A New Approach to the Synthesis of Pyridazino[4,5-*c*]pyridazinones

Tetsuo Yamasaki, Yuji Yoshihara, Yoshinari Okamoto,
Tadashi Okawara and Mitsuru Furukawa*

Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-hon-machi, Kumamoto 862, Japan

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The reaction of 5-hydrazinopyridazin-3(2*H*)-ones **1** with α-keto diester **2** in acetic acid afforded the corresponding 4,6-dihydropyridazino[4,5-*c*]pyridazin-5(1*H*)-ones **3** and pyrrolo[2,3-*d*]pyridazin-4(5*H*)-ones **4**. Compounds **3** were also obtained from 4-bromo-5-hydrazinopyridazin-3(2*H*)-ones **8** and **2** under milder conditions. 5-Bromo-4-hydrazinopyridazin-3(2*H*)-one **9**, the regioisomer of **8b**, also reacted readily with **2a** to give 4,7-dihydropyridazino[4,5-*c*]pyridazin-8(1*H*)-one **10b**, the regioisomer of **3b**.

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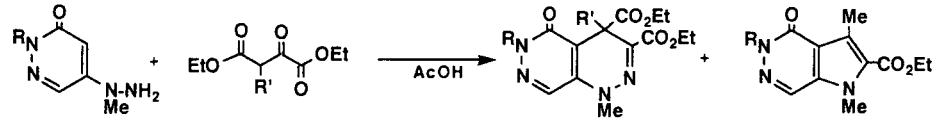
Fused pyridazinones comprise a very interesting class of compounds because of their significant biological and pharmaceutical activities [1-5]. As one of our studies on the preparation of novel heterocyclic ring systems, we previously reported that 5-hydrazinopyridazin-3(2*H*)-ones **1** and the bromo compounds **8** and **9** reacted with dimethyl acethylenedicarboxylate to give 1,4-dihydropyridazino-[4,5-*c*]pyridazinones by cyclization with dehydrogenation and rearrangement [6,7]. So far, little is known about the preparation of 1,4-dihydropyridazino[4,5-*c*]pyridazinones. The only example is the preparation of 1,4,7,8-tetrahydropyridazino[4,5-*c*]pyridazinones from 4-acyl-3*H*-imidazo-[1,5-*b*]pyridazine-5,7(6*H*)-diones and hydrazine [8]. We now describe a new heterocyclization to 1,4-dihydropyridazino[4,5-*c*]pyridazinones by the reaction of hydrazinopyridazinones **1**, **8** and **9** with α-keto diester **2**.

When 5-(1-methylhydrazino)pyridazin-3(2*H*)-ones **1** [9] were heated with diethyl oxalpropionate **2a** and diethyl oxalacetate **2b** in acetic acid at 50° or 100°, 4,6-dihydropyridazino[4,5-*c*]pyridazin-5(1*H*)-ones **3** were provided in

Scheme 1



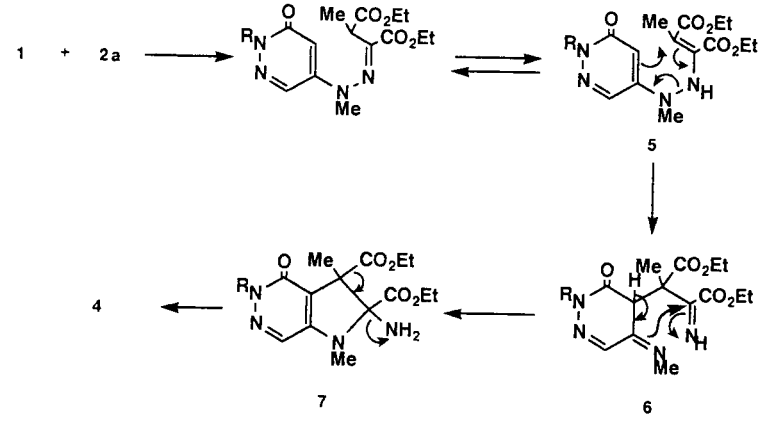
1a, R=Ph
b, R=Me
c, R=H
d, R=Bzl

2a, R'=Me
b, R'=H

3a, R=Ph,R'=Me
b, R=Me,R'=Me
c, R=H,R'=Me
d, R=Bzl,R'=Me
e, R=Ph,R'=H
f, R=Me,R'=H
g, R=H,R'=H

