A NEW SYNTHETIC APPROACH TO FUSED 1,4-DIHYDROPYRIDAZINES

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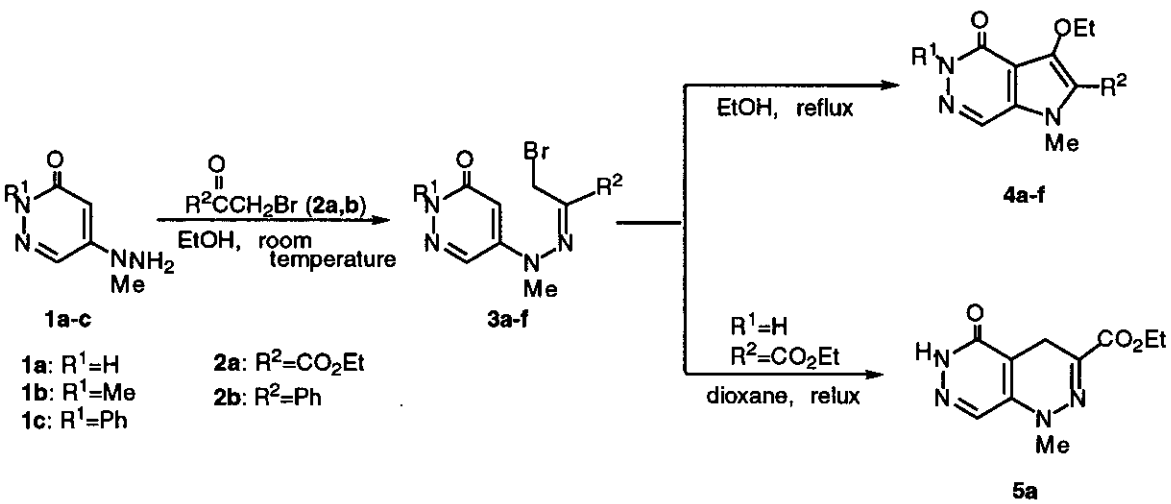
Abstract - Cyclization of the halohydrazones (**3**) prepared by the reaction of 5-hydrazinopyridazinones (**1**) with ethyl bromopyruvate (**2a**) and phenacyl bromide (**2b**) in EtOH produced pyrrolo[2,3-*d*]pyridazinones (**4**). On the other hand, heating of ethyl bromopyruvate pyridazinylhydrazone (**3a**) in dioxane afforded 1,4-dihydropyridazino[4,5-*c*]pyridazine (**5a**) in low yield. Compounds (**5**) were also obtained in good yields by heating the dihalohydrazones (**7**), which were synthesized from 4-chloro-5-hydrazinopyridazinones (**6**) and **2a,b** in the presence of Zn(Cu). Heating of furylhydrazone (**9**) under similar conditions to those of the cyclization of **7** provided 3,6-dihydrofuro[3,4-*c*]pyridazine (**10**).

There have been many reports on a fused pyridazine ring so far because of showing herbicidal,[1] antiviral,[2] antiulcer,[3] anxiolytic[4] and antibacterial[5] activities. Recently, Chiou reported that a certain 1,4-dihydropyridazino[4,5-*c*]pyridazinones showed ocular anti-inflammatory activity as an interleukin-1 blocker.[6]

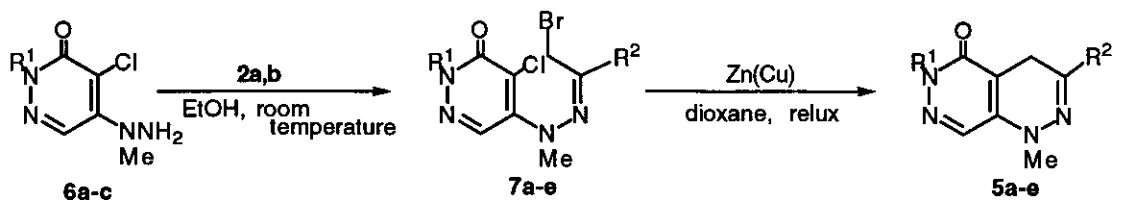
As a continuation of our previous work on the synthesis of fused 1,4-dihydropyridazines from enhydrazines and α-keto esters,[7,8] we examined the preparation of fused 1,4-dihydropyridazines by the reactions of 5-hydrazinopyridazinones (**1**), 4-chloro-5-hydrazinopyridazinones (**6**) and 3-chloro-4-hydrazinofuranone (**8**) with ethyl bromopyruvate (**2a**) and phenacyl bromide (**2b**).

