino-3-furancarbonitrile [6] (1.94 g, 10 mmol). Colorless prisms; *m.p*. 117–118 °C (diethyl ether). – ^{13}C NMR (100 MHz): 21.0, 46. 1, 49.5, 51.1, 52.5, 52.7, 55.1, 66.1, 81.6, 119.6, 165.0, 167.8, 168.1. – MS(EI) *m/z* (%): 324 (30) [M^+].

Dimethyl (4-Cyano-2,3-dihydro-2-phenyl-5-pyrrolidino-furan-3-yl)propanedioate **4f**

From 4,5-dihydro-5-phenyl-2-pyrrolidino-3-furancarbonitrile [6] (2.40 g, 10 mmol). Colorless prisms; *m.p*. 178–179 °C (acetone). – ^{13}C NMR (100 MHz): 25.2, 47.8, 49.4, 50.9, 52.5, 52.6, 55.5, 85.5, 120.2, 125.5, 128.5, 128.6, 139.9, 164.4, 167.8, 168.2.

Dimethyl (4-Cyano-2,3-dihydro-2-phenyl-5-piperidino-furan-3-yl)propanedioate **4g**

From 4,5-dihydro-5-phenyl-2-piperidino-3-furancarbonitrile [7] (2.54 g, 10 mmol). Colorless prisms; *m.p*. 101–102 °C (diethyl ether). – ^{13}C NMR (100 MHz): 24.0, 25.6, 47.5, 49.9, 51.1, 52.5, 52.6, 55.2, 84.3, 119.9, 125.3, 128.5, 128.6, 140.0, 165.3, 167.8, 168.1.

Dimethyl (4-Cyano-2,3-dihydro-5-morpholino-2-phenyl-furan-3-yl)propanedioate **4h**

From 4,5-dihydro-2-morpholino-5-phenyl-3-furancarbonitrile [6] (2.56 g, 10 mmol). Colorless needles; *m.p*. 124–125 °C (acetone/petroleum ether). – ^{13}C NMR (125 MHz): 46.3, 50.9, 51.6, 52.6, 52.7, 55.0, 66.2, 84.8, 119.1, 125.4, 128.7, 128.8, 139.5, 165.4, 167.7, 168.0. – MS (EI) *m/z* (%): 386 (32) [M^+].

Diethyl (4-Cyano-2,3-dihydro-2-phenyl-5-pyrrolidino-furan-3-yl)propanedioate **4i**

From 4,5-dihydro-5-phenyl-2-pyrrolidino-3-furancarbonitrile [6] (2.40 g,10 mmol). Colorless columns; *m.p*. 90 °C (diethyl ether/petroleum ether). – ^{13}C NMR (100 MHz): 13.9, 14.0, 25.3, 47.8, 49.5, 50.8, 55.6, 61.5, 61.7, 85.3, 120.3, 125.5, 128.4, 128.6, 140.1, 164.4, 167.6, 167.8.

Diethyl (4-Cyano-2,3-dihydro-2-phenyl-5-piperidino-furan-3-yl)propanedioate **4j**

From 4,5-dihydro-5-phenyl-2-piperidino-3-furancarbonitrile [7] (2.54 g, 10 mmol). Colorless prisms; *m.p*. 77–78 °C (diethyl ether/petroleum ether). – ^{13}C NMR (100 MHz): 13.9, 14.0, 24.0, 25.6, 47.4, 50.1, 51.0, 55.3, 61.5, 61.7, 84.2, 120.0, 125.4, 128.4, 128.6, 140.1, 165.3, 167.6, 167.8.

Diethyl (4-Cyano-2,3-dihydro-5-morpholino-2-phenyl-furan-3-yl)propanedioate **4k**

From 4,5-dihydro-2-morpholino-5-phenyl-3-furancarbonitrile [6] (2.56 g, 10 mmol). Colorless prisms; *m.p*. 92–93 °C (diethyl ether/petroleum ether). – ^{13}C NMR (100 MHz): 13.9, 14.0, 46.2, 50.8, 51.8, 55.1, 61.6, 61.8, 66.1, 84.7, 119.2, 125.5, 128.6, 139.7, 165.3, 167.4, 167.6.

