RING TRANSFORMATION OF FUSED PYRIDAZINES. IV. REACTION OF HALO-SUBSTITUTED FUSED PYRIDAZINES WITH YNAMINES[1]

Ken-ichi Iwamoto,*[a] Sumiko Suzuki,[a] Etuso Oishi,[b] Akira Miyashita,[a] and Takeo Higashino[a]

School of Pharmaceutical Sciences,[a] and Division of Environmental Health Sciences, Graduate School of Nutritional & Environmental Sciences,[b] University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

Abstract - Halo-substituted phthalazines reacted with two equivalents of ynamines to give penta-substituted pyridines through the N-N bond cleavage of pyridazine moiety. And it was proved that the N-N bond cleavage reaction of pyridazine ring is common to halo-substituted condensed pyridazines.

During the course of our work concerning the reactivities of fused pyridazines with ynamines, we have reported that 1-chlorophthalazine (**1**) reacted with two equivalents of ynamines to give penta-substituted pyridines with nitrogen-nitrogen bond cleavage in the pyridazine ring with moderate yields.[1-3] We now wish to report the scope and limitation of the N-N bond cleavage of pyridazine ring in the reaction of fused pyridazines with ynamines.

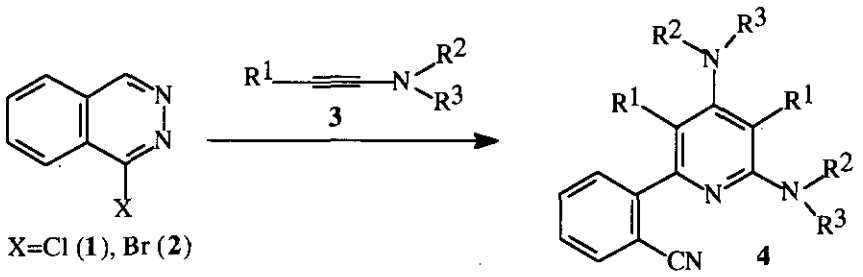
At first, we examined the reactivities of 1-bromophthalazine (**2**)[4] with several ynamines (**3**). In the result, **2** reacted with two equivalents of ynamines to give penta-substituted pyridines (**4**) as observed in 1-chlorophthalazine with ynamines (Scheme 1).

Further we employed 1-iodophthalazine (**5**) in this reaction, but it failed to produce pyridines (**4**) because the starting material (**5**) decomposed even under refluxing in dioxane for 10 minutes.

In addition, we applied this reaction to the other halo-substituted condensed pyridazines. We examined the reaction of 7-bromo-2-methylfuro[2,3-*d*]pyridazine (**6**) with ynamine and obtained the N-N bond cleavage product as well as 7-chloro-2-methylfuro[2,3-*d*]pyridazine[1] with ynamines.

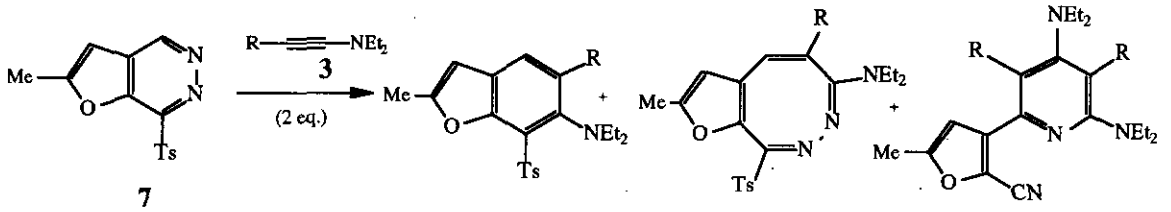
In further investigation of this reaction, 2-methyl-7-tosylfuro[2,3-*d*]pyridazine (**7**) underwent not only N-N bond cleavage reaction but also cycloaddition-denitrogen reaction and [2+2] cycloaddition-ring expansion reaction simultaneously (Scheme 2).