4a, R=Ph
b, R=Me
c, R=H
d, R=Bzl

Scheme 2



15-47% yield, along with 2-8% yield of unexpected pyrrolo[2,3-*d*]pyridazin-4(5*H*)-ones **4** in the reaction of compound **1** with the diester **2a** (Scheme 1). The products **3a-d** and **4** were purified by column chromatography on silica gel (benzene/ethyl acetate, 2/1). The structures of the products **3** and **4** were assigned as follows. The ir spectra of **3** showed two ester carbonyl absorptions at 1760-1700 cm^{-1}. In the ^{1}H-nmr spectra of **3**, the sp^2 methine proton signal of the enhydrazine moiety disappeared. Moreover, the ^{13}C-nmr spectrum of **3c** exhibited the sp^3 quaternary carbon signal at 41.00 ppm. These data support the assigned structure **3** for the products. As to the structure of **4**, the ir spectra showed the absorption assignable to the ester carbonyl groups near 1705 cm^{-1}, and the mass spectral data indicated the molecular ion peak corresponding to the elimination of amino and ethoxycarbonyl groups from the hydrazone formed by the reaction of the enhydrazin **1** with the diester **2a**. The ^{1}H-nmr spectra and elemental analyses also strongly supported the structural assignment of the product as compounds **4**.

The formation of compounds **3** is presumed to proceed through the initial hydrazone formation at the most reactive α-ketone function of compounds **2** followed by cyclization with dehydrogenation. On the other hand, our pro-

Table 1

4,6-Dihydropyridazino[4,5-*c*]pyridazin-5(1*H*)-ones **3a-g** and Pyrrolo[2,3-*d*]pyridazin-4(5*H*)-ones **4a-d**