Reactions of 4 with DDQ (General Procedure)

Procedure A: A mixture of **4a**–**d**, **f**–**k** (3 mmol) and DDQ (0. 89 g, 3.9 mmol) in benzene (20 ml) was refluxed for 1 h. After the solvent had been removed under reduced pressure, CH_2Cl_2 (20 ml) was added to the residue. The mixture was filtered to remove the insoluble material, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on alumina with CH_2Cl_2 as eluent. Yield **5a** (0.52 g, 59%), **5b** (0.52 g, 57%), **5c** (0.34 g, 37%), **5d** (0.20 g, 22%), **5f** (0.54 g, 49%), **5g** (0.55 g, 48%), **5h** (0.54 g, 47%), **5i** (0.62 g, 52%), **5j** (0.56 g, 46%), and **5k** (0.69 g, 56%).

Procedure B: From **4e** (0.97 g, 3 mmol) and DDQ (0.82 g, 3.6 mmol) as described for *Procedure A*. Yield **5e** (0. 17 g, 18%).

Dimethyl (4-Cyano-5-pyrrolidino-(2H)-furan-3-ylidene)propanedioate **5a**

From **4a** (0. 88 g, 3 mmol). Colorless prisms; *m.p*. 181–182 °C (CH_2Cl_2/petroleum ether). – MS (FAB) *m/z* (%): 293 (54) [M^+ + H].

Dimethyl (4-Cyano-5-piperidino-(2H)-furan-3-ylidene)propanedioate **5b**

From **4b** (0.92 g, 3 mmol). Colorless needles; *m.p*. 151–152 °C (CH_2Cl_2/petroleum ether). – MS (FAB) *m/z* (%): 307 (55) [M^+ + H].

Dimethyl (4-Cyano-5-morpholino-(2H)-furan-3-ylidene)propanedioate **5c**

From **4c** (0.93 g, 3 mmol). Colorless prisms; *m.p*. 172–173 °C (CH_2Cl_2/petroleum ether). – MS (FAB) *m/z* (%): 309 (67)[M^+ + H].

Dimethyl (4-Cyano-2-methyl-5-pyrrolidino-(2H)-furan-3-ylidene)propanedioate **5d**

From **4d** (0.92 g, 3 mmol). Colorless prisms; *m.p*. 163–164 °C (CH_2Cl_2/petroleum ether).

Dimethyl (4-Cyano-2-methyl-5-morpholino-furan-3-yl)propanedioate **5e**

From **4e**. Colorless needles; *m.p*. 58–59 °C (diethyl ether/petroleum ether).

Dimethyl (4-Cyano-2-phenyl-5-pyrrolidino-furan-3-yl)propanedioate **5f**

From **4f** (1.11 g, 3 mmol). Colorless prisms; *m.p.* 169–170 °C (CH_2Cl_2/petroleum ether).

Dimethyl (4-Cyano-2-phenyl-5-piperidino-furan-3-yl)propanedioate **5g**

From **4g** (1.15 g, 3 mmol). Colorless prisms; *m.p.* 145–146 °C (CH_2Cl_2/petroleum ether).

Dimethyl (4-Cyano-2-methyl-5-morpholino-furan-3-yl)propanedioate **5h**

From **4h** (1.16 g, 3 mmol). Colorless columns; *m.p.* 159–160 °C (CH_2Cl_2/petroleum ether).

Diethyl (4-Cyano-2-phenyl-5-pyrrolidino-furan-3-yl)propanedioate **5i**

From **4i** (1.19 g, 3 mmol). Colorless prisms; *m.p.* 118–119 °C (diethyl ether/petroleum ether).

Diethyl (4-Cyano-2-phenyl-5-piperidino-furan-3-yl)propanediate **5j**

From **4j** (1.24 g, 3 mmol). Colorless prisms; *m.p.* 109–110 °C (diethyl ether/petroleum ether). – MS (FAB) *m/z* (%): 411 (56) [M^+ + H].

Diethyl (4-Cyano-5-morpholino-2-phenyl-furan-3-yl)propanedioate **5k**

From **4k** (1.24 g, 3 mmol). Colorless prisms; *m.p.* 116–117 °C (diethyl ether/petroleum ether).