From this outcome, it is assumed that the N-N bond cleavage reaction is common to halo-substituted condensed pyridazines. And it can be presumed that when electron-withdrawing substituent is introduced to pyridazines



X	R^1	R^2	R^3	Yield (%)
Cl	Me	Et	Et	68 [1]
Cl	Et	Et	Et	35 [1]
Cl	H	$(CH_2)_2$-O-$(CH_2)_2$		63
Cl	Me	$(CH_2)_2$-O-$(CH_2)_2$		44
Br	Me	Et	Et	70
Br	Et	Et	Et	52
Br	H	$(CH_2)_2$-O-$(CH_2)_2$		65
Br	Me	$(CH_2)_2$-O-$(CH_2)_2$		50

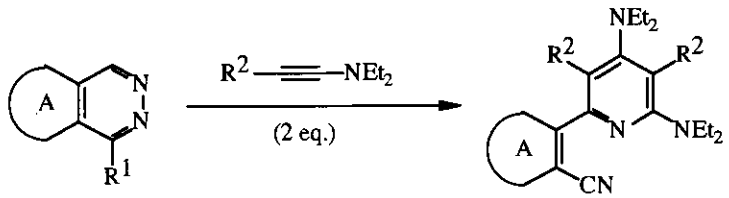
Scheme 1



R	Yield (%)		
	Type A	**Type B**	**Type C**
Me	31	20	14
Et	34	14	14

Scheme 2

fused to electron-rich heteroarenes, the N-N bond cleavage of pyridazine ring is observed with ynamines. So we surveyed the reactivities of the other systems such as 2-methyl-1-phenyl-7-tosyl-1*H*-pyrrolo[2,3-*d*]pyridazine (**8**) with ynamines. The result was in accord with the expectations based on the above estimation. The N-N bond cleavage reaction occurred also when electron-donating group was introduced to pyridazines fused to electron-rich heteroarenes. The example is representative for 8-methylthiopyrido[2,3-*d*]pyridazine (**9**) with ynamines.

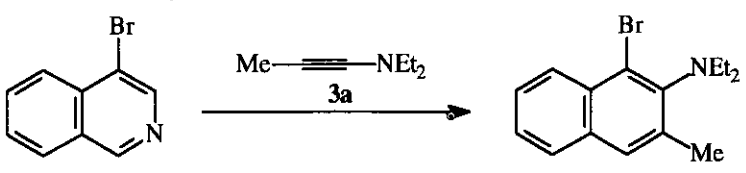


A	R^1	R^2	Yield (%)
Me, N, Ph	Ts	Me	42
	Ts	Et	48
	CN	Me	20
N	SMe	Me	15

Scheme 3

In conclusion, the N-N bond cleavage reaction of fused pyridazines with two equivalents of ynamines is common to halo-substituted condensed pyridazines. And the reaction is observed in the reaction of ynamines with other fused pyridazines when appropriate substituent is introduced considering the electronic property of the fused ring.

We scrutinized the reactivity of isoquinoline with ynamines because the structure is related to that of phthalazine. When 4-bromoisoquinoline (**10**) is employed in the reaction with ynamines, **10** underwent the inverse Diels-Alder type reaction at the 1, 4-position of isoquinoline and smoothly loosed hydrogen cyanide, giving naphthalene derivative (Scheme 4). That is, the nitrogen atom at the 2-position of phthalazine plays an important role in the N-N bond cleavage reaction. The theoretical explanation based upon molecular orbital calculations will be a subject of future communications.



10

Scheme 4

EXPERIMENTAL

All melting points are uncorrected. Infrared absorption spectra were recorded on a Jasco A-102 diffraction grating ir spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were measured at 270 MHz on a JEOL instrument. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-nmr signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Mass spectra were recorded with a JEOL JMS D-100 mass spectrometer. Column chromatgraphy was carried out on silica gel (Merck Co. Ltd., 200 mesh).

Reaction of 1-Bromophthalazine[4] (2) with Ynamines (3)

Compound (**2**) (100 mg, 0.478 mmol) was dissolved in dioxane (2 ml), and to this solution was added ynamines (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. 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 **4**.

