Dehalogenation of 1-Methyl-5-halo-4-substituted-pyridazin-6-ones

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In order to confirm the regiochemistry for the functionalization of 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones, the dehalogenation of 1-methyl-5-halo-4-substituted-pyridazin-6-ones using Pd/C and hydrogen was carried out. The results of the title reaction are reported.

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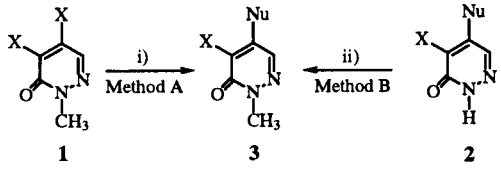
In the previous paper [1], we reported the functionalization of 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones with some nucleophiles in acetonitrile or methanol to give only 5-halo-4-substituted-pyridazin-6-ones. Lyga [2] has also reported the effect of solvents on the regiospecificity of the displacement of 1-substituted-4,5-dichloropyridazin-6-ones. According to Lyga's results, the treatment of 1-phenyl-4,5-dichloropyridazin-6-one with sodium ethoxide in acetonitrile afforded 4-substituted and 5-substituted isomers, whereas the reaction of it with sodium methoxide in methanol gave only the 4-methoxy isomer in good yield. Due to the different results, however, we decided to investigate the regiochemistry for the substitution of 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones with some nucleophiles. It is easy to distinguish between 4-substituted and 5-substituted pyridazin-6-ones by the coupling constants of the proton magnetic resonance spectra. According to Katz, *et al.* [3], the coupling constant between the C3-H and C5-H for 4-substituted-pyridazin-6-ones is smaller than it is between C3-H and C4-H for the 5-substituted isomer ($J_{3,5}$ = about 2 Hz, $J_{3,4}$ = about 5 Hz). The coupling constant between the C4-H and C5-H for 3-substituted-pyridazin-6-ones also is about 9-10 Hz.

Because of the low solubility of 5-halo-4-substituted-pyridazin-6-ones, we selected the corresponding 1-methyl isomers **3** as the starting material for the dehalogenation.

First, compounds **3** were synthesized by the methylation of **2** that was prepared by our reported method [1] to establish the regiochemistry of the functionalization for 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones (Method B). The substitution of 1-methyl-4,5-dihalopyridazin-6-ones **1** with nucleophiles in acetonitrile or methanol also gave **3** as the main product (Method A). The structures of **3** were established by ir, nmr and elemental analyses.

Dehalogenation of **3** with Pd/C and hydrogen yielded only the corresponding 4-substituted isomers **4** (Method C). Reaction of **3c** (3.19 mmoles) with Pd/C (0.2 g) and hydrogen gave the 4-amino-5-chloro derivative **5** in 36% yield and the 4-amino derivative **6** in 38% yield (Method D), whereas **3c** or **3d** (2 mmoles) was dehalogenated with Pd/C (0.4 g) and hydrogen afforded only the corresponding **6** in excellent yields (Method E). According to the our observation during the reaction, **5** was formed at first step and **6** was then formed at second step.

Scheme I



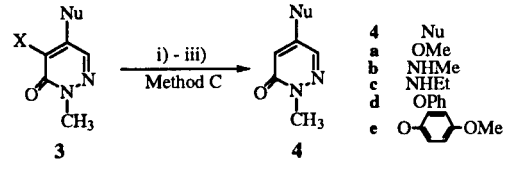
1 3 2

i) Nucleophiles, K_2CO_3 (or Et_3N), CH_3CN (or Methanol), reflux,
ii) MeI, K_2CO_3, dimethylformamide (or Acetone), 35-40°.

2,3	a	b	c	d	e	f	g	h
X	Cl	Br	Cl	Br	Cl	Br	Cl	Br
Nu	OMe	OMe	N_3	N_3	NHMe	NHMe	OPh	OPh

2,3	i	j	k	l	m	n
X	Cl	Br	Cl	Br	Cl	Br
Nu	O-⟨⟩-OMe		O-⟨⟩-CN		NHEt	

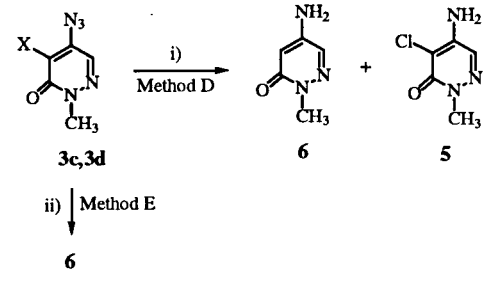
Scheme II



3 4

i) H_2, Pd/C, NaOH (10%), Methanol for **4a**.
ii) H_2, Pd/C, NaOH (10%), Ethanol for **4b**, **4c** and **4e**.
iii) H_2, Pd/C, EtOH for **4d**.