Table 1 Analytical and IR spectral data of **4a**–**k**, **5a**–**k**

	Formula	Analysis Calcd./Found			IR ν (cm^{-1})	
		C	H	N	C≡N	C=O
4a	$C_{14}H_{18}N_2O_5$	57.13	6.17	9.52	2 170	1 730
	(294.3)	57.29	6.20	9.52		
4b	$C_{15}H_{20}N_2O_5$	58.43	6.54	9.09	2 170	1 740
	(308.3)	58.46	6.64	9.11		
4c	$C_{14}H_{18}N_2O_6$	54.19	5.85	9.03	2 170	1 740
	(310.3)	54.30	5.97	9.05		1 727 (sh)
4d	$C_{15}H_{20}N_2O_5$	58.43	6.54	9.09	2 170	1 745
	(308.3)	58.50	6.53	9.16		1 727
4e	$C_{15}H_{20}N_2O_6$	55.55	6.22	8.64	2 170	1 750
	(324.3)	55.69	6.25	8.67		1 730
4f	$C_{20}H_{22}N_2O_5$	64.85	5.99	7.65	2 170	1 750 (sh)
	(370.4)	64.94	6.02	7.62		1 735
4g	$C_{21}H_{24}N_2O_5$	65.61	6.29	7.29	2 175	1 740
	(384.4)	65.75	6.43	7.39		
4h	$C_{20}H_{22}N_2O_6$	62.17	5.74	7.25	2 180	1 744
	(386.4)	62.30	5.81	7.32		1 728
4i	$C_{22}H_{26}N_2O_5$	66.32	6.58	7.03	2 195	1 745
	(398.5)	66.51	6.74	7.16		1 730
4j	$C_{23}H_{28}N_2O_5$	67.02	6.84	6.79	2 190	1 750 (sh)
	(412.5)	66.95	6.67	6.74		1 735
4k	$C_{22}H_{26}N_2O_6$	63.76	6.32	6.76	2 180	1 750 (sh)
	(414.5)	63.90	6.28	6.95		1 730
5a	$C_{14}H_{16}N_2O_5$	57.53	5.52	9.58	2 200	1 720
	(292.3)	57.42	5.55	9.39		1 690
5b	$C_{15}H_{18}N_2O_5$	58.82	5.92	9.15	2 200	1 725
	(306.3)	58.81	5.87	9.02		1 685
5c	$C_{14}H_{16}N_2O_6$	54.54	5.23	9.09	2 200	1 720
	(308.3)	54.59	5.30	8.87		1 690
5d	$C_{15}H_{18}N_2O_5$	58.82	5.92	9.15	2 205	1 730
	(306.3)	58.80	5.86	9.08		1 680
5e	$C_{15}H_{18}N_2O_6$	55.90	5.63	8.69	2 210	1 760
	(322.3)	55.89	5.68	8.47		1 735
5f	$C_{20}H_{20}N_2O_5$	65.21	5.47	7.60	2 190	1 750 (sh)
	(368.4)	65.30	5.39	7.69		1 725
5g	$C_{21}H_{22}N_2O_5$	65.96	5.80	7.33	2 200	1 755
	(382.4)	65.95	5.78	7.30		1 735 (sh)
5h	$C_{20}H_{20}N_2O_6$	62.49	5.24	7.29	2 200	1 750 (sh)
	(384.4)	62.27	5.23	7.22		1 735
5i	$C_{22}H_{24}N_2O_5$	66.65	6.10	7.07	2 200	1 740
	(396.4)	66.69	6.05	6.94		1 735 (sh)
5j	$C_{23}H_{26}N_2O_5$	67.30	6.38	6.82	2 205	1 745 (sh)
	(410.5)	67.31	6.40	6.79		1 735
5k	$C_{22}H_{24}N_2O_6$	64.07	5.87	6.79	2 210	1 745 (sh)
	(412.4)	64.08	5.85	6.69		1 730

