

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

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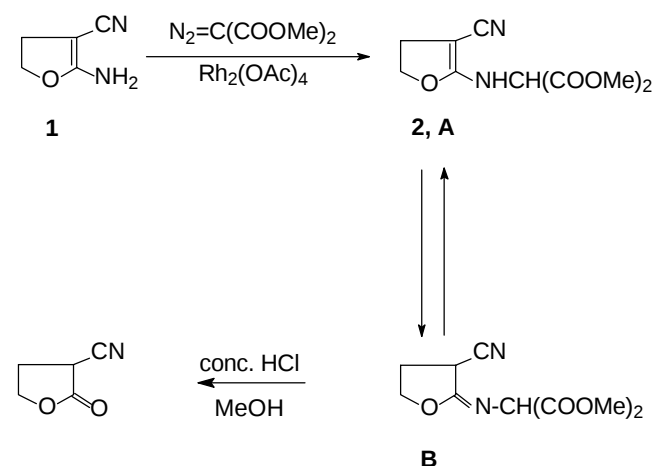
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Abstract. 2-Amino-4,5-dihydro-3-furancarbonitriles **3** react with dialkyl diazomalonates in the presence of rhodium(II) acetate to yield dialkyl (5-amino-4-cyano-2,3-di-

hydro-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].

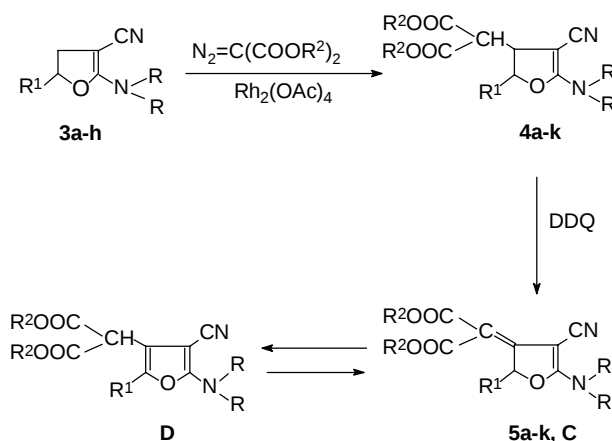
When a mixture of 2-amino-4,5-dihydro-3-furancarbonitrile **1** [4], dimethyl diazomalonate, and a catalytic amount of rhodium(II) acetate in 1,2-dichloroethane was refluxed for 1 h, an N–H insertion product, dimethyl [(3-cyano-4,5-dihydro-2-furanyl)amino]propanedioate (**2**) was obtained in 75% yield, 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 ¹H 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	R ¹	R ²	N $\begin{smallmatrix} \diagup R \\ \diagdown R \end{smallmatrix}$
a	H	Me	
b	H	Me	
c	H	Me	
d	Me	Me	
e	Me	Me	
f	Ph	Me	
g	Ph	Me	
h	Ph	Me	

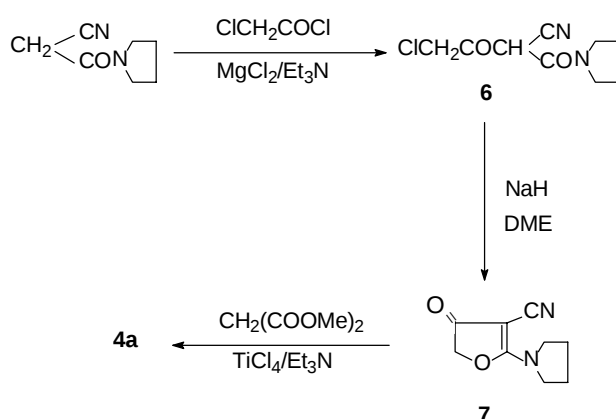
4,5	R ¹	R ²	N $\begin{smallmatrix} \diagup R \\ \diagdown R \end{smallmatrix}$
i	Ph	Et	
j	Ph	Et	
k	Ph	Et	

Scheme 2

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, 1H 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 1680–1690 and 1720–1730 cm^{-1} . The 1H NMR spectra of **5a–d** show a singlet at $\delta = 5.50–5.20$ ppm (**5a–c**) or a quartet at $\delta = 6.05$ 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 (1725–1735 and 1740–1760 cm^{-1}) shift to higher frequencies from 20 to 30 cm^{-1} than those of **5a–d**. The 1H NMR spectra of **5e–k** reveal the signal of the malonate methine proton as a singlet at $\delta = 4.48–4.83$ ppm, and no the signal of a methine proton (2-H) of the furan ring observed around $\delta = 5.50–6.50$ ppm. These spectral data suggest that **5a–d** are the 3(2H)-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. 1H 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, 70 eV.