Yoneda[9] has reported the cyclization of hydrazinopyrimidine containing an enhydrazine moiety with phenacyl bromide to 1,4-dihydropyridazines. We applied this method to the cyclization of **1** with β-halo α-

keto ester (**2a**), 2-halo ketone (**2b**) under similar conditions. However when the halohydrazones (**3**) were refluxed in EtOH, pyrrolo[2,3-*d*]pyridazines (**4**) were produced as a sole product in low yields without formation of the expected 1,4-dihydropyridazino[4,5-*c*]pyridazines (**5**). Probably, this result is attributed to the ethoxylation of the bromomethyl group followed by the [3,3]sigmatropic reaction with cleavage of the N-N bond of **3** rather than nucleophilic attack of C-4 of the pyridazinone ring to the bromomethyl carbon of **3** because of the weak nucleophilicity of the C-4 (Scheme 1). The resulting products (**4**) were purified by a silica gel column chromatography. The spectral and elemental data are shown in Tables 1 and 2. In the ^{1}H-nmr spectra, the methine signal of C-4 on the pyridazinone ring was disappeared, and methyl and methylene signals assignable to the ethoxyl group newly appeared at δ 1.20-1.43 and 4.29-4.56, respectively. The mass spectral data indicated the corresponding molecular ion peak and elemental analyses also supported the assigned structure for the product.



Scheme 1



Scheme 2

Table 1: Preparative Data of Halohydrazones (**3**) and 2,5-Disubstituted 3-Ethoxypyrrolo[2,3-*d*]-pyridazin-4(5*H*)-ones (**4**)

Compd No	R^1	R^2	Yield(%)	Mp(℃) (solvent)	*Formula*	Analysis (%) Calcd (Found) C H N
3a	H	CO_2Et	84	179-181 (dioxane)	$C_{10}H_{13}N_4O_3Br$	37.87 4.13 17.67 (38.48)(4.17)(17.36)
3b	Me	CO_2Et	57	160-162 (CH_2Cl_2-isopropyl ether)	$C_{11}H_{15}N_4O_3Br$	39.90 4.57 16.92 (39.77)(4.55)(16.70)
3c	Ph	CO_2Et	84	103-106 (CH_2Cl_2-isopropyl ether)	$C_{16}H_{17}N_4O_3Br$	48.87 4.36 14.25 (49.07)(4.24)(14.33)
3d	H	Ph	81	250-252 (EtOH)	$C_{13}H_{13}N_4OBr$	48.62 4.08 17.44 (49.14)(4.01)(17.81)
3e	Me	Ph	39	135-137 (EtOH)	$C_{14}H_{15}N_4OBr$	50.16 4.51 16.71 (50.66)(4.44)(16.96)
3f	Ph	Ph	56	135-137 (EtOH)	$C_{19}H_{17}N_4OBr$	57.44 4.31 14.10 (57.21)(4.52)(13.67)
4a	H	CO_2Et	14	220-222 (EtOH)	$C_{12}H_{15}N_3O_4$	54.33 5.70 15.84 (54.44)(5.69)(15.92)
4b	Me	CO_2Et	23	125-127 (CH_2Cl_2-isopropyl ether)	$C_{13}H_{17}N_3O_4$	55.91 6.13 15.05 (55.85)(6.28)(14.72)
4c	Ph	CO_2Et	19	115-116 (CH_2Cl_2-isopropyl ether)	$C_{18}H_{19}N_3O_4$	63.33 5.61 12.31 (63.09)(5.60)(12.22)
4d	H	Ph	19	249-251 (EtOH)	$C_{15}H_{15}N_3O_2$	66.90 5.61 15.60 (67.37)(5.68)(15.75)
4e	Me	Ph	24	94-95 (CH_2Cl_2-isopropyl ether)	$C_{16}H_{17}N_3O_2$	67.83 6.05 14.83 (67.91)(6.00)(14.79)
4f	Ph	Ph	29	205-207 (CH_2Cl_2-isopropyl ether)	$C_{21}H_{19}N_3O_2$	73.03 5.54 12.17 (73.09)(5.49)(12.31)