Table 2 ^{1}H NMR spectral data of **4a**–**k**, **5a**–**k**

	^{1}H NMR δ (ppm), J (Hz)
4a	1.85–1.95 [m, 4H, 2CH_2 (pyrrolidine)], 3.47–3.57 [m, 4H, 2CH_2 (pyrrolidine)], 3.60(d, J = 7.5, 1H, CH), 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (ddd, J = 4.5/7.5/8, 1H, 3-H), 4.38 (dd, J = 4.5/8, 1H, 2-H), 4.52 (t, J = 8, 1H, 2-H)
4b	1.55–1.65 [m, 6H, 3CH_2 (piperidine)], 3.44–3.52 [m, 4H, 2CH_2 (piperidine)], 3.61 (d, J = 6.5, 1H, CH), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.80(ddd, J = 3/6.5/9.5, 1H, 3-H), 4.40 (dd, J = 3/10, 1H, 2-H), 4.47 (dd, J = 9.5/10, 1H, 2-H)
4c	3.47–3.59 [m, 4H, 2CH_2 (morpholine)], 3.62 (d, J = 7.5, 1H, CH), 3.67–3.72 [m, 4H, 2CH_2 (morpholine)], 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.82 (ddd, J= 4.5/7.5/9, 1H, 3-H), 4.42 (dd, J = 4.5/10, 1H, 2-H), 4.50 (dd, J = 9/10, 1H, 2-H)
4d	1.39 (d, J = 7, 3H, CH_3), 1.85–1.95 [m, 4H, 2CH_2 (pyrrolidine)], 3.38 (dd, J = 3.5/8, 1H, 3-H), 3.45–3.55 [m, 4H, 2CH_2 (pyrrolidine)], 3.58 (d, J = 8, 1H, CH), 3.73(s, 3H, OCH_3), 3.79 (s, 3H, OCH_3),4.63 (dq, J = 3.5/7, 1H, 2-H)
4e	1.39 (d, J = 6.5, 3H, CH_3), 3.37 (dd, J = 3.5/7.5, 1H, 3-H), 3.45–3.56 [m, 4H, 2CH_2 (morpholine)], 3.60 (d, J = 7.5, 1H, CH), 3.65–3.72 [m, 4H, 2CH_2 (morpholine)], 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.67 (dq, J = 3.5/6.5, 1H, 2-H)
4f	1.90–2.00 [m, 4H, 2CH_2 (pyrrolidine)], 3.55–3.65 [m, 4H, 2CH_2(pyrrolidine)], 3.73 (s, 3H, OCH_3), 3.74 (dd, J = 3/6.5, 1H, 3-H), 3.75(d, J = 6.5, 1H, CH), 3.77(s, 3H, OCH_3), 5.55 (d, J = 3, 1H, 2-H), 7.30–7.40 (m, 5H, aryl)
4g	1.60–1.70 [m, 6H, 3CH_2 (piperidine)], 3.50–3.60 [m, 4H, 2CH_2 (piperidine)], 3.71 (dd, J = 2.5/7,1H, 3-H), 3.74 (d, J =7, 1H, CH), 3.76 (s, 3H, OCH_3),3.77 (s, 3H, OCH_3), 5.56 (d, J = 2.5, 1H, 2-H), 7.30–7.40 (m, 5H, aryl)
4h	3.55–3.75 [m, l0H, CH, 3-H, 4CH_2 (morpholine)], 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.60 (d, J = 2, 1H, 2-H), 7.30–7.40 (m, 5H, aryl)
4i	1.24 (t, J = 7, 3H, $OCH_2C\underline{H}_3$), 1.27 (t, J = 7, 3H, $OCH_2C\underline{H}_3$, 1.90–2.00 [m, 4H, 2CH_2 (pyrrolidine)], 3.50–3.65 [m, 4H, 2CH_2 (pyrrolidine)], 3.7l (d, J = 7.5, 1H, CH), 3.75 (dd, J = 2.5/7.5, 1H, 3-H), 4.21(q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.23(q, J = 7, 2H, $OC\underline{H}_2CH_3$), 5.63 (d, J = 2.5, 1H, 2-H), 7.30–7.40 (s, 5H, aryl)
4j	1.24 (t, J =7, 3H, $OCH_2C\underline{H}_3$),1.28 (t, J = 7, 3H, $OCH_2C\underline{H}_3$),1.60–1.70 [m, 6H, 3CH_2 (piperidine)], 3.50–3.60 [m, 4H, 2CH_2 (piperidine)], 3.71 (d, J = 2, 2H, CH, 3-H), 4.22 (q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.24(q, J = 7, 2H, $OC\underline{H}_2CH_3$), 5.62 (s, 1H, 2-H), 7.30–7.40 (m, 5H, aryl)
