New N–N Bond Cleavage of Fused Chloropyridazines with Ynamines[1]

Etsuo OISHI,[b] Ken-ichi IWAMOTO,*[,a] Tomomi OKADA,[b] Sumiko SUZUKI,[a] Ken-ichi TANJI,[c]
Akira MIYASHITA,[a] and Takeo HIGASHINO[a]

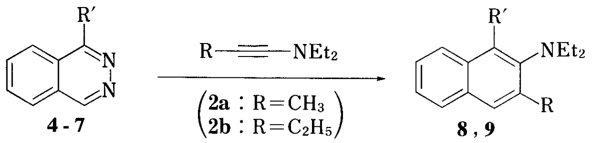
School of Pharmaceutical Sciences,[a] Division of Environmental Health Sciences, Graduate School of Nutritional & Environmental Sciences,[b] and School of Food and Nutritional Sciences,[c] University of Shizuoka, 52–1 Yada, Shizuoka 422, Japan. Received March 30, 1994; accepted May 27, 1994

1-Chlorophthalazine (1) reacts with a 2-fold molar excess of ynamines 2a, b to give penta-substituted pyridine derivatives 3a ,b by nitrogen-nitrogen bond cleavage of the pyridazine ring with release of hydrogen chloride. Similarly, other fused pyridazines having a chloro substituent α to nitrogen in the pyridazine ring, *i.e.*, pyrido[3,4-*d*]- (10a), pyrido[2,3-*d*]- (10b), thiazolo[4,5-*d*]- (10c, d), furo[2,3-*d*]- (10e) and pyrrolo[2,3-*d*]- (10f, g) pyridazine derivatives, gave the corresponding penta-substituted pyridines 11a—11k.

Keywords phthalazine; bond cleavage; ynamine; condensed pyridazine

It has been reported by us that electron-poor condensed pyridazines react with electron-rich enamines and ynamines in an inverse-electron-demand Diels–Alder reaction, resulting in ring transformation into the corresponding benzoheteroarenes through the [4+2] cycloadduct. For example, 1-phthalazinecarbonitrile (**4**) reacted with ynamines to give naphthalene derivatives *via* [4+2] cycloaddition followed by elimination of nitrogen.[2] It has also been reported by us that the reaction of condensed pyridazines with ynamines gives condensed diazocines through the [2+2] cycloadducts.[3]

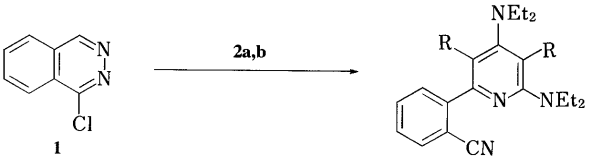
During the course of our investigation on the reactivities of condensed pyridazines with ynamines, we found that an unusual reaction occurred between 1-chlorophthalazine (**1**) and 2 eq of ynamines **2a, b** to give penta-substituted



4-7 **8, 9**

starting material	R'	R	product (% yield)
4	CN	CH_3	**8** (90)[1]
5	Ts	CH_3	**9a** (57)
5	Ts	CH_3CH_2	**9b** (31)
6	OCH_3	CH_3	--- (0)
7	SCH_3	CH_3	--- (0)

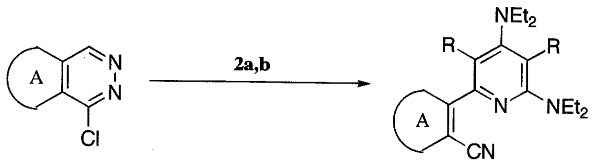
Chart 1



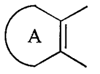
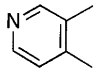
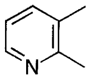
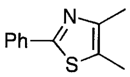
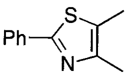
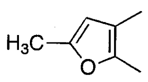
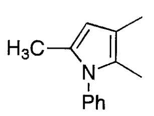
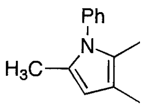
1 **3a,b**

		yield
R=CH_3	**3a**	68%
R=CH_3CH_2	**3b**	35%

Chart 2



10a—g **11a—k**

starting material		R	product (% yield)
10a		CH_3	**11a** (42)[a]
10b		CH_3	**11b** (10)
10c		CH_3 CH_3CH_2	**11c** (33)[a] **11d** (18)[a]
10d		CH_3 CH_3CH_2	**11e** (39)[a] **11f** (33)[a]
10e		CH_3 CH_3CH_2	**11g** (44) **11h** (48)
10f		CH_3 CH_3CH_2	**11i** (54)[a] **11j** (48)[a]
10g		CH_3	**11k** (36)

a) Purified as the picrate.

Chart 3

pyridines with nitrogen–nitrogen (N–N) bond cleavage.[1] To our knowledge, no prior example of N–N bond cleavage in the phthalazine ring is available. In the present paper, we show that various condensed pyridazines having a halogen substituent alpha to nitrogen in the pyridazine ring react with a 2-fold molar excess of ynamines, resulting in N–N bond cleavage to afford penta-substituted pyridines.

We examined the scope of the reaction of fused pyridazines with ynamines. 1-Tosylphthalazine (**5**) having an electron-withdrawing substituent underwent an inverse-electron-demand Diels–Alder reaction with **2a, b**, as observed in the case of **4**, to give naphthalene derivatives **9a, b**. In contrast, 1-substituted phthalazines having an electron-donating substituent such as 1-methoxyphthalazine (**6**) and 1-methylthiophthalazine (**7**) did not react with ynamines (Chart 1).

But, when a solution of 1-chlorophthalazine (**1**) and a 2-fold molar excess of ynamines, **2a** and **2b**, in dioxane was heated at 80 °C for 10 min, N–N bond cleavage proceeded to give the penta-substituted pyridines **3a** and **3b** (Chart 2), respectively.