No.	R	R'	Mp (°C)	Yield (%) (Yield from **8** and **2**)	IR (cm^{-1})	Mass (M^+)	^{1}H-NMR (ppm) (Deuteriochloroform)
3a	Ph	Me	161 [a]	41 (84)	1735 (C=O) 1715 (C=O) 1650 (C=O)	399 $(M+1)^+$ [d]	1.28 (t, 3H, J = 7 Hz, CH_3), 1.34 (t, 3H, J = 7 Hz, CH_3), 1.60 (s, 3H, CH_3), 3.68 (s, 3H, NCH_3), 4.27 (q, 2H, J = 7 Hz, CH_2), 4.31 (q, 2H, J = 7 Hz, CH_2), 7.22-7.67 (m, 5H, Ph), 7.79 (s, 1H, CH=)
3b	Me	Me	108-109 [a]	15 (61)	1760 (C=O) 1710 (C=O) 1660 (C=O)	337 $(M+1)^+$ [d]	1.31 (t, 3H, J = 7 Hz, CH_3), 1.34 (t, 3H, J = 7 Hz, CH_3), 1.54 (s, 3H, CH_3), 3.66 (s, 3H, NCH_3), 3.73 (s, 3H, NCH_3), 4.29 (q, 2H, J = 7 Hz, CH_2), 4.32 (q, 2H, J = 7 Hz, CH_2), 7.63 (s, 1H, CH=)
3c	H	Me	202-203 [a]	40 (72)	3150 (NH) 1735 (C=O) 1715 (C=O) 1640 (C=O)	323 $(M+1)^+$ [d]	1.31 (t, 3H, J = 7 Hz, CH_3), 1.36 (t, 3H, J = 7 Hz, CH_3), 1.57 (s, 3H, CH_3), 3.69 (s, 3H, NCH_3), 4.33 (q, 4H, J = 7 Hz, CH_2 x 2), 7.71 (s, 3H, CH=), 12.45 (br, 1H, NH)
3d	Bzl	Me	119-120 [a]	47 (72)	1730 (C=O) 1715 (C=O) 1650 (C=O)	413 $(M+1)^+$ [d]	1.21 (t, 3H, J = 7 Hz, CH_3), 1.33 (t, 3H, J = 7 Hz, CH_3), 1.54 (s, 3H, CH_3), 3.61 (s, 3H, NCH_3), 4.23 (q, 2H, J = 7 Hz, CH_2), 4.29 (q, 2H, J = 7 Hz, CH_2), 5.26 (s, 2H, CH_2), 7.33 (s, 5H, Ph), 7.66 (s, 1H, CH=)
3e	Ph	H	153 [b]	50 (73)	1725 (C=O) 1700 (C=O) 1650(C=O)	344	1.23 (t, 3H, J = 7 Hz, CH_3), 1.37 (t, 3H, J = 7 Hz, CH_3), 3.71 (s, 3H, NCH_3), 4.15 (q, 2H, J = 7 Hz, CH_2), 4.39 (q, 2H, J = 7 Hz, CH_2), 5.34 (s, 1H, CH), 7.30-7.80 (m, 5H, Ph), 7.88 (s, 1H, CH=)
3f	Me	H	116 [c]	40 (62)	1730 (C=O) 1720 (C=O) 1640 (C=O)	322	1.22 (t, 3H, J = 7 Hz, CH_3), 1.36 (t, 3H, J = 7 Hz, CH_3), 3.66 (s, 3H, NCH_3), 3.78 (s, 3H, NCH_3), 3.78 (s, 3H, NCH_3), 4.26 (q, 4H, J = 7 Hz, CH_2 x 2), 5.29 (s, 1H, CH), 7.70 (s, 1H, CH=)
3g	H	H	204 [b]	52 (68)	3140 (NH) 1730 (C=O) 1715 (C=O) 1640 (C=O)	308	1.23 (t, 3H, J = 7 Hz, CH_3), 1.37 (t, 3H, J = 7 Hz, CH_3), 3.71 (s, 3H, NCH_3), 4.15 (q, 2H, J = 7 Hz, CH_2), 4.39 (q, 2H, J = 7 Hz, CH_2), 5.33 (s, 1H, CH), 7.84 (s, 1H, CH), 12.83 (br, 1H, NH)
4a	Ph	-	167-168 [a]	8	1700 (C=O) 1660 (C=O)	311	1.45 (t, 3H, J = 7 Hz, CH_3), 2.80 (s, 3H, CH_3), 4.08 (s, 3H, NCH_3), 4.45 (q, 2H, J = 7 Hz, CH_2), 7.16-7.77 (m, 5H, Ph), 8.16 (s, 1H, CH=)
4b	Me	-	137-138 [a]	7	1710 (C=O) 1640 (C=O)	249	1.42 (t, 3H, J = 7 Hz, CH_3), 2.76 (s, 3H, CH_3), 3.80 (s, 3H, NCH_3), 4.01 (s, 3H, NCH_3), 4.41 (q, 2H, J = 7 Hz, CH_2), 7.98 (s, 1H, CH=)
4c	H	-	257 [a]	3	3200 (NH) 1700 (C=O) 1655 (C=O)	235	1.37 (t, 3H, J = 7 Hz, CH_3), 2.58 (s, 3H, CH_3), 3.95 (s, 3H, NCH_3), 4.37 (q, 2H, J = 7 Hz, CH_2), 8.38 (s, 1H, CH=), 12.28 (br, 1H. NH)
4d	Bzl	-	189-190 [a]	2	1705 (C=O) 1650 (C=O)	325	1.41 (t, 3H, J = 7 Hz, CH_3), 2.75 (s, 3H, CH_3), 3.99 (s, 3H, NCH_3), 4.40 (q, 2H, J = 7 Hz, CH_2), 5.38 (s, 2H, CH_2), 7.14-7.39 (m, 5H, Ph), 8.04 (s, 1H, CH=)

[a] Recrystallization from ethanol. [b] Recrystallization from ethyl acetate. [c] Recrystallization from benzene. [d] The parent ion was determined with ms (CI). Compound **3c** had ^{13}C-nmr (deuteriochloroform): δ 13.86 (CH_3), 14.01 (CH_3), 21.66 (CH_3), 41.00 (C), 41.21 (NCH_3), 61.76 (CH_2), 61.91 (CH_2), 113.64 (C), 126.03 (CH), 136.68 (C), 137.00 (C), 160.49 (C=O), 162.15 (C=O), 171.26 (C=O).