Scheme III



3c,3d 6 5

6

i) **3c** (3.18 mmoles), H_2, Pd/C (0.2 g), Ethanol, 22 hours at 24°.
ii) **3** (2.2 mmoles), H_2, Pd/C (0.4 g), Ethanol, 24 hours at 24°.

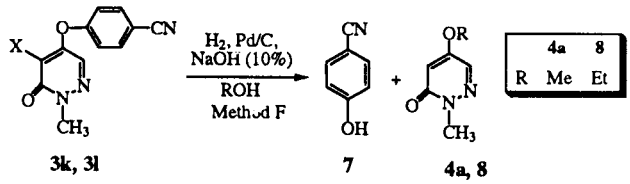
On the other hand, treatment of **3k** or **3l** with Pd/C and hydrogen in the presence of aqueous sodium hydroxide

(10%) in methanol or ethanol furnished *p*-cyanophenol and 4-methoxy **4a** or 4-ethoxy-1-methylpyridazin-6-one (**8**) instead of the corresponding 4-(4-cyanophenoxy) isomers (Method F). However, we could not observe this phenomenon in the case of **3g**, **3h**, **3i** and **3j**.

Compound **10** was also reacted with Pd/C and hydrogen in the presence of aqueous sodium hydroxide (10%) in methanol to give 5-chloro-4-methoxypyridazin-6-one (**2a**) in 74% yield.

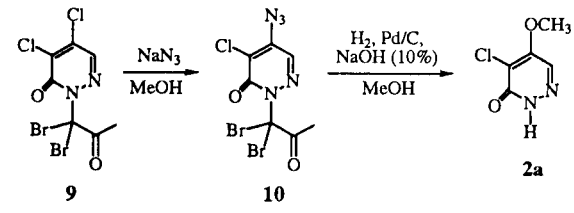
The structures of **2a**, **4**, **5**, **6**, **8** and **10** were established by ir, nmr and elemental analyses. The proton magnetic resonance spectra of **4**, **6** and **8** showed protons signals at C-3 in the δ 7.31-7.75 ppm range ($J_{3,5}$ = 2.2-2.9 Hz), at C-5 in the δ 5.57-6.26 ppm range ($J_{3,5}$ = 2.2-2.9 Hz) and at N1-CH_3 in the δ 3.50-3.74 ppm range involving other proton signals of the proposed structures. Comparing the coupling constants between C3-H and C5-H, for **4**, **6** and **8** with Katz's values, compounds **4**, **6**, and **8** are 4-substituted

Scheme IV



3k, 3l **7** **4a, 8**

Scheme V



9 **10** **2a**

Table 1

Yields, Melting Points and Infrared Spectral Data of **2a**, **3**, **4**, **5**, **6**, **8** and **10**