In view of the above results, we expected that other condensed pyridazines having a halogen substituent alpha to nitrogen in a pyridazine moiety would undergo N–N bond cleavage reaction with ynamines. In this investigation, pyrido[3,4-*d*]- (**10a**), pyrido[2,3-*d*]- (**10b**), thiazolo[4,5-*d*]- (**10c, 10d**), furo[2,3-*d*]- (**10e**), and pyrrolo-[2,3-*d*]- (**10f, g**) pyridazine were used. Although the electron-density of the condensed pyridazines **10a**—**g** varies widely, they reacted with the ynamines **2a, b**, undergoing N–N bond cleavage with release of hydrogen chloride to give corresponding penta-substituted pyridines **11a**—**k** (Chart 3).

At first, it was considered that the N–N bond cleavage proceeded *via* condensed diazocines. When the diazocine (**13b**), which was obtained in the reaction of 2-phenyl-7-(*p*-tolylsulfonyl)thiazolo[4,5-*d*]pyridazine (**12**) with 1.0 eq of ynamine **2b**, was further treated with **2b**, however the starting **13b** was recovered (Chart 4).

Moreover, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the N–N bond-cleaved compound, the signals of two CH_3 and two NEt_2 moieties in the pyridine ring were observed in different positions, so it is considered that the substituents exist in unsymmetrical positions in the pyridine. Finally, we determined the structure by X-ray crystallography to be the picrate of **3a** (Fig. 1).

On the basis of the above-mentioned results, a plausible reaction mechanism is presented in Chart 5.

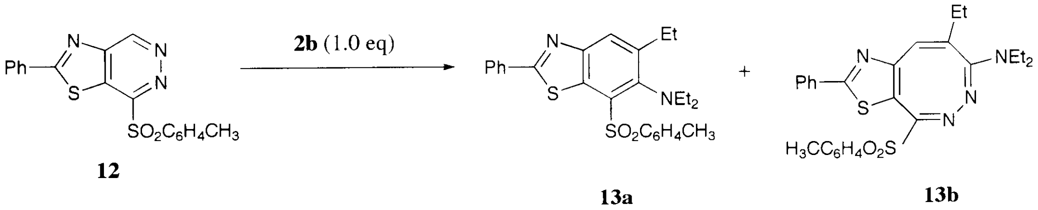


Chart 4

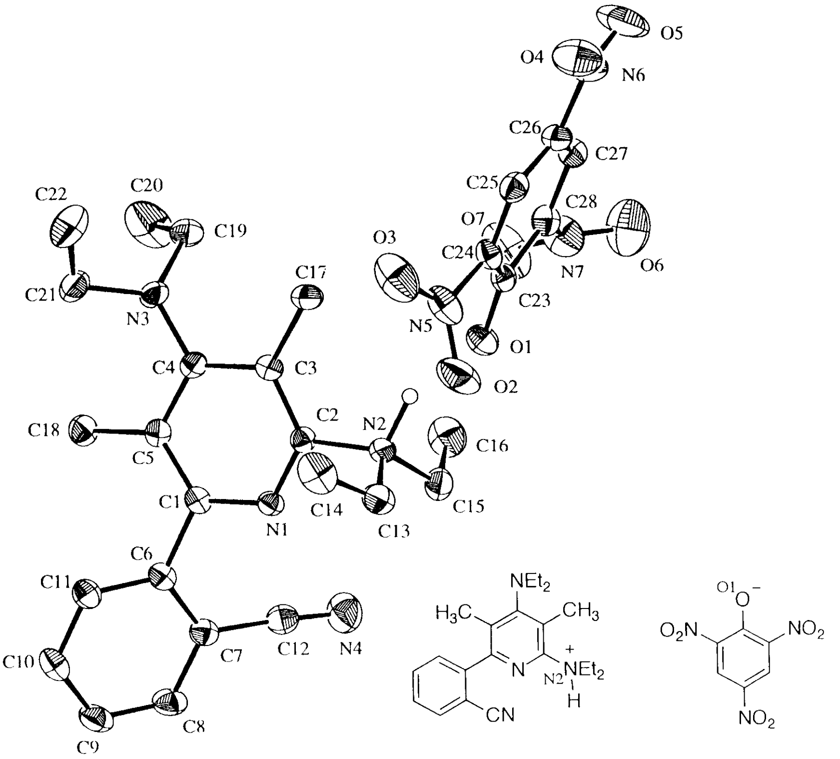


Fig. 1. X-Ray Crystal Structure of **3a** (Picrate)

TABLE I. Final Atomic Coordinates and Equivalent Isotropic Thermal Parameters for Non-hydrogen Atoms of **3a**