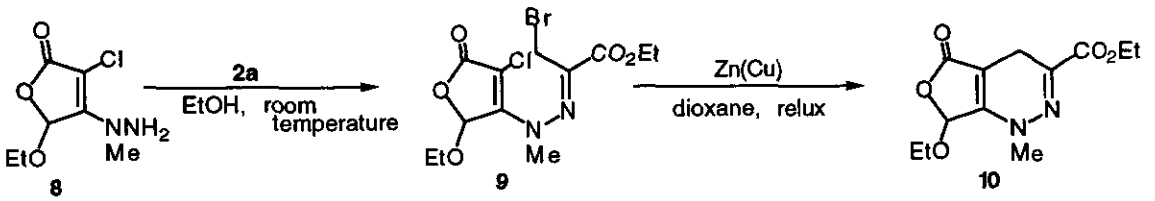
On the other hand, the halohydrazones (**3a**) when heated at 80°C in dioxane instead of EtOH provided 1,4-dihydropyridazino[4,5-*c*]pyridazinone (**5a**) in 7% yield (Scheme 1). The structure of **5a** was assigned on the basis of the spectral data and elemental analysis data. The ir spectrum showed the ester carbonyl absorption at 1705 cm^{-1} and the ^{1}H-nmr spectrum exhibited the singlet signal of the methylene group at δ 3.48. The mass spectral datum and elemental analysis also supported the structural assignment of the product as **5a**.

Next, we tried cyclization to 1,4-dihydropyridazine through the Wurtz reaction in order to prepare **5**

Table 2: Spectral Data of Halohydrazones (**3**) and 2,5-Disubstituted 3-Ethoxypyrrolo[2,3-*d*]-pyridazin-4(5*H*)-ones (**4**)

Compd No	Ir(cm^{-1}) (C=O)	Ms (M^+) m/z	^{1}H-Nmr (solvent) δ, *J*(Hz)
3a	1710 1660	316 318	(DMSO-d_6) 1.29 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.8), 3.73 (3H, s, NCH_3), 4.28 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.8), 4.61 (2H, s, CH_2), 6.37 (1H, d, CH=, *J*=2.4), 8.24 (1H, d, CH=, *J*=2.4), 12.71 (1H, br, NH)
3b	1700 1650	330 332	($CDCl_3$) 1.31(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.65 (3H, s, NCH_3), 3.68 (3H, s, NCH_3), 4.28 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 4.35 (2H, s, CH_2), 6.19(1H, d, CH=, *J*=2.4), 8.24 (1H, d, CH=, *J*=2.4)
3c	1705 1650	392 394	($CDCl_3$) 1.38 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.76 (3H, s, NCH_3), 4.39 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 4.42 (2H, s, CH_2), 6.32 (1H, d, CH=, *J*=3.0), 7.27-7.72 (5H, m, Ph), 8.52 (1H, d, CH=, *J*=3.0)
3d	1640	320 322	(DMSO-d_6) 3.30 (3H, s, NCH_3), 4.68 (2H, s, CH_2), 5.77 (1H, d, CH=, *J*= 2.4), 7.49-8.07 (6H, m, Ph and CH=), 12.42 (1H, br, NH)
3e	1630	334 336	($CDCl_3$) 3.32 (3H, s, NCH_3), 3.73 (3H, s, NCH_3), 4.36 (2H, s, CH_2), 6.04 (1H, s, CH=), 7.34-8.04 (6H, m, Ph and CH=)
3f	1640	396 398	($CDCl_3$) 2.81 (3H, s, NCH_3), 4.42 (2H, s, CH_2), 6.05 (1H, d, CH=, *J*=3.0), 7.26-7.74 (10H, m, Ph x 2), 8.37 (1H, d, CH=, *J*=3.0)
4a	1700 1670	265	($CDCl_3$) 1.28 (3H, t, $OCH_2C\underline{H}_3$, *J*=6.6), 1.33 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.91 (3H, s, NCH_3), 4.13-4.48 (4H, m, $OC\underline{H}_2CH_3$ x 2), 8.39 (1H, s, CH=), 12.33 (1H, br, NH)
4b	1705 1660	279	($CDCl_3$) 1.41 (6H, t, $OCH_2C\underline{H}_3$ x 2, *J*=7.2), 3.80 (3H, s, NCH_3), 3.99 (3H, s, NCH_3), 4.39 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 4.42 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 7.99 (1H, s, CH=)
4c	1700 1670	341	($CDCl_3$) 1.40 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 1.43 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 4.04 (3H, s, NCH_3), 4.42 (4H, q, $OC\underline{H}_2CH_3$ x 2, *J*= 7.2), 7.25-7.62 (5H, m Ph), 8.16 (1H, s, CH=)
4d	1640	269	($CDCl_3$) 1.14 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.64 (3H, s, NCH_3), 4.56 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 7.04-7.79 (5H, m, Ph), 8.00 (1H, s, CH=), 10.78 (1H, br, NH)
4e	1640	283	($CDCl_3$) 1.21 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.67 (3H, s, NCH_3), 3.82 (3H, s, NCH_3), 4.29 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 7.25-7.29 (5H, m, Ph), 7.98 (1H, s, CH=)
4f	1650	345	($CDCl_3$) 1.20 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.72 (3H, s, NCH_3), 4.29 (2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 7.22-8.07 (10H, m, Ph x 2), 8.14 (1H, s, CH=)