Table 1 (Continued)

No.	R	R'	Formula	Analysis (%) Calcd./Found C	H	N
3a	Ph	Me	$C_{20}H_{22}N_4O_5$	60.29	5.57	14.05
				60.45	5.60	14.11
3b	Me	Me	$C_{15}H_{20}N_4O_5$	53.57	5.99	16.66
				53.68	6.01	16.66
3c	H	Me	$C_{14}H_{18}N_4O_5$	52.17	5.63	17.38
				52.00	5.60	17.45
3d	Bzl	Me	$C_{21}H_{24}N_4O_5$	61.16	5.86	13.53
				61.22	5.89	13.50
3e	Ph	H	$C_{19}H_{20}N_4O_5$	59.37	5.25	14.58
				59.55	5.27	14.33
3f	Me	H	$C_{14}H_{18}N_4O_5$	52.17	5.63	17.38
				52.45	5.57	17.54
3g	H	H	$C_{13}H_{16}N_4O_5$	50.65	5.23	18.17
				50.73	5.21	18.25
4a	Ph	-	$C_{17}H_{17}N_3O_3$	65.58	5.50	13.50
				65.83	5.59	13.67
4b	Me	-	$C_{12}H_{15}N_3O_3$	57.82	6.07	16.86
				58.21	6.26	16.91
4c	H	-	$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86
				56.33	5.71	17.59
4d	Bzl	-	$C_{18}H_{19}N_3O_3$	66.45	5.89	12.91
				66.27	5.88	12.72

posed pathway for the formation of compounds **4** is shown in Scheme 2. It is reasonable to assume that 3,3-sigmatropic migration with the cleavage of the N-N bond occurs to provide the intermediate compound **6**, in which the methylimino group at the C-5 of the pyridazinone ring attacks another imino carbon to form the compound **7** followed by aromatization with the elimination of amino and ethoxycarbonyl groups to give the product **4**.

Compound **3** was also obtained by the treatment of 4-bromo-5-hydrazinopyridazin-3(2*H*)-ones **8** with **2** in dimethylformamide or acetic acid at room temperature in 61-84% yield, without any formation of the expected regioisomer **10** of **3**. The isomer **10b**, 4,7-dihydropyridazino[4,5-*c*]pyridazin-8(1*H*)-one was successfully provided in 51% yield by the cyclization of 5-bromo-4-(1-methylhydrazono)pyridazin-3(2*H*)-one **9**, a regioisomer of **8**, with diethyl oxalpropionate **2a** under similar conditions (Scheme 3). As the regioisomers, **10b** and **3b**, possess the same mass spectral and elemental analysis values, in order to confirm the structure of **10b**, we measured the NOE difference spectra of isomers **3b** and **10b** by irradiation of the sp^2-methine proton of the pyridazinone ring. An NOE was observed on the methyl proton substituted at N-1 in compound **3b** and on the methyl proton substituted at C-4 in compound **10b**. This supports the assigned structure **10b**.

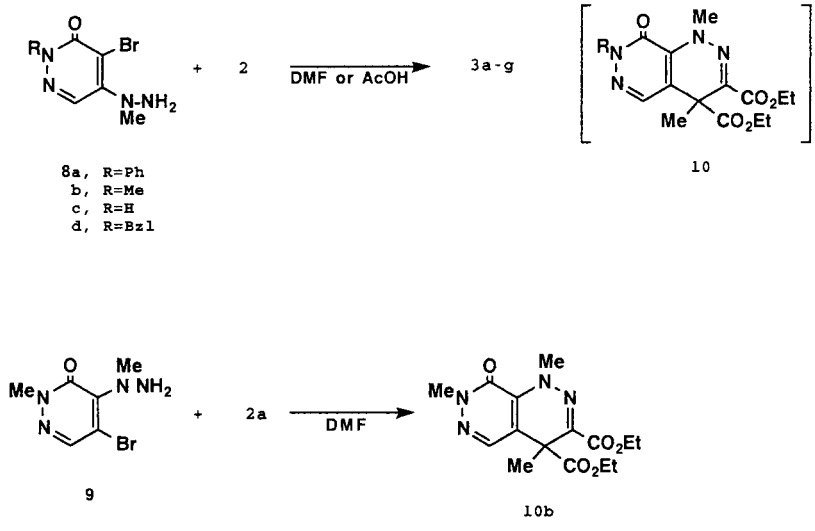
Analogous heterocyclization between 1,4-dihydropyridazinopyridazines and other tricyclic compounds is currently being under investigation.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO IRA-1 grating ir spectrometer. The ^{1}H-nmr spectra were determined with a HITACHI R-600 spectrometer and the ^{13}C-nmr spectra were measured with a JEOL JNM-GX 400 spectrometer using tetramethylsilan as an internal standard. Mass spectra were measured with a JEOL JMS-DX 303 mass spectrometer.