From the reaction of **2** with *N,N*-diethyl-1-propynylamine (**3a**), 2-[4,6-bis(diethylamino)-3,5 dimethylpyridin-2-yl]benzonitrile [2] was obtained in 70% yield.

From the reaction of **2** with *N,N*-diethyl-1-butynylamine (**3b**), 2-[4,6-bis(diethylamino)-3,5 diethylpyridin-2-yl]benzonitrile [2] was obtained in 52% yield.

From the reaction of **2** with 1-morpholinoacetylene (**3c**), 2-(4,6-bismorpholinopyridin-2-yl)benzonitrile was obtained as colorless needles from ether in 65% yield. Ms m/z: 350 (M^+). Ir (KBr): 2240 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 7.82 (1H, dd, *J*=7.7, 1.1 Hz), 7.81 (1H, dd, *J*=7.7, 1.1 Hz), 7.61 (1H, ddd, *J*=7.7, 7.7, 1.1 Hz), 7.44 (1H, ddd, *J*=7.7, 7.7, 1.1 Hz), 6.66 (1H, d, *J*=1.8 Hz), 5.98 (1H, d, *J*=1.8 Hz), 3.87-3.82 (8H, m), 3.60 (4H, t, *J*=4.9 Hz), 3.33 (4H, t, *J*=4.9 Hz). ^{13}C-Nmr ($CDCl_3$): 160.8, 158.2, 153.9, 134.4, 132.4, 129.5, 128.3, 119.3, 111.1, 100.7, 90.1, 66.9, 66.5, 47.1, 46.0. *Anal.* Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.62; H, 6.22; N, 15.89.

From the reaction of **2** with 1-morpholino-1-butyne (**3d**), 2-(4,6-bismorpholino-3,5-dimethylpyridin-2-yl)benzonitrile was obtained as colorless needles from ether in 50% yield. Ms m/z: 378 (M^+). Ir (KBr): 2240 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 7.74 (1H, dd, *J*=7.7, 1.5 Hz), 7.64 (1H, ddd, *J*=7.7, 7.7, 1.5 Hz), 7.55 (1H, dd, *J*=7.7,1.5 Hz), 7.45 (1H, ddd, *J*=7.7, 7.7, 1.5 Hz), 3.85-3.81 (8H, m), 3.22-2.12 (8H, m), 2.30 (3H, s), 2.15 (3H, s). ^{13}C-Nmr ($CDCl_3$): 160.6, 158.3, 151.6, 133.0, 132.2, 130.7, 127.9, 122.7, 119.9, 118.6, 112.9, 102.9, 67.8, 67.1, 50.3, 16.0, 15.6. *Anal.* Calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80. Found: C, 69.90; H, 6.87; N, 14.99.

Reaction of 7-Bromo-2-methylfuro[2,3-*d*]pyridazine (6) with *N,N*-Diethyl-1-propynylamine (3a)

Compound (**6**) (100 mg, 0.478 mmol) was dissolved in dioxane (2 ml), and to this solution was added *N,N*-diethyl-1-propynylamine (**3a**) (111 mg, 1.00 mmol). The solution was heated to 80°C and stirred for 2 h. The reaction mixture was quenched with water and extracted with chloroform. The organic layer was washed with water. 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-[4,6-bis(diethylamino)-3,5-dimethlpyridin-2-yl]-5-methylfuran-2-carbonitrile [3] *in 53% (88.2 mg) yield.*

Reaction of 2-Methyl-7-(*p*-tolylsulfonyl)furo[2,3-*d*]pyridazine (7) with Ynamines (3a, b)