selectively in good yield. Dihalohydrazones (**7**) were synthesized in 44-92% yields by the reaction of 4-chloro-5-hydrazinopyridazinones (**6**) with β-halo α-keto ester (**2a**) and 2-halo ketone (**2b**) under similar conditions to those in the preparation of halohydrazones (**3**), and the compounds (**7a-d**) were successfully converted to fused 1,4-dihydropyridazines (**5a-d**) in 54-82% yields by heating in dioxane in the presence of Zn(Cu) (Scheme 2). However, compound (**5e**) could not be formed by refluxing **7e** in dioxane and was provided in low yield by heating in diglyme. The low yield of **5e** is supposed to be due to the lower reactivity of the bromomethyl carbon of **7e** than that of **7a-d** because of the conjugation between the imino group next to the bromomethyl carbon of **7e** and the phenyl group. The structure of **5a-e** was determined



Scheme 3

Table 3: Preparative Data of Dihalohydrazones (**7**) and 6-Substituted 4,6-Dihydropyridazino[4,5-*c*]-pyridazin-5(1*H*)-ones (**5**)

Compd No	R^1	R^2	Yield(%)	Mp(℃) (solvent)	*Formula*	Analysis (%) *Calcd (Found)* C H N
7a	H	CO_2Et	92	118-119 (EtOH)	$C_{10}H_{12}N_4O_3BrCl$	34.18 3.44 15.94 (34.61)(3.43)(16.10)
7b	Me	CO_2Et	44	62-64 (CH_2Cl_2-isopropyl ether)	$C_{11}H_{14}N_4O_3BrCl$	36.14 3.86 15.32 (36.22)(3.94)(15.39)
7c	Ph	CO_2Et	69	139-141 (EtOH)	$C_{16}H_{16}N_4O_3BrCl$	44.93 3.77 13.10 (44.88)(3.69)(12.96)
7d	Bn	CO_2Et	53	100-102 (CH_2Cl_2-isopropyl ether)	$C_{17}H_{18}N_4O_3BrCl$	46.23 4.11 12.68 (46.50)(4.09)(12.72)
7e	H	Ph	89	147-149 (CH_2Cl_2-isopropyl ether)	$C_{13}H_{12}N_4OBrCl$	43.91 3.40 15.75 (43.82)(3.28)(15.68)
5a	H	CO_2Et	82	221-223 (decomp.) (AcOEt)	$C_{10}H_{12}N_4O_3$	50.84 5.12 23.72 (50.45)(5.06)(23.28)
5b	Me	CO_2Et	68	245-250 (decomp.) (AcOEt)	$C_{11}H_{14}N_4O_3$	52.79 5.64 22.39 (53.05)(5.54)(22.68)
5c	Ph	CO_2Et	79	180-182 (AcOEt)	$C_{16}H_{16}N_4O_3$	61.53 5.16 17.94 (61.25)(5.19)(17.78)
5d	Bn	CO_2Et	54	143-145 (CH_2Cl_2-isopropyl ether)	$C_{17}H_{18}N_4O_3$	62.57 5.56 17.17 (62.49)(5.54)(17.15)
5e	H	Ph	10	248-249 (EtOH)	$C_{13}H_{12}N_4O$	64.99 5.03 23.32 (64.93)(5.14)(23.19)