Atom	x	y	z	B_{eq}
O(1)	0.2177 (2)	0.3540 (2)	0.9823 (2)	4.49 (5)
O(2)	0.2210 (3)	0.5147 (3)	0.8655 (5)	6.9 (1)
O(2′)	0.299 (2)	0.523 (1)	0.981 (3)	9.9 (6)
O(3)	0.2520 (5)	0.6451 (3)	1.0633 (7)	8.1 (1)
O(3′)	0.173 (2)	0.6450 (10)	0.968 (2)	6.5 (4)
O(4)	−0.0660 (3)	0.7518 (2)	1.3436 (3)	7.77 (8)
O(5)	−0.1095 (3)	0.6365 (3)	1.4278 (4)	8.93 (10)
O(6)	0.0159 (5)	0.2657 (4)	1.1411 (9)	9.6 (2)
O(6′)	0.046 (2)	0.274 (1)	1.251 (2)	8.9 (6)
O(7)	0.1901 (4)	0.2462 (3)	1.1885 (6)	8.8 (1)
O(7′)	0.086 (1)	0.2277 (9)	1.023 (2)	8.3 (4)
N(1)	0.5867 (2)	0.1595 (2)	0.8717 (2)	2.69 (5)
N(2)	0.4044 (2)	0.2403 (2)	0.8708 (2)	3.26 (5)
N(3)	0.6664 (2)	0.2872 (2)	1.3414 (2)	3.76 (6)
N(4)	0.5699 (3)	−0.0922 (2)	0.6876 (4)	6.41 (9)
N(5)	0.2112 (2)	0.5676 (3)	1.0004 (4)	5.11 (8)
N(6)	−0.0574 (3)	0.6619 (3)	1.3506 (3)	5.95 (8)
N(7)	0.0980 (3)	0.2964 (3)	1.1594 (4)	6.21 (10)
C(1)	0.6888 (2)	0.1371 (2)	0.9398 (3)	2.68 (5)
C(2)	0.5142 (2)	0.2201 (2)	0.9591 (3)	2.70 (5)
C(3)	0.5323 (2)	0.2674 (2)	1.1145 (3)	2.84 (6)
C(4)	0.6396 (2)	0.2413 (2)	1.1853 (3)	2.76 (6)
C(5)	0.7187 (2)	0.1728 (2)	1.0970 (3)	2.80 (6)
C(6)	0.7690 (2)	0.0729 (2)	0.8337 (3)	2.81 (6)
C(7)	0.7465 (2)	−0.0175 (2)	0.7213 (3)	3.16 (6)
C(8)	0.8226 (2)	−0.0741 (2)	0.6225 (3)	4.03 (7)
C(9)	0.9175 (2)	−0.0395 (3)	0.6293 (4)	4.33 (7)
C(10)	0.9403 (2)	0.0501 (2)	0.7383 (4)	4.10 (7)
C(11)	0.8666 (2)	0.1057 (2)	0.8406 (3)	3.37 (6)
C(12)	0.6470 (3)	−0.0568 (2)	0.7062 (3)	4.09 (7)
C(13)	0.4087 (2)	0.2956 (3)	0.7508 (3)	4.44 (7)
C(14)	0.4638 (3)	0.3882 (3)	0.8148 (5)	5.9 (1)
C(15)	0.3588 (2)	0.1417 (3)	0.7953 (4)	4.48 (7)
C(16)	0.3489 (3)	0.0884 (3)	0.9076 (5)	5.99 (10)
C(17)	0.4471 (2)	0.3463 (2)	1.2016 (3)	3.92 (7)
C(18)	0.8286 (2)	0.1313 (3)	1.1724 (3)	2.96 (7)
C(19)	0.6132 (3)	0.2662 (3)	1.4533 (3)	4.18 (7)
C(20)	0.6797 (4)	0.1881 (5)	1.5274 (6)	8.5 (1)
C(21)	0.7584 (3)	0.3429 (3)	1.3957 (3)	4.31 (7)
C(22)	0.7264 (3)	0.4536 (3)	1.4826 (5)	6.3 (1)
C(23)	0.1590 (2)	0.4239 (2)	1.0689 (3)	3.28 (6)
C(24)	0.1480 (2)	0.5332 (2)	1.0867 (3)	3.36 (6)
C(25)	0.0810 (2)	0.6093 (2)	1.1775 (3)	3.71 (6)
C(26)	0.0180 (2)	0.5810 (2)	1.2591 (3)	3.90 (7)
C(27)	0.0240 (2)	0.4785 (3)	1.2543 (3)	4.11 (7)
C(28)	0.0933 (2)	0.4038 (2)	1.1636 (3)	3.65 (7)

Initially, the ynamine attacks the 4-position of **1**, and the very reactive ketene-immonium ion **14** is formed (step 1: in this step, 1.0 eq of ynamine **2a** is consumed). Intermediate **14** is neutralized not by the delocalized anion in the pyridazine ring moiety (intramolecular neutralization), but by another molecule of **2a** (intermolecular neutralization) (step 2: in this step, another 1.0 eq of **2a** is consumed). Then it forms a six-membered ring **16** (step 3), and aromatization occurs through N–N bond cleavage to give the penta-substituted pyridine **3a** (step 4). Delocalization of the anion in the pyridazine ring moiety will be influenced by the substituent in the pyridazine ring, and therefore the nucleophilicity is modified. Thus the neutralization pathway of the ketene-immonium ion (whether intra- or intermolecular) is determined. In fact, when 1 eq of the ynamine **2a** was used in the reaction of **1**, this reaction produced **3a** in poor yield (19%). It has been reported that in the synthesis of stabilized cyclobutadienes, in which 2 eq of ynamine participates, the ketene-immonium ion is neutralized with the second ynamine,[4] and this also supports our proposed mechanism.

In conclusion, the reaction pathways for the reaction of condensed pyridazines with electron-rich ynamines can be classified into three types (A—C), as shown in Chart 6. Type C, which we have described here for chloro-substituted condensed pyridazines, is very interesting, and may be general for halogen-substituted condensed pyridazines.

Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a Jasco A-102 diffraction grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer and at 270 MHz on a JEOL instrument, and ^{13}C-NMR spectra were obtained with a JEOL JNM-FX90Q FTNMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, and br = broad. Mass spectra (MS) were recorded on a JEOL JMS D-100 mass spectrometer. Samples were vaporized in a direct inlet system. Unit-cell parameters and intensity data for X-ray crystallography were measured on a Rigaku AFC-5R automatic four-circle diffractometer with graphite-monochromated CuK_{α} radiation at −100 °C. Column chromatography was carried out on SiO_2