5-(1-Methylhydrazino)pyridazin-3(2*H*)-one (**1**), 4-Bromo-5-(1-methylhydrazino)pyridazin-3(2*H*)-one (**8**) and 5-Bromo-4-(1-methylhydrazino)pyridazin-3(2*H*)-one (**9**).

Scheme 3



These compounds were prepared according to literature procedures [7,9].

General Procedure for the Preparation of 4,6-Dihydropyridazino-[4,5-*c*]pyridazin-5(1*H*)-one (**3**) and Pyrrolo[2,3-*d*]pyridazin-4(5*H*)-one (**4**) from Compound **1** and α-Keto Diester **2**.

To a stirred solution of **1a-d** (10 mmoles) in acetic acid (20 ml) was added dropwise **2a** (2.26 ml, 12 mmoles). The mixture was stirred for 12-24 hours at room temperature until the material **1a-d** had disappeared (tlc) and then heated at 100° for additional 24-48 hours. After evaporation of acetic acid under reduced pressure, the residue was purified by column chromatography on silica gel with benzene/ethyl acetate (2/1) as eluent to give **3a-d** and **4a-d**. Analytical samples were purified by recrystallization from the appropriate solvent.

For the preparation of **3e-g**, to a solution of **1a-c** (10 mmoles) in acetic acid (20 ml), sodium salt (2.52 g, 12 mmoles) of **2b** was added. After being stirred for 12-24 hours at room temperature, the mixture was heated at 50° for additional 24-48 hours. The solvent was evaporated under reduced pressure, and the residue was treated with water (200 ml) and then extracted with dichloromethane (3 x 100 ml). The extract was dried over anhydrous magnesium sulfate and evaporated to dryness, and a small amount of ethanol was added to the resulting oil. The separated crystals were collected by filtration and recrystallized from the appropriate solvent to give **3e-g**. The results are summarized in Table 1.

General Procedure for the Preparation of **3** from **8** and **2**.

Compound **2a** (2.26 ml, 12 mmoles) was added dropwise to a stirred solution of **8a-d** (10 mmoles) in dimethylformamide (20 ml) at room temperature. After being stirred for 24-48 hours, the reaction mixture was poured into water (200 ml) and extracted with dichloromethane (3 x 100 ml). The extract was dried over anhydrous magnesium sulfate and evaporated to dryness, and the residue was chromatographed on silica gel with benzene/ethyl acetate (6/1) as eluent to give **3a-d**.

For preparation of **3e-g**, to a solution of **8a-c** (10 mmoles) in acetic acid (20 ml), sodium salt (2.52 g, 12 mmoles) of **2b** was added. After being stirred for 24-48 hours at room temperature, the reaction mixture was poured into water (200 ml) and then extracted with dichloromethane (3 x 100 ml), and the extract was dried over anhydrous magnesium sulfate. After removal of dichloromethane, a small amount of ethanol was added to the residue and the resulting crystals were collected by filtration and recrystallized from the appropriate solvent to give **3e-g** (see Table 1 for the yield of **3a-g**).

4,7-Dihydropyridazino[4,5-*c*]pyridazin-8(1*H*)-one (**10b**).

Compound **9** (2.33 g, 10 mmoles) was allowed to react with **2a** (2.26 ml, 12 mmoles) in the same manner as described for the preparation of **3a-d** from **8** and **2a** to afford **10b** (1.70 g, 51%), mp 70-71° (ethanol-*n*-hexane); ir (potassium bromide): ν max cm^{-1} 1740, 1715, 1650 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 8 Hz, CH_3), 1.34 (t, 3H, J = 8 Hz, CH_3), 1.54 (s, 3H, CH_3), 3.70 (s, 3H, NCH_3), 4.07 (s, 3H, NCH_3), 4.25 (q, 2H, J = 8 Hz, CH_2), 4.32 (q, 2H, J = 8 Hz, CH_2), 7.38 (s, 1H, CH=); ms: m/z 336 (M^+).

Anal. Calcd. for $C_{15}H_{20}N_4O_5$: C, 53.57; H, 5.99; N, 16.66. Found: C, 53.82; H, 5.89; N, 16.79.

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