to be 1,4-dihydropyridazino[4,5-*c*]pyridazinone by the spectral and satisfactory elemental analysis data. The results are shown in Tables 3 and 4.

Furthermore, as an extension of the cyclization to 1,4-dihydropyridazine by use of Zn(Cu), heating of furyldihalohydrazone (**9**) formed from hydrazinofuranone (**8**) and **2a** under similar conditions to those in the cyclization of dihalohydrazones (**7**) gave 3,6-dihydrofuro[3,4-*c*]pyridazine (**10**) in 25% yield (Scheme

3). The ir spectrum of **10** showed two carbonyl absorptions of the lactone ring and the ester group at 1745 cm^{-1} and 1700 cm^{-1}, respectively, and the ^{1}H-nmr spectrum exhibited a singlet signal at δ 3.38 assignable to methylene protons of the 1,4-dihydropyridazine ring. The assigned structure (**10**) was also supported by the elemental analysis and mass spectral datum.

Another novel synthetic approach to 1,4-dihydropyridazine from enhydrazine compounds is currently under investigation.

Table 4: Spectral Data of Dihalohydrazones (**7**) and 6-Substituted 4,6-Dihydropyridazino[4,5-*c*]-pyridazin-5(1*H*)-ones (**5**)

Compd No	Ir(cm^{-1}) (C=O)	Ms (M^+) m/z	^{1}H-Nmr (solvent) δ, *J* (Hz)
7a	1720 1645	350, 352 354	(DMSO-d_6) 1.27(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.73(3H, s, NCH_3), 4.22(2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 4.55(2H, s, CH_2), 8.10(1H, s, CH=), 13.32(1H, br, NH)
7b	1710 1650	364, 366 368	($CDCl_3$) 1.37(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.37(3H, s, NCH_3), 3.80(3H, s, NCH_3), 4.38(2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 4.40(2H, s, CH_2), 8.21(1H, s, CH=)
7c	1700 1660	426, 428 430	($CDCl_3$) 1.37(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.82(3H, s, NCH_3), 4.35(2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 4.40(2H, s, CH_2), 7.10-7.87 (5H, m, Ph), 8.40(1H, s, CH=)
7d	1710 1650	440, 442 444	($CDCl_3$) 1.36(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.74(3H, s, NCH_3), 4.34(2H, s, CH_2), 4.37(2H, q, $OC\underline{H}_2CH_3$, *J*=7.2), 5.34(2H, s, CH_2), 7.10-7.60(5H, m, Ph), 8.25(1H, s, CH=)
7e	1660	354, 356 358	(DMSO-d_6) 3.40(3H, s, NCH_3), 4.38(2H, s, CH_2), 7.27-8.72(6H, m, Ph and CH=), 11.78(1H, br,NH)
5a	1705 1645	236	(DMSO-d_6) 1.25(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.32(3H, s, NCH_3), 3.48(2H, s, CH_2), 4.22(2H, q, $OC\underline{H}_2CH_3$, *J*=7.2), 7.88(1H, s, CH=), 12.83(1H, br, NH)
5b	1700 1645	250	(DMSO-d_6) 1.36(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.54(5H, s, NCH_3 and CH_2), 3.75(3H, s, NCH_3), 4.34(2H, q, $OC\underline{H}_2CH_3$, *J*=7.2), 7.56(1H, s, CH=)
5c	1705 1650	312	(DMSO-d_6) 1.36(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.58(5H, s, NCH_3 and CH_2), 4.36(2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 7.23-8.10(5H, m, Ph), 7.72(1H, s, CH=)
5d	1700 1640	326	($CDCl_3$) 1.33(3H, t, $OCH_2C\underline{H}_3$, *J*=7.2), 3.52(5H, s, NCH_3 and CH_2), 4.32(2H, q, $OC\underline{H}_2CH_3$, *J*= 7.2), 5.29(2H, s, CH_2), 7.18-7.64(5H, m, Ph), 7.58(1H, s, CH=)
5e	1635	240	(DMSO-d_6) 3.57(3H, s, NCH_3), 3.68(2H, s, CH_2), 7.30-8.12(6H, m, Ph and CH=), 11.85(1H, br, NH)