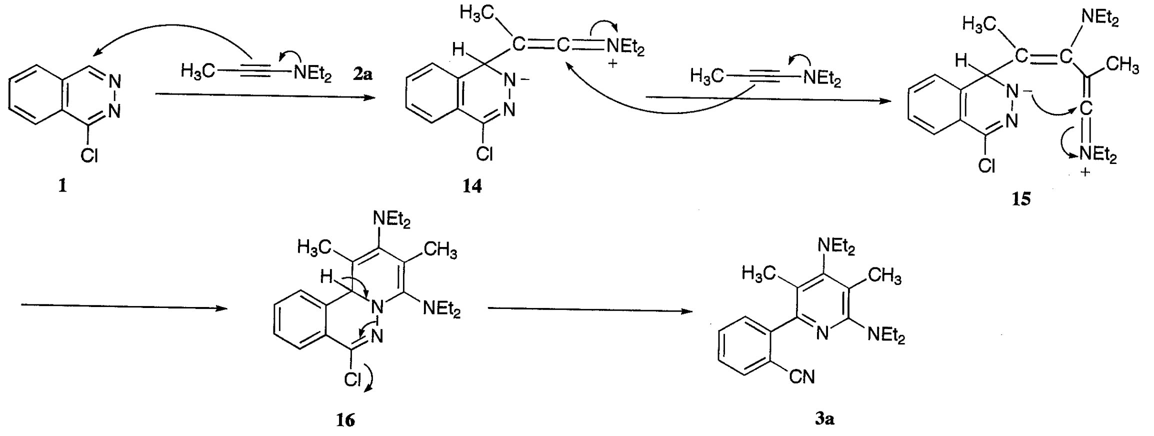


Chart 5

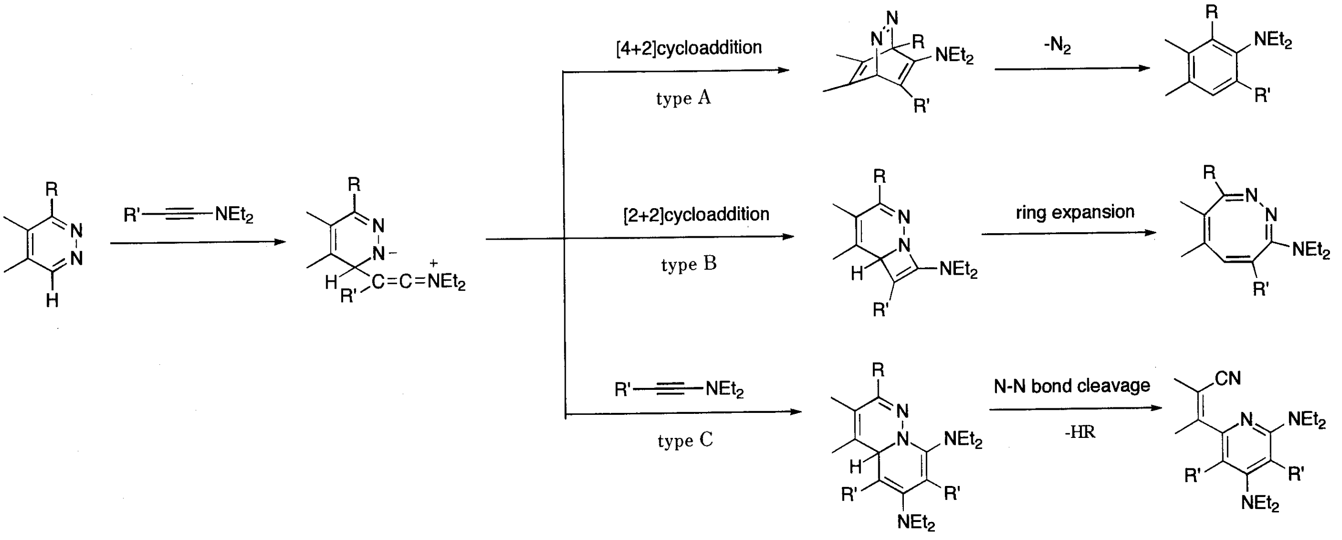


Chart 6

from Merck Co., Ltd. (200 mesh).

Reaction of 1-Chlorophthalazine (1) [5] **with Ynamines (2a, b)**[6] Compound **1** (200 mg, 1.22 mmol) was dissolved in dioxane (2 ml), and to this solution was added **2** (2.1 molar eq). The solution was heated to 80 °C and stirred for 10 min. The reaction mixture was quenched with water and extracted with chloroform. The organic layer was washed with water and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, benzene/chloroform = 10/1) to give **3**.

From the reaction of **1** with *N*,*N*-diethyl-1-propynylamine (**2a**), 4,6-bis(diethylamino)-3,5-dimethylpyridin-2-ylbenzonitrile (**3**) was obtained as pale yellow oil in 68% yield (290 mg) and purified as the picrate, mp 169—171 °C. *Anal.* Calcd for $C_{28}H_{33}N_7O_7$ (picrate): C, 58.02; H, 5.74; N, 16.92. Found: C, 57.78; H, 5.69; N, 16.72. MS *m*/*z*: 350 (M^+). IR (neat): 2230 (CN) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 7.72 (1H, ddd, J=7.7, 1.3, 0.7 Hz), 7.60 (1H, ddd, J=7.7, 7.7, 1.3 Hz), 7.52 (1H, ddd, J=7.7, 1.3, 0.7 Hz), 7.42 (1H, ddd, J=7.7, 7.7, 1.3 Hz), 3.89 (8H, q, J=7.1 Hz), 2.20 (3H, s), 2.05 (3H, s), 1.07 (12H, t, J=7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 160.8, 158.2, 151.0, 146.1, 133.0, 132.0, 130.7, 127.4, 122.5, 121.9, 118.7, 112.8, 46.0, 44.7, 16.1, 15.9, 14.4, 13.1.

From the reaction of **1** with *N*,*N*-diethyl-1-butynylamine (**2b**), 4,6-bis(diethylamino)-3,5-diethylpyridin-2-ylbenzonitrile (**3b**) was obtained as a pale yellow oil in 35% yield (162 mg) and purified as the picrate, mp 129—131 °C. *Anal.* Calcd for $C_{30}H_{37}N_7O_7$ (picrate): C, 59.02; H, 5.76; N, 16.25. Found: C, 59.29; H, 6.15; N, 16.14. MS *m*/*z*: 378 (M^+). IR (neat): 2230 (CN) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 7.73 (1H, ddd, J=7.7, 1.3, 0.7 Hz), 7.60 (1H, ddd, J=7.7, 7.7, 1.3 Hz), 7.49 (1H, ddd, J=7.7, 1.3, 0.7 Hz), 7.43 (1H, ddd, J=7.7, 7.7, 1.3 Hz), 3.14 (4H, q, J=7.1 Hz), 3.10 (4H, q, J=7.1 Hz), 2.73 (2H, q, J=7.4 Hz), 2.60 (2H, q, J=7.4 Hz), 1.19 (3H, t, J=7.4 Hz), 1.08 (6H, t, J=7.1 Hz), 1.05 (6H, t, J=7.1 Hz), 0.78 (3H, t, J=7.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 160.9, 157.5, 151.8, 146.2, 133.4, 132.6, 118.3, 113.1, 133.0, 131.9, 130.1, 127.4, 48.2, 46.5, 21.2, 21.0, 14.8, 14.6, 13.9, 13.3.