4k	1.24 (t, J =7,3H, $OCH_2C\underline{H}_3$), 1.28 (t, J = 7,3H, $OCH_2C\underline{H}_3$), 3.65–3.80 [m, l0H, CH, 3-H, 4CH_2 (morpholine)], 4.21 (q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.24(q, J = 7, 2H, $OC\underline{H}_2CH_3$), 5.65 (d, J = 2, 1H, 2-H), 7.30–7.40 (m, 5H,aryl)
5a	1.90–2.10 [m, 4H, 2CH_2 (pyrrolidine)], 3.55–3.65 [m, 2H, CH_2 (pyrrolidine)], 3.71(s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90–4.00 [m, 2H, CH_2 (pyrrolidine)] 5.52(s, 2H, 2-H)
5b	1.70–1.80 [m, 6H, 3CH_2 (piperidine)], 3.65–3.90 [m, 4H, 2CH_2 (piperidine)], 3.71 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.50 (s, 2H, 2-H)
5c	3.72 (s, 3H, OCH_3), 3.80–3.90 [m, 8H, 4CH_2 (morpholine)], 3.85 (s, 3H, OCH_3), 5.52(s, 2H, 2-H)
5d	1.55 (d, J = 7, 3H, CH_3), 1.90–2.10 [m, 4H, 2CH_2 (pyrrolidine)], 3.50–3.60 [m, 2H, CH_2 (pyrrolidine)], 3.69 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.85–3.95 [m, 2H, CH_2 (pyrrolidine)], 6.05 (q, J = 7, 1H, 2-H)
5e	2.16 (s, 3H, CH_3), 3.50–3.60 [m, 4H, 2CH_2(morpholine)], 3.80–3.90 [m, 4H, 2CH_2 (morpholine)], 3.80 (s, 6H, 2OCH_3), 4.48 (s, 1H, CH)
5f	1.95–2.05 [m, 4H, 2CH_2 (pyrrolidine)], 3.65–3.75 [m, 4H, 2CH_2 (pyrrolidine)], 3.8l (s, 6H, 2OCH_3), 4.83 (s, 1H, CH), 7.25–7.45 (m, 5H, aryl)
5g	1.60–1.75 [m, 6H, 3CH_2 (piperidine)], 3.60–3.65 [m, 4H, 2CH_2 (piperidine)], 3.80 (s, 6H, 2OCH_3), 4.82 (s, 1H, CH), 7.30–7.50 (m, 5H, aryl)
5h	3.60–3.70 [m, 4H, 2CH_2 (morpholine)], 3.80–3.85 [m, 4H, 2CH_2 (morpholine)], 3.81 (s, 6H, 2OCH_3), 4.82 (s, 1H, CH), 7.30–7.50 (m, 5H, aryl)
5i	1.30 (t, J = 7, 6H, $2OCH_2C\underline{H}_3$), 1.95–2.05 [m, 4H, 2CH_2 (pyrrolidine)], 3.65–3.75 [m, 4H, 2CH_2 (pyrrolidine)], 4.265 (q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.27 (q, J = 7, 2H, $OC\underline{H}_2CH_3$),4.78 (s, 1H, CH), 7.25–7.50 (m, 5H, aryl)
5j	1.29 (t, J = 7, 6H, $2OCH_2C\underline{H}_3$), 1.60–1.75 [m, 6H, 3CH_2 (piperidine)], 3.60–3.65 [m, 4H, 2CH_2 (piperidine)], 4.25 (q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.255 (q, J = 7,2H, $OC\underline{H}_2CH_3$), 4.77 (s, 1H, CH), 7.30–7.50 (m, 5H, aryl)
5k	1.30 (t, J = 7, 6H, $2OCH_2C\underline{H}_3$), 3.63–3.67 [m, 4H, 2CH_2 (morpholine)], 3.80–3.84 [m, 4H, 2CH_2 (morpholine)],4.26 (q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.265 (q, J = 7, 2H, $OC\underline{H}_2CH_3$), 4.78 (s, 1H, CH), 7.31–7.50 (m, 5 H, aryl)