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 measured with a HITACHI R-600 spectrophotometer using tetramethylsilane as an internal standard. The

mass spectra were obtained with a JEOL JMS-DX 303 mass spectrometer.

2-Substituted 5-(1-Methylhydrazino)pyridazin-3(2*H*)-ones (1) ----- These compounds were prepared by the reported method.[10]

General Procedure for the Preparation of Halohydrazones (3) from 1 and β-Halo α-Keto Ester (2a) and 2-Halo Ketone (2b) ---- To a solution of **1** (10 mmol) in EtOH (10 mml) was added **2** (12 mmol) and the mixture was stirred for 24 h at room temperature. Precipitated solid was collected and recrystallized from appropriate solvents to give **3** (see Tables 1 and 2 for **3**).

General Procedure for the Preparation of 2,5-Disubstituted 3-Ethoxypyrrolo[2,3-*d*]pyridazin-4(5*H*)-ones (4) from 3 ---- A solution of **3** (5 mmol) in EtOH (30 ml) was refluxed for 18 h. After evaporation of EtOH, $CHCl_3$ (50 ml) was added to the residue and the insoluble solid was filtered off. The filtrate was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography ($CHCl_3$:MeOH=50:1) to give **4**. Analytical samples were purified by recrystallization from appropriate solvents (see Tables 1 and 2 for **4**).

The Preparation of 4-Ethoxycarbonyl-4,6-dihydropyridazino[4,5-*c*]pyridazin-4(5*H*)-one (5a) from 3a ---- A solution of **3a** (5 mmol, 1.59 g) in dioxane (20 ml) was heated at 80°C for 12h. Precipitated solid was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by a silica gel column chromatography ($CHCl_3$:MeOH=20:1) to give **5a** (0.10 g, 7%). The analytical sample was purified by recrystallization from ethyl acetate (see Tables 3 and 4 for analytical data of **5a**).

General Procedure for the Preparation of Dihalohydrazones (7) from 4-Chloro-5-(1-methylhydrazino)pyridazin-3(2*H*)-ones (6) and β-Halo α-Keto Ester (2a) and 2-Halo Ketone (2b) ---- To a solution of **6**[10] (10 mmol) in EtOH (10 ml) was added **2** (12 mmol) and the mixture was stirred for 18h at room temperature. Precipitated solid was filtered and recrystallized from appropriate solvents to give **7** (see Tables 3 and 4 for **7**).

General Procedure for the Preparation of 6-Substituted 4,6-Dihydropyridazino[4,5-c]pyridazin-5(1*H*)-ones (5) from Dihalohydrazones (7) ---- A suspension of **7** (5 mmol) in dioxane (30 ml) (diglyme for **7e**) containing Zn(Cu) (6 mmol, 0.39 g) was refluxed for 18h. Unchanged Zn(Cu) was filtered off and the filtrate was condensed. To the residue was added 1N HCl (15 ml) and the resulting precipitate was collected to give **7a-c**. In the case of **7d** and **7e**, the residue was purified by a

silica gel column chromatography ($CHCl_3$ for **7d**; benzene : ethyl acetate=1 : 2 for **7e**) to give **7d,e**. Analytical samples were purified by recrystallization from appropriate solvents (see Tables 3 and 4 for **7**).