X-Ray Crystallographic Analysis Crystal Data of **3a**: A crystal of **3a** for X-ray crystallographic analysis was obtained from a saturated solution of 3a in MeOH. The crystal data are as follows: $C_{28}H_{33}N_7O_7$, F.W. = 579.61, crystal system: triclinic, space group: $P\bar{1}$, lattice parameters: a=12.564(4) Å, b=13.658(2) Å, c=9.134(3) Å, a=107.36(2) Å, b=100.71(3) Å, g=77.10(2) Å, V=1446.1(7) Å, D=1.331 g/cm^3, Z=2, R=0.047.

Reaction of 1-Tosylphthalazine (5) with Ynamines 2a, b Compound **5** (174 mg, 0.61 mmol) was dissolved in dioxane (2 ml), and to this solution was added **2** (2.1 molar eq). The solution was heated to 80 °C and stirred for 10 min. The reaction mixture was quenched with water, neutralized with AcOH, and extracted with chloroform. The organic layer was washed with water and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, benzene) to give **9**.

From the reaction of **5** with **2a**, 2-diethylamino-3-methyl-1-tosylnaphthalene (**9a**) was obtained as colorless needles from benzene–petroleum benzin in 57% yield (127 mg), mp 129—131 °C. *Anal.* Calcd for $C_{22}H_{25}NO_2S$: C, 71.90; H, 6.86; N, 3.81. Found: C, 72.01; H, 6.53; N, 3.84. MS *m*/*z*: 367 (M^+). IR (neat): 1285, 1145 (SO_2) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 8.79—8.75 (1H, m), 7.75 (1H, s), 7.66—7.61 (1H, m), 7.52 (2H, d, J=8.1 Hz), 7.38—7.30 (2H, m), 7.13 (2H, d, J=8.1 Hz), 3.35 (4H, q, J=7.0 Hz), 2.46 (3H, s), 2.31 (3H, s), 0.93 (6H, t, J=7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 151.7, 142.8,142.4, 137.9, 135.9, 131.1, 130.8, 130.5, 128.9, 127.4, 126.6, 126.5, 125.3, 125.2, 49.1, 21.4, 20.6, 13.8.

From the reaction of **5** with **2b**, 2-diethylamino-3-ethyl-1-tosylnaphthalene (**9b**) was obtained as colorless needles from benzene–petroleum benzin in 31% yield (104 mg), mp 97—99 °C. *Anal.* Calcd for $C_{23}H_{27}NO_2S$: C, 72.41; H, 7.25; N, 3.69. Found: C, 72.41; H, 7.13; N, 3.67. MS *m*/*z*: 381 (M^+). IR (neat): 1295, 1145 (SO_2) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 8.73—8.67 (1H, m), 7.81 (1H, s), 7.71—7.64 (1H, m), 7.55 (2H, d, J=8.2 Hz), 7.36—7.29 (2H, m), 7.12 (2H, d, J=7.0 Hz), 3.37 (4H, q, J=7.0 Hz), 2.81 (2H, q, J=7.7 Hz), 2.31 (3H, s), 1.37 (3H, t, J=7.7 Hz), 0.97 (6H, t, J=7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 151.6, 144.0, 142.8, 142.4, 133.5, 131.3, 131.0, 130.2, 129.0, 127.6, 126.5, 126.3, 125.3, 125.1, 49.6, 24.6, 21.4, 14.5, 14.1.

7-Chloro-2-phenylthiazolo[4,5-*d*]pyridazine (10c) and 4-Chloro-2-phenylthiazolo[4,5-*d*]pyridazine (10d) 2-Phenylthiazole-4,5-dicarbohydrazide (**17**) (45 g, 0.162 mol) was suspended in AcOH (900 ml), and this suspension was refluxed for 3 h. After cooling, the white precipitate was collected by filtration, and washed with methanol to give 2-phenylthiazolo[4,5-*d*]pyridazin-4,7-dione (**18**) (38.6 g, 97%), mp >330 °C (lit. 347.3—350.3 °C[7]).

Compound **18** (50 g, 0.2 mol) was refluxed with phosphorus oxychloride (400 ml) and pyridine (40 ml) for 1 h, then allowed to cool. Excess $POCl_3$ was evaporated, and the residue was poured into ice-water with vigorous stirring. The solution was made alkaline, and extracted with $CHCl_3$ (500 ml) twice. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to give 4,7-dichloro-2-phenylthiazolo[4,5-*d*]pyridazine (**19**) as a white powder from $CHCl_3$ in 97% yield (55 g), mp 215—217 °C. *Anal.* Calcd for $C_{11}H_5Cl_2N_3S$: C, 46.83; H, 1.79; N, 14.89. Found: C, 46.73; H, 1.90; N, 14.98. ^1H-NMR ($CDCl_3$) δ: 8.18—8.16 (2H, m), 7.66—7.63 (1H, m), 7.59—7.56 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 176.18, 149.93, 149.66, 148.96, 137.11, 133.93, 149.66, 148.96, 137.11, 133.67, 131.27, 129.61, 128.46.