4-Chloro-3-oxo-2-(pyrrolidinocarbonyl)butanenitrile **6**

A mixture of 1-(cyanoacetyl)pyrrolidine [9] (4.14 g, 30 mmol), magnesium chloride (2.85 g, 30 mmol), and Et_3N (6.06 g, 60 mmol) in acetonitrile (30 ml) was stirred at 0 °C for 1 h, and then chloroacetyl chloride (3.39 g, 30 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h and at room temp. for 20 h. The solvent was removed, and 5% HCl (20 ml) was added to the residue. The mixture was extracted with CH_2Cl_2. The extract was washed with satd. NaCl solution and dried with Na_2SO_4, and concentrated. The residue was chromatographed on silica gel. Elution with CH_2Cl_2 yielded **6** (3.48 g, 54% crude) as pale yellow oil. The product **6** was employed for the successive reaction without further purification.

4,5-Dihydro-4-oxo-2-pyrrolidino-3-furancarbonitrile **7**

To an ice-cooled and stirred solution of **6** in DME (20 ml) was added 60% NaH (0.70 g, 18 mmol). Stirring was continued at room temp. until the evolution of gas ceased, and then the mixture was refluxed for 2 h. After removal of the DME *in vacuo*, H_2O was added to the residue. The mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on alumina with CH_2Cl_2 as eluent to give **7** (1.85 g, 66%). Colorless columns; *m.p.* 116–117 °C (acetone/petroleum ether). – IR (KBr): ν/cm^{-1} = 2 200 (C≡N),1 690(C=O). – ^{1}H NMR (90MHz): δ/ppm = 1.80–2.20 [m, 4H, 2CH_2 (pyrrolidine)], 3.50–4.00 [m,4H, 2CH_2 (pyrrolidine)], 4.59 (s, 2H, 5-H).

$C_9H_{10}N_2O_2$	Calcd.:	C 60.66	H 5.66	N 15.72
(178.2)	Found:	C 60.66	H 5.70	N 15.67.

Reaction of 7 with Dimethyl Malonate

To an ice-cooled and stirred solution of **7** (1.78 g, 10 mmol) and dimethyl malonate (1.98 *g*, 15 mmol) in CH_2Cl_2 (20 ml) $TiCl_4$(3.87 g, 20 mmol) in CH_2Cl_2 (5 ml) and Et_3N (2.02 g, 20 mmol) in CH_2Cl_2 (5ml) were successively added. The mixture was stirred at room temp. overnight, and then H_2O (20 ml) was added. The organic layer was separated and washed with H_2O, dried with Na_2SO, and concentrated. The solvent was evaporated, and the residue was chromatographed on alumina with CH_2Cl_2 as eluent to afford **5a** (1.10 g, 38%), which was identical with a sample prepared from **4a** and DDQ on the basis of a mixed melting point determination and a comparison of the IR spectra.

References

[1] K. Yamagata, K. Akizuki, M. Yamazaki, J. Prakt. Chem. **1998**, *340*, 627
[2] B. W. Peace, F. Carman, D. S. Wulfman, Synthesis **1971**, 658
[3] M. Regitz, Chem. Ber. **1966,** *99*, 3128
[4] T. Matsuda, K. Yamagata, Y. Tomioka, M. Yamazaki, Chem. Pharm. Bull. **1985**, *33*, 937
[5] S. Morgenlie, Acta. Chem. Scand. **1970**, *24*, 365
[6] K. Yamagata, M. Takaki, M. Yamazaki, Liebigs Ann. Chem. **1992**, 1109
[7] K. Yamagata, K. Akizuki, M. Yamazaki, J. Prakt. Chem. **1998**, *340*, 51
[8] a) D. S. Wulfman, R. S.McDaniel Jr, B. W. Peace, Tetrahedron **1976,** *32*, 1241; b) D.S. Wulfman, B.G. McGibboney, E.K.Steffen, N.V. Thinh, R.S.McDaniel Jr, B.W.Peace, Tetrahedron **1976**, *32*, 1257
[9] H. F. Schwartz, L.F.Worrell, J. N. Delgado, J. Pharm Sci. **1967**, *56*, 80
[10] W. Lehnert, Tetrahedron **1973**, *29*, 635

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