N,N-Diethyl-1-propynylamine (**3a**) (339 mg, 3.05 mmol) was added to a solution of **7** (400 mg, 1.39 mmol) in dioxane (8 ml), and the mixture was heated at 90°C for 40min with stirring and then allowed to cool. Water was added, and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed (silica-gel, hexane). The first fraction eluted with hexane gave 3-[4,6 bis(diethylamino)-3,5-dimethylpyridin-2-yl]-5-methylfuran-4-carbonitrile [3] in 31% (152 mg) yield. The second fraction eluted with hexane/AcOEt = 20/1 gave 6-(*N,N*-diethylamino)-2,5-dimethyl-7-(*p*-tolylsulfonyl)benzofuran as colorless prisms from hexane, mp 118-119°C, in 20% (101 mg) yield. Ms m/z: 371 (M^+). Ir (KBr):1315, 1155 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 7.91-7.87 (2H, m), 7.37 (1H, s), 7.26-7.23 (2H, m), 6.26 (1H, d, *J*=1.1 Hz), 3.11 (4H, q, *J*=7.3 Hz), 2.43 (3H, d, *J*=1.1 Hz), 2.40 (3H, s), 2.30 (3H, s), 0.74 (6H, t, *J*=7.3 Hz). ^{13}C-Nmr($CDCl_3$):157.2, 150.4, 144.1, 143.2, 141.1, 135.0, 128.9, 128.7, 128.3, 126.5, 125.7, 101.6, 48.0, 21.5, 19.9, 14.1, 12.9. *Anal.* Calcd for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.00; H, 6.88; N, 3.56. The third fraction eluted with hexane/AcOEt = 10/1 gave 6-diethylamino-2,5-dimethyl-9-(*p*-tolylsulfonyl)furo[4,5-*d*][1,2]diazocine as yellow needles from ether, mp 128-129°C, in 13.5% (75 mg) yield. Ir (KBr): 1320, 1160 cm^{-1}. ^{1}H-Nmr ($CDCl_3$):7.84-7.80 (2H, m), 7.31-7.29 (2H, m), 6.08 (1H, q, *J*=1.5 Hz), 5.91 (1H, d, *J*=1.1 Hz), 3.23 (2H, q, *J*=7.0 Hz), 3.00 (2H, q, *J*=7.0 Hz), 2.43 (3H, s), 2.33 (3H, d, *J*=1.1 Hz), 1.94 (3H, d, *J*=1.5 Hz), 0.97 (6H, t, *J*=7.0 Hz). ^{13}C-Nmr ($CDCl_3$):157.9, 151.2, 151.1, 144.6, 138.6, 137.3, 136.1, 132.7, 129.5, 129.1, 125.1, 107.1, 41.6, 21.7, 20.9, 14.0, 12.9. *Anal.* Calcd for $C_{21}H_{25}N_3O_3S$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.13; H, 6.29; N, 10.47.