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): $\nu/cm^{-1} = 2190$ ($C\equiv N$), 1750 ($C=O$). – 1H NMR (500 MHz): $\delta/ppm = 2.50–2.70$ (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, $NHCH$), 5.04 (s, 0.4H, $=N-CH$), 5.54 (d, $J = 8.5$, 0.6H, $NHCH$).

$C_{10}H_{12}N_2O_5$ 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 (CH₂Cl₂/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 (CH₂Cl₂/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 (CH₂Cl₂/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)propanedioate 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 ₂ O ₅ (294.3)	57.13 57.29	6.17 6.20	9.52 9.52	2 170	1 730
4b	C ₁₅ H ₂₀ N ₂ O ₅ (308.3)	58.43 58.46	6.54 6.64	9.09 9.11	2 170	1 740
4c	C ₁₄ H ₁₈ N ₂ O ₆ (310.3)	54.19 54.30	5.85 5.97	9.03 9.05	2 170	1 740 1 727 (sh)
4d	C ₁₅ H ₂₀ N ₂ O ₅ (308.3)	58.43 58.50	6.54 6.53	9.09 9.16	2 170	1 745 1 727
4e	C ₁₅ H ₂₀ N ₂ O ₆ (324.3)	55.55 55.69	6.22 6.25	8.64 8.67	2 170	1 750 1 730
4f	C ₂₀ H ₂₂ N ₂ O ₅ (370.4)	64.85 64.94	5.99 6.02	7.65 7.62	2 170	1 750 (sh) 1 735
4g	C ₂₁ H ₂₄ N ₂ O ₅ (384.4)	65.61 65.75	6.29 6.43	7.29 7.39	2 175	1 740
4h	C ₂₀ H ₂₂ N ₂ O ₆ (386.4)	62.17 62.30	5.74 5.81	7.25 7.32	2 180	1 744 1 728
4i	C ₂₂ H ₂₆ N ₂ O ₅ (398.5)	66.32 66.51	6.58 6.74	7.03 7.16	2 195	1 745 1 730
4j	C ₂₃ H ₂₈ N ₂ O ₅ (412.5)	67.02 66.95	6.84 6.67	6.79 6.74	2 190	1 750 (sh) 1 735
4k	C ₂₂ H ₂₆ N ₂ O ₆ (414.5)	63.76 63.90	6.32 6.28	6.76 6.95	2 180	1 750 (sh) 1 730
5a	C ₁₄ H ₁₆ N ₂ O ₅ (292.3)	57.53 57.42	5.52 5.55	9.58 9.39	2 200	1 720 1 690
5b	C ₁₅ H ₁₈ N ₂ O ₅ (306.3)	58.82 58.81	5.92 5.87	9.15 9.02	2 200	1 725 1 685
5c	C ₁₄ H ₁₆ N ₂ O ₆ (308.3)	54.54 54.59	5.23 5.30	9.09 8.87	2 200	1 720 1 690
5d	C ₁₅ H ₁₈ N ₂ O ₅ (306.3)	58.82 58.80	5.92 5.86	9.15 9.08	2 205	1 730 1 680
5e	C ₁₅ H ₁₈ N ₂ O ₆ (322.3)	55.90 55.89	5.63 5.68	8.69 8.47	2 210	1 760 1 735
5f	C ₂₀ H ₂₀ N ₂ O ₅ (368.4)	65.21 65.30	5.47 5.39	7.60 7.69	2 190	1 750 (sh) 1 725
5g	C ₂₁ H ₂₂ N ₂ O ₅ (382.4)	65.96 65.95	5.80 5.78	7.33 7.30	2 200	1 755 1 735 (sh)
5h	C ₂₀ H ₂₀ N ₂ O ₆ (384.4)	62.49 62.27	5.24 5.23	7.29 7.22	2 200	1 750 (sh) 1 735
5i	C ₂₂ H ₂₄ N ₂ O ₅ (396.4)	66.65 66.69	6.10 6.05	7.07 6.94	2 200	1 740 1 735 (sh)
5j	C ₂₃ H ₂₆ N ₂ O ₅ (410.5)	67.30 67.31	6.38 6.40	6.82 6.79	2 205	1 745 (sh) 1 735
5k	C ₂₂ H ₂₄ N ₂ O ₆ (412.4)	64.07 64.08	5.87 5.85	6.79 6.69	2 210	1 745 (sh) 1 730