A solution of **19** (10 g, 35.4 mmol), hydrazine monohydrate (9 g, 180 mmol) in $CHCl_3$ (200 ml)/methanol (200 ml) was refluxed for 2 h. The solution was left overnight at room temperature, then the precipitate was collected by filtration to give a crude solid consisting of 7-chloro-2-phenylthiazolo[4,5-*d*]pyridazin-4-ylhydrazine (**20**) and 4-chloro-2-phenylthiazolo[4,5-*d*]pyridazin-7-ylhydrazine (**21**). The mixture of **20** and **21** was added in small portions to a suspension of HgO (40 g) in H_2O (800 ml). The whole was stirred for 3 h, CHCl3 (800ml) was added, and stirring was continued for an additional 30 min. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, concentrated and chromatographed on a column of SiO_2. The first fraction eluted with $CHCl_3$ gave 7-chloro-2-phenylthiazolo[4,5-*d*]pyridazine (**10c**) as a brown powder from benzene–petroleum benzin in 43% yield (44 g), mp 176 °C (lit. 175—176 °C[7]). ^{1}H-NMR (CDCl$_3$) δ: 9.67 (1H, s), 8.13—8.10 (2H, m), 7.65—7.52 (3H, m). ^{13}C-NMR (CDCl$_3$) δ: 175.53, 152.35, 149.65, 145.38, 136.13, 133.22, 131.44, 129.49, 128.19. The second fraction eluted with CHCl$_3$ gave 4-chloro-2-phenylthiazolo[4,5-*d*]pyridazine (**10d**) as brown prisms from benzene-petroleum benzin in 11% yield (0.86 g), mp 178—180 °C. *Anal.* Calcd for $C_{11}H_6ClN_3S$: C, 53.34; H, 2.44; N, 16.96. Found: C, 53.16; H, 2.44; N, 16.90. ^{1}H-NMR (CDCl$_3$) δ: 9.65 (1H, s), 8.15—8.14 (2H, m), 7.62—7.59 (1H, m), 7.55—7.52 (2H, m). ^{13}C-NMR (CDCl$_3$) δ: 175.24, 150.32, 149.25, 145.30, 136.38, 133.26, 131.46, 129.45, 128.40.

Reaction of Fused Chloropyridazines (10a—g) with Ynamines 2a, b The procedure for the reaction of 1-chloropyrido[3,4-*d*]pyridazine (**10a**)[8] with **2a** is described as a typical example.

To a solution of **10a** (200 mg, 1.0 mmol) in dioxane (2 ml) was added **2a** (245 mg, 2.2 mmol), and the mixture was heated at 80 °C for 15 min. The same work-up of the reaction mixture as described for the reaction of **1** with **2** afforded 4′,6′-bis(diethylamino)-3′,5′-dimethyl-2′,3-bipyridyl-4-carbonitrile (**11a**) in 42% yield (154 mg). IR (neat): 2230 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 8.94 (1H, d, J=0.7 Hz), 8.78 (1H, d, J=5.1 Hz), 7.50 (1H, dd, J=5.1, 0.7 Hz), 3.21 (8H, q, J=7.0 Hz), 3.21 (8H, q, J=7.0 Hz), 2.20 (3H, s), 2.09 (3H, s), 1.08 (12H, t, J=7.0 Hz). ^{13}C-NMR (CDCl$_3$) δ: 161.2, 158.7, 153.5, 152.0, 148.3, 124.9, 123.9, 122.4, 122.3, 116.9, 110.4, 46.0, 44.6, 16.2, 16.1, 14.4, 13.1.

From the reaction of 8-chloropyrido[2,3-*d*]pyridazine (**10b**)[9] (200 mg, 1.0 mmol) with **2a**, 4′,6′-bis(diethylamino)-3′,5′-dimethyl-2′,3-bipyridyl-2-carbonitrile (**11b**) was obtained in 10% yield (44 mg). MS *m*/*z*: 351 (M$^+$). IR (neat): 2230 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 8.56 (1H, dd, J=4.0, 1.5 Hz), 7.82 (1H, dd, J=8.0, 1.5 Hz), 7.44 (1H, dd, J=8.0, 4.0 Hz), 3.16 (8H, q, J=7.0 Hz), 2.18 (3H, s), 2.06 (3H, s), 1.06 (12H, t, J=7.0Hz). ^{13}C-NMR (CDCl$_3$) δ: 161.2, 158.5, 149.2, 148.4, 142.6, 138.5, 133.6, 126.0, 122.8, 122.1, 117.2, 46.1, 44.7, 16.2, 16.1, 14.4, 13.1.

From the reaction of 7-chloro-2-phenylthiazolo[4,5-*d*]pyridazine (**10c**) (124 mg, 0.5 mmol) with **2a**, 4-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-2-phenylthiazole-5-carbonitrile (**11c**) was obtained in 33% yield (110 mg) and purified as the picrate, mp 191—192 °C. *Anal.* Calcd for $C_{31}H_{34}N_8O_7S$ (picrate): C, 56.18; H, 5.17; N, 16.91. Found: C, 56.56; H, 5.14; N, 17.07. MS *m*/*z*: 433 (M$^+$). IR (KBr): 2200 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 8.01—7.98 (2H, m), 7.53—7.52 (3H, m), 3.32—3.17 (8H, m), 2.41 (3H, s), 2.23 (3H, s), 1.13—1.05 (12H, m). ^{13}C-NMR (CDCl$_3$) δ: 169.3, 165.7, 160.0, 158.7, 144.8, 132.5, 131.4, 129.1, 126.9, 124.3, 123.9, 113.5, 103.0, 46.1, 45.1, 16.3, 16.1, 14.4, 13.2.

From the reaction of **10c** (124 mg, 0.5 mmol) with **2b**, 4-[4,6-bis(diethylamino)-3,5-diethylpyridin-2-yl]-2-phenylthiazole-5-carbonitrile (**11d**) was obtained in 18% yield (62 mg) and purified as the picrate, mp 187—189 °C. *Anal.* Calcd for $C_{33}H_{38}N_8O_7S$ (picrate): C, 57.38; H, 5.54; N, 16.22. Found: C, 57.60; H, 5.53; N, 16.14. MS *m*/*z*: 461 (M$^+$). IR (KBr): 2200 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 8.00—7.97 (2H, m), 7.50—7.40 (3H, m), 3.28—3.09 (10H, m), 2.76 (2H, q, J=7.0Hz), 1.21—0.99 (18H, m). ^{13}C-NMR (CDCl$_3$) δ: 169.6, 165.5, 160.8, 158.3, 145.1, 135.2, 134.8, 132.5, 131.5, 129.2, 126.9, 113.5, 103.1, 48.3, 46.7, 21.3, 20.8, 15.4, 14.8, 14.0, 13.5.