From the reaction of **7** *(400 mg, 1.39 mmol) with N,N-diethyl-1-butynylamine* (**3b**) (382 mg, 3.05 mmol), 3-[4,6-bis(diethylamino)-3,5-diethylpyridin-2-yl]-5-methylfuran-4-carbonitrile was obtained as pale yellow oil in 34% (178 mg) yield from the first fraction eluted with hexane. Ms m/z: 382 (M^+). Ir (KBr): 2225 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 6.42 (1H, d, *J*=1.1 Hz), 3.20-3.08 (8H, m), 2.79(2H, q, *J*=7.3 Hz), 2.37 (3H, d, *J*=1.1 Hz), 1.16 (3H, t, *J*=7.3 Hz), 1.07 (12H, t, *J*=7.3 Hz), 0.99 (3H, t, *J*=7.3 Hz). The second fraction eluted with hexane/AcOEt=20/1 gave 6-(*N,N*-diethylamino)-5-ethyl-2-methyl-7-(*p*-tolylsulfonyl)benzofuran as colorless prisms from hexane, mp 132-133°C, in 14% (77mg) yield. Ms m/z: 385 (M^+). Ir (KBr): 1310, 1140 cm^{-1}. ^{1}H-Nmr($CDCl_3$): 7.92-7.88 (2H, m), 7.46 (1H, s), 7.27-7.23 (2H, m), 6.28 (1H, d, *J*=1.1 Hz), 3.14 (4H, q, *J*=7.1 Hz), 2.68 (2H, q, *J*=7.4 Hz), 2.40 (3H, d, *J*=1.1 Hz), 2.39(3H, s), 1.24 (3H, t, *J*=7.4 Hz), 0.80 (6H, t, *J*=7.1 Hz). ^{13}C-Nmr($CDCl_3$):157.1, 150.1, 143.8, 143.2, 141.5, 141.0, 128.8, 128.2, 125.6, 124.4, 101.8, 48.8, 24.2, 21.5, 15.3, 14.1, 13.4. *Anal.* Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.57; H, 7.14; N, 3.50. The third fraction eluted with hexane/AcOEt=10/1 gave 6-diethylamino-5-ethyl-2-methyl-9-(*p*-tolylsulfonyl)furo[4,5-*d*][1,2]diazocine as yellow prisms from ether, mp 131-132°C, in 14% (81 mg) yield. Ir (KBr): 1315,1155 cm^{-1}. ^{1}H-Nmr($CDCl_3$): 7.81-7.78 (2H, m), 7.30-7.27 (2H, m), 6.04 (1H, t, *J*=1.5 Hz), 5.93 (1H, d, *J*=1.1 Hz), 3.23 (2H, q, *J*=7.1 Hz), 2.98 (2H, q, *J*=7.1 Hz), 2.43 (3H, s), 2.35 (3H, d, *J*=1.1 Hz), 2.20 (2H, qd, *J*=7.3, 1.5 Hz), 1.01 (3H, t, *J*=7.3 Hz), 0.96 (6H, t, *J*=7.1 Hz) . ^{13}C-Nmr($CDCl_3$):157.9,

151.1, 150.6, 144.5, 144.2, 138.5, 136.2, 132.5, 129.4, 129.1, 123.2, 107.0, 41.7, 28.5, 21.7, 14.0, 13.6, 12.9. *Anal.* Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found: C, 63.78; H, 6.63; N, 10.14.

From the reaction of 2-methyl-1-phenyl-7-tosyl-1*H*-pyrrolo[2,3-*d*]pyridazine (**8**) with **3a**, 3-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-5-methyl-1-phenyl-1*H*-pyrrolo-2-carbonitrile[3] was obtained in 42% yield.

From the reaction of **8** with **3b**, 3-[4,6-bis(diethylamino)-3,5-diethylpyridin-2-yl]-5-methyl-1-phenyl-1*H*-pyrrolo-2-carbonitrile[3] was obtained in 48% yield.

From the reaction of 8-methylthiopyrido[2,3-*d*]pyridazine (**9**) with **3a**, 4',6'-bis(diethylamino)-3',5'-dimethyl-2',3-bipyridyl-2-carbonitrile[4] was obtained in 15% yield.

Reaction of 4-Bromoisoquinoline (10) with *N,N*-Diethyl-1-propynylamine (3a)

N,N-Diethyl-1-propynylamine (**3a**) (339 mg, 3.05 mmol) was added to a solution of **10** (300 mg, 1.44 mmol) in dioxane (6 ml), and the mixture was refluxed for 150 min with stirring and then allowed to cool. Water was added, and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed (silica-gel, hexane) to give 1-bromo-2-diethylamino-3-methylnaphthalene in 78% (328.6 mg) yield as yellow oil. Ms m/z: 292 (M^+). Ir (neat): 2970cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.25 (1H, dd, *J*=7.3, 1.1 Hz), 7.65 (1H, dd, *J*=7.3, 1.1 Hz), 7.56 (1H, s), 7.44 (1H, ddd, *J*=7.3, 7.3, 1.1 Hz), 7.37 (1H, ddd, *J*=7.3, 7.3, 1.1 Hz), 3.26 (4H, q, *J*=7.3 Hz), 2.46 (3H, s), 1.03 (6H, t, *J*=7.3 Hz). ^{13}C-Nmr ($CDCl_3$): 146.6, 139.3, 132.4, 132.2, 128.4, 127.2, 127.1, 127.0, 126.1, 125.7, 47.1, 20.4, 14.6.

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