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

	^1H 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, 10H, 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_2CH_3), 1.27 (t, $J = 7$, 3H, OCH_2CH_3), 1.90–2.00 [m, 4H, 2CH_2 (pyrrolidine)], 3.50–3.65 [m, 4H, 2CH_2 (pyrrolidine)], 3.71 (d, $J = 7.5$, 1H, CH), 3.75 (dd, $J = 2.5/7.5$, 1H, 3-H), 4.21(q, $J = 7$, 2H, OCH_2CH_3), 4.23(q, $J = 7$, 2H, OCH_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_2CH_3), 1.28 (t, $J = 7$, 3H, OCH_2CH_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, OCH_2CH_3), 4.24(q, $J = 7$, 2H, OCH_2CH_3), 5.62 (s, 1H, 2-H), 7.30–7.40 (m, 5H, aryl)
4k	1.24 (t, $J = 7$, 3H, OCH_2CH_3), 1.28 (t, $J = 7$, 3H, OCH_2CH_3), 3.65–3.80 [m, 10H, CH, 3-H, 4CH_2 (morpholine)], 4.21 (q, $J = 7$, 2H, OCH_2CH_3), 4.24(q, $J = 7$, 2H, OCH_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)], 3.81 (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, $2\text{OCH}_2\text{CH}_3$), 1.95–2.05 [m, 4H, 2CH_2 (pyrrolidine)], 3.65–3.75 [m, 4H, 2CH_2 (pyrrolidine)], 4.265 (q, $J = 7$, 2H, OCH_2CH_3), 4.27 (q, $J = 7$, 2H, OCH_2CH_3), 4.78 (s, 1H, CH), 7.25–7.50 (m, 5H, aryl)
5j	1.29 (t, $J = 7$, 6H, $2\text{OCH}_2\text{CH}_3$), 1.60–1.75 [m, 6H, 3CH_2 (piperidine)], 3.60–3.65 [m, 4H, 2CH_2 (piperidine)], 4.25 (q, $J = 7$, 2H, OCH_2CH_3), 4.255 (q, $J = 7$, 2H, OCH_2CH_3), 4.77 (s, 1H, CH), 7.30–7.50 (m, 5H, aryl)
5k	1.30 (t, $J = 7$, 6H, $2\text{OCH}_2\text{CH}_3$), 3.63–3.67 [m, 4H, 2CH_2 (morpholine)], 3.80–3.84 [m, 4H, 2CH_2 (morpholine)], 4.26 (q, $J = 7$, 2H, OCH_2CH_3), 4.265 (q, $J = 7$, 2H, OCH_2CH_3), 4.78 (s, 1H, CH), 7.31–7.50 (m, 5H, 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): $\nu/\text{cm}^{-1} = 2200 (\text{C}\equiv\text{N}), 1690 (\text{C}=\text{O})$. – ^1H NMR (90MHz): $\delta/\text{ppm} = 1.80–2.20$ [m, 4H, 2CH_2 (pyrrolidine)], 3.50–4.00 [m, 4H, 2CH_2 (pyrrolidine)], 4.59 (s, 2H, 5-H).

C₉H₁₀N₂O₂ 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 CH₂Cl₂ (20 ml) TiCl₄ (3.87 g, 20 mmol) in CH₂Cl₂ (5 ml) and Et₃N (2.02 g, 20 mmol) in CH₂Cl₂ (5 ml) were successively added. The mixture was stirred at room temp. overnight, and then H₂O (20 ml) was added. The organic layer was separated and washed with H₂O, dried with Na₂SO₄, and concentrated. The solvent was evaporated, and the residue was chromatographed on alumina with CH₂Cl₂ 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.

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