From the reaction of 4-chloro-2-phenylthiazolo[4,5-*d*]pyridazine (**10d**) (248 mg, 1.0 mmol) with **2a**, 5-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-2-phenylthiazole-4-carbonitrile (**11e**) was obtained in 39% yield (260 mg) and purified as the picrate, mp 148—151 °C. *Anal.* Calcd for $C_{31}H_{34}N_8O_7S$ (picrate): C, 56.18; H, 5.17; N, 16.91. Found: C, 56.36; H, 5.11; N, 16.78. MS *m*/*z*: 433 (M$^+$). IR (KBr): 2225 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.99—7.97 (2H, m), 7.46—7.24 (3H, m), 3.27—3.20 (8H, m), 2.34 (3H, s), 2.18 (3H, s), 1.13 (6H, t, J=7.0 Hz), 1.08 (6H, t, J=7.0 Hz). ^{13}C-NMR (CDCl$_3$) δ: 168.2, 161.1, 158.9, 151.5, 141.8, 132.4, 131.0, 129.1, 126.6, 124.4, 122.8, 121.5, 115.1, 46.0, 44.4, 16.9, 16.6, 14.4, 13.1.

From the reaction of **10d** (248 mg, 1.0 mmol) with **2b**, 5-[4,6-bis(diethylamino)-3,5-diethylpyridin-2-yl]-2-phenylthiazole-4-carbonitrile (**11f**) was obtained in 33% yield (230 mg) and purified as the picrate, mp 131—133 °C. *Anal.* Calcd for $C_{33}H_{38}N_8O_7S$ (picrate): C, 57.38; H, 5.54; N, 16.22. Found: C, 57.42; H, 5.41; N, 16.11. MS *m*/*z*: 461 (M$^+$). IR (KBr): 2225 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.99—7.97 (2H, m), 7.47—7.25 (3H, m), 3.20 (4H, q, J=7.0 Hz), 3.16 (4H, q, J=7.0 Hz), 2.90 (2H, q, J=7.0 Hz), 2.71 (2H, q, J=7.0 Hz), 1.16 (3H, t, J=7.0 Hz), 1.12—1.07 (12H, m), 0.97 (3H, t, J=7.0 Hz). ^{13}C-NMR (CDCl$_3$) δ: 167.7, 160.9, 157.8, 149.9, 141.6, 133.2, 132.9, 132.3, 131.0, 129.1, 126.7, 125.3, 114.9, 48.1, 46.0, 21.7, 21.4, 15.1, 14.5, 13.4, 13.3.

From the reaction of 7-chloro-2-methylfuro[2,3-*d*]pyridazine (**10e**)[10] (168 mg, 1.0 mmol) with **2a**, 3-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-5-methylfuran-2-carbonitrile (**11g**), mp 76—79 °C, was obtained in 44% yield (155 mg). *Anal.* Calcd for $C_{21}H_{30}N_4O$: C, 71.19; H, 8.48; N, 15.82. Found: C, 71.09; H, 8.64; N, 15.76. MS *m*/*z*: 354 (M$^+$). IR (KBr): 2220 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 6.36 (1H, s), 3.18 (8H, q, J=7.1 Hz), 2.38 (3H, s), 2.23 (3H, s), 2.18 (3H, s), 2.08 (12H, t, J=7.1 Hz). ^{13}C-NMR (CDCl$_3$) δ: 161.0, 158.4, 156.6, 143.4, 140.0, 123.3, 122.4, 121.9, 113.2, 109.7, 46.1, 44.8, 16.1, 16.1, 14.0, 14.0, 13.2.

From the reaction of **10e** (168 mg, 1.0 mmol) with **2b**, 3-[4,6-bis(diethylamino)-3,5-diethylpyridin-2-yl]-5-methylfuran-2-carbonitrile (**11h**) was obtained in 48% yield (176 mg). IR (neat): 2220 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 6.40 (1H, s), 3.15 (4H, q, J=7.3 Hz), 3.11 (4H, q, J=7.3 Hz), 2.77 (2H, q, J=7.3 Hz), 2.69 (2H, q, J=7.3 Hz), 1.15 (3H, t, J=7.3 Hz), 1.06 (12H, t, J=7.3 Hz), 0.98 (3H, t, J=7.3 Hz). ^{13}C-NMR (CDCl$_3$) δ: 161.1, 157.7, 156.9, 143.8, 139.9, 133.5, 133.0, 123.5, 113.0, 109.1, 48.2, 46.5, 21.1, 20.9, 15.1, 14.7, 14.1, 13.8, 13.4.

From the reaction of 7-chloro-2-methyl-1-phenyl-1*H*-pyrrolo[2,3-*d*]pyridazine (**10f**)[10] (200 mg, 0.82 mmol) with **2a**, 3-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-5-methyl-1-phenyl-1*H*-pyrrole-2-carbonitrile (**11i**) was obtained in 54% yield (191 mg) and purified as the picrate, mp 109—111 °C. *Anal.* Calcd for $C_{33}H_{38}N_8O_7$ (picrate): C, 71.19; H, 8.48; N, 15.82. Found: C, 71.09; H, 8.64; N, 15.76. IR (neat): 2220(CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.56—7.26 (5H, m), 6.32 (1H, s), 3.23 (4H, q, J=7.0 Hz), 3.19 (4H, q, J=7.0 Hz), 2.29 (3H, s), 2.18 (3H, s), 2.17 (3H, s), 1.09 (6H, t, J=7.0 Hz), 1.06 (6H, t, J=7.0 Hz)

From the reaction of **10f** (200 mg, 0.82 mmol) with **2b**, 3-[4,6-bis(diethylamino)-3,5-diethylpyridin-2-yl]-5-methyl-1-phenyl-1*H*-pyrrole-2-carbonitrile (**11j**) was obtained in 48% yield (180 mg) and purified as the picrate, mp 177—178 °C. *Anal.* Calcd for $C_{35}H_{42}N_8O_7$ (picrate): C, 61.21; H, 6.16; N, 16.32. Found: C, 61.30; H, 6.20; N, 16.33. IR (neat): 2220 (CN) cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 7.55—7.38 (5H, m), 6.32 (1H, s), 3.38—3.11 (8H, m), 2.85 (2H, q, J=7.0 Hz), 2.71 (2H, q, J=7.0 Hz), 2.18 (3H, s), 1.17 (3H, t, J=7.0 Hz), 1.09—0.98 (15H, m).