3,4-Dichloro-5-ethoxy-2-furanone[11] ---- Mucochloric acid (100 mmol, 16.90 g) was refluxed for 2 days in EtOH (150 ml) containing concentrated sulfuric acid (5 drops). After removal of EtOH, CH_2Cl_2 (150 ml) was added to the residue and then the mixture was washed with saturated aqueous $NaHCO_3$ (30 ml x 2) and saturated brine (30 ml x 2). The organic layer was dried over anhydrous $MgSO_4$, evaporated to dryness and the resulting crude product was purified by distillation to give 3,4-dichloro-5-ethoxy-2-furanone. bp 96 °C / 7 mmHg; Yield 13.0 g (66%); ir (film) ν 1790, 1640 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$, TMS) δ 1.06 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 3.61 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 5.58 (1H, s, CH); ms (EI): m/z 196 (M^+).

3-Chloro-5-ethoxy-4-(1-methylhydrazino)-2-furanone (8) ---- To a solution of 3,4-dichloro-5-ethoxy-2-furanone (100 mmol, 19.70 g) in benzene (40 ml) was added methylhydrazine (180 mmol, 9.58 ml). After being stirred for 2.5 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (50 ml) and saturated brine (50 ml), evaporated to dryness and then the residue was purified by a silica gel column chromatography ($CHCl_3$) to give **8**. mp 78-79 °C (from CH_2Cl_2 - n-hexane); Yield 10.90 g (53%); ir (KBr) ν 3320, 3230(NH), 1740, 1670(C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6, TMS) δ 1.18 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 3.32 (3H, s, NCH_3), 3.73 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 5.11 (2H, br, NH_2), 5.97 (1H, s, CH); ms(EI): m/z 206 (M^+); *Anal.* Calcd for $C_7H_{11}N_2O_3Cl$: C, 40.69; H, 5.37; N, 13.56. Found: C, 40.51; H, 5.37; N, 13.34.

3-(4-Chloro-2,5-dihydro-2-ethoxy-5-oxofuranyl)hydrazone (9) ---- To a solution of **8** (10 mmol, 2.07 g) in EtOH (10 ml) was added ethyl bromopyruvate (**2a**) (12 mmol, 1.51 ml) and the mixture was stirred for 10 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography ($CHCl_3$) to give **9**. mp 57 °C (from CH_2Cl_2 - n-hexane); Yield 2.30 g (68%); ir (KBr) ν 1760, 1710(C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$, TMS) δ 1.35 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 1.39 (3H, t, $OCH_2C\underline{H}_3$, *J*=6.6 Hz), 3.96(3H, s, NCH_3), 4.16-4.84 (4H, m, $OC\underline{H}_2CH_3$ x 2), 4.40 (2H, s, CH_2), 6.04 (1H, s, CH); ms(EI): m/z 382, 384, 386 (M^+); *Anal.* Calcd for $C_{12}H_{16}N_2O_5BrCl$: C, 37.57; H, 4.20; N, 7.30. Found: C, 37.89; H, 4.30; N, 7.45.

2-Ethoxy-5-ethoxycarbonyl-3-methyl-2,3,6,7-tetrahydrofuro[3,4-*c*]pyridazin-7-one (10) ---- A suspended solution of furanylhydrazone (**9**) (4 mmol, 1.53 g) in dioxane (15 ml) containing Zn(Cu)

(5.6 mmol, 0.37 g) was refluxed for 6 h. Unchanged Zn(Cu) was filtered off and the filtrate was evaporated *in vacuo*. The residue was purified by a silica gel column chromatography ($CHCl_3$: MeOH = 30 : 1) to give **10**. mp 75-76 °C (from CH_2Cl_2 - isopropyl ether); Yield 0.26 g (25 %); ir (KBr) ν 1745, 1700 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$, TMS) δ 1.31 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.35 (3H, t, OCH_2CH_3, *J*=6.6 Hz), 3.38 (2H, s, CH_2), 3.44 (3H, s, NCH_3), 3.71-3.95 (2H, m, OCH_2CH_3), 4.33 (2H, q, OCH_2CH_3, *J*=6.6 Hz), 5.85 (1H, s, CH). ms(EI): m/z 268 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.70; H, 5.94; N, 10.36.

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