From the reaction of 4-chloro-2-methyl-1-phenyl-1*H*-pyrrolo[2,3-*d*]pyridazine (**10g**)[10] (200 mg, 0.82 mmol) with **2a**, 2-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-5-methyl-1-phenyl-1*H*-pyrrole-3-carbonitrile (**11k**) was obtained in 36% yield (127 mg). ^{1}H-NMR (CDCl$_3$) δ: 7.26—7.18 (3H, m), 7.08—7.40 (2H, m), 6.32 (1H, s), 3.05—2.85 (8H, m), 2.11 (3H, s), 2.07 (3H, s), 2.01 (3H, s), 0.99—0.70 (12H, m).

2-Phenyl-7-(*p*-tolylsulfonyl)thiazolo[4,5-*d*]pyridazine (12) *p*-Toluenesulfinic acid sodium salt (1.44 g, 8 mmol) and **10c** (1.0 g, 4 mmol) were dissolved in *N*,*N*-dimethylformamide (DMF) (24 ml), and the solution was heated at 100 °C for 1.5 h, then allowed to cool. Ice-water (100 ml) was added, and the mixture was extracted with CHCl$_3$. The organic layer was dried over Na$_2$SO$_4$ and evaporated to give 2-phenyl-7-(*p*-tolylsulfonyl)thiazolo[4,5-*d*]pyridazine (**12**) as colorless needles from benzene–methanol in 86% yield (1.27 g), mp 251—252 °C.

7-Diethylamino-8-ethyl-2-phenyl-4-(*p*-tolylsulfonyl)thiazolo[5,4-*d*]-[1,2]diazocine (13b) Compound **2b** (313 mg, 2.5 mmol) was added to a solution of **12** (184 mg, 0.5 mmol) in dioxane (2 ml), and the mixture was heated at 90 °C for 1 h, then allowed to cool. H$_2$O (3 ml) was added, and the mixture was extracted with CHCl$_3$. The organic layer was dried over Na$_2$SO$_4$ and evaporated, and the residue was chromatographed (silica-gel, benzene/chloroform = 5/1). The first fraction eluted with benzene/chloroform = 5/1 gave 6-(*N*,*N*-diethylamino)-5-ethyl-2-phenyl-7-(*p*-tolylsulfonyl)benzothiazole (**13a**) in 75% yield (174 mg). The second fraction eluted with benzene/chloroform = 5/1 gave 7-diethylamino-8-ethyl-2-phenyl-4-(*p*-tolylsulfonyl)thiazolo[5,4-*d*][1,2]diazocine (**13b**) as yellow needles from benzene–petroleum benzin in 4% yield (10 mg), mp 122—123 °C. *Anal.* Calcd for $C_{26}H_{28}N_4O_2S_2$ (picrate): C, 63.39; H, 5.73; N, 11.37. Found: C, 63.79; H, 5.71; N, 11.21. IR (KBr): 1310, 1150 (SO$_2$) cm^{-1}. ^{1}H-NMR (CDCl$_3$): 7.97—7.93 (2H, m), 7.73 (2H, d, J=7.4Hz), 7.47—7.45 (3H, m), 7.29 (2H, d, J=7.4 Hz), 6.23 (1H, s), 3.23—3.00 (4H, m), 2.42 (3H, s), 2.24 (2H, q, J=7.3 Hz), 1.06—0.93 (9H, m). ^{13}C-NMR (CDCl$_3$): 172.85, 158.72, 153.43, 150.47, 144.93, 144.17, 134.88, 132.63, 131.03, 129.55, 129.07, 126.71, 124.89, 119.54, 41.61, 27.92, 21.63, 13.01, 12.81.

Acknowledgment The authors are greatly indebted to the staff of the Rigaku X-Ray Research Laboratory for the X-ray crystallography.

References

1) This paper forms Ring Transformation of Fused Pyridazines. II. Part I: K. Iwamoto, S. Suzuki, E. Oishi, K. Tanji, A. Miyashita, T. Higashino, *Chem. Pharm. Bull.*, **42**, 413 (1994).
2) *a*) E. Oishi, A. Yamada, E.Hayashi, K. Tanji, A. Miyashita, T. Higashino, *Chem. Pharm. Bull.*, **37**, 13 (1989); *b*) E. Oishi, N. Taido, K. Iwamoto, A. Miyashita, T. Higashino, *ibid.*, **38**, 3268 (1990).
3) E. Oishi, N. Taido, A. Miyashita, S. Sato, S. Ohta, H. Ishida, K. Tanji, T. Higashino, *Chem. Pharm. Bull.*, **39**, 1713 (1991).
4) R. Gompper, G. Seybold, *Angew. Chem., Int. Ed. Engl.*, **7**, 824 (1968).
5) E. Hayashi, T. Higashino, C. Iijima, Y. Kono, T. Doihara, *Yakugaku Zasshi*, **82**, 584 (1962).
6) J. Ficini, C. Barbara, *Bull. Soc. Chim. Fr.*, **10**, 2787 (1965).
7) I. Simiti, K. Pfister, *J. Am. Chem. Soc.*, **65**, 2167 (1943).
8) I. Matsuura, K. Okui, *Chem. Pharm. Bull.*, **17**, 2266 (1969).
9) D. B. Paul, H. J. Rodda, *Aust. J. Chem.*, **22**, 1759 (1969).
10) *a*) R. G. Jones, *J. Am. Chem. Soc.*, **77**, 4069 (1955); *b*) *Idem*, *ibid.*, **78**, 159 (1956); *c*) S. Yoshina, I. Maeba, K. Hirano, *Chem. Pharm. Bull.*, **17**, 2158 (1969).