Compound No.	Method	Isolated Yield (%)	mp (°C) (lit mp)	IR (KBr, cm^{-1})
2a		74	233-235 (233-235) [1]	3300, 3100, 2950, 2850, 1670, 1610, 1480, 1420, 1340, 1290
3a	A	86	154-155	3110, 3070, 2980, 1650, 1610, 1470, 1430, 1400, 1330, 1300, 1220, 1190, 1110
	B	74		
3b	A	60	156-157	3100, 3050, 2950, 1650, 1610, 1400, 1300, 1200, 1100, 980, 860, 760
	B	98		
3c	A	80	90-91	3100, 3050, 2950, 2150, 1640, 1600, 1520, 1400, 1340, 1320, 1240, 1145
	B	96		
3d	A	70	103-104	3100, 3050, 2950, 2150, 1640, 1400, 1340, 1320, 860, 700
	B	96		
3e	A	70	160-161	3350, 2950, 1650, 1620, 1525, 1460, 1430, 1400, 1350, 1320, 1230, 1160, 1090
	B	75		
3f	A	77	156-157	3355, 3050, 2970, 1655, 1620, 1530, 1470, 1440, 1410, 1360, 1320, 1235, 1100
	B	91		
3g	A	88	132-133	3100, 3020, 2900, 1660, 1600, 1500, 1400, 1290, 1230, 880, 750
	B	64		
3h	A	79	144-145	3100, 3050, 3000, 1660, 1600, 1500, 1400, 1290, 1230, 840, 750
	B	85		
3i	A	67	160-161	3070, 2970, 1670, 1620, 1520, 1390, 1330, 1290, 1260, 1220
	B	86		
3j	A	81	163-165	3050, 2950, 2850, 1660, 1610, 1510, 1450, 1390, 1320, 1280, 1250, 1215, 1100
	B	98		
3k	A	75	183-184	3100, 3050, 2980, 2245, 1670, 1620, 1600, 1510, 1390, 1330, 1280, 1240
	B	98		
3l	A	65	198-199	3110, 3070, 2970, 2240, 1660, 1620, 1600, 1510, 1385, 1320, 1270, 1230, 1180, 1070
	B	99		
3m	A	80	135-137	3330, 3000, 3025, 2900, 1640, 1610, 1520, 1320, 1010, 870, 810
	B	67		
3n	A	60	147-148	3350, 3000, 2900, 1640, 1620, 1530, 1020, 820
	B	60		
4a	C	89	111-112	3080, 3050, 2995, 2950, 1650, 1600, 1550, 1460, 1400, 1340, 1290, 1240
	F	62		
4b	C	78	185-186	3430, 3370, 3260, 3100, 2950, 1700, 1645, 1580, 1540, 1420, 1400, 1355, 1295, 1060
4c	C	98	176-177	3440, 3250, 3080, 2980, 2910, 1650, 1600, 1545, 1430, 1395, 1375, 1345, 1290, 1140
4d	C	97	74-75	3050, 2970, 1670, 1620, 1600, 1500, 1410, 1360, 1230, 1160
4e	C	69	116-117	3080, 2980, 2930, 2850, 1655, 1620, 1510, 1400, 1350, 1260, 1220, 1030
5	D	36	202-204 (203-204) [6]	3500, 3330, 3200, 3100, 2980, 1655, 1630, 1610, 1540, 1440, 1420, 1380, 1325, 1270

Table 1 (continued)

Compound No.	Method	Isolated Yield (%)	mp (°C) (lit mp)	IR (KBr, cm^{-1})
6	D	38	190-193	3440, 3340, 3210, 2920, 1640, 1580, 1460, 1420, 1370, 1310, 1270, 1250, 1035, 990
	E	99		
8	F	68	104-105	3100, 3050, 3000, 2960, 1740, 1660, 1615, 1560, 1490, 1360, 1300, 1240
10		96	137-139	3070, 2940, 2150, 1750, 1670, 1610, 1530, 1410, 1375, 1340, 1220, 1200, 1150, 1020

Table 2

^{1}H Nmr Spectral Data of Compounds **2a**, **3**, **4**, **5**, **6**, **8** and **10**

Compound No.	Solvent [b]	$^1H_3$ (s)	N-CH_3 (s)	^{1}H nmr (ppm)[a] Others
2a	D	8.10	—	4.06 (s, OMe), 13.26 (bs, NH)
3a	C	7.80	3.84	4.09 (s, OMe)
3b	C	7.63	3.76	4.00 (s, OMe)
3c	C	7.60	3.81	—
3d	C	7.61	3.83	—
3e	D	7.79	3.59	2.92 (d, CH_3, J = 4.9), 6.61 (bs, NH)
3f	C	7.47	3.76	3.05 (d, CH_3, J = 5), 4.90 (bs, NH)
3g	C	7.47	3.84	7.11 (d, Ar. 2H, J = 7.9), 7.30 (t, Ar. 1H), 7.46 (t, Ar. 2H)
3h	C	7.13	3.60	6.87 (d, Ar. 2H, J = 7.8), 7.06 (t, Ar. 1H), 7.22 (t, Ar. 2H)
3i	C	7.40	3.80	3.83 (s, OMe), 6.95 (d, Ar. 2H, J = 9), 7.04 (d, Ar. 2H, J = 9)
3j	C	7.32	3.82	3.84 (s, OMe), 6.95 (d, Ar. 2H, J = 9), 7.05 (d, Ar. 2H, J = 9.1)
3k	C	7.58	3.86	7.17 (d, Ar. 2H, J = 9), 7.76 (d, Ar. 2H, J = 9)
3l	C	7.48	3.87	7.16 (d, Ar. 2H, J = 8.7), 7.75 (d, Ar. 2H, J = 8.8)

[a] Abbreviations used: Ar = Aromatic, bs = broad singlet, s = singlet, d = doublet, m = multiplet, q = quartet, J = Hz unit. The proton signals of all NH were exchangeable with deuterium oxide. [b] C = Deuteriochloroform, D = dimethyl-d_6 sulfoxide.

Table 2 (continued)

Compound No.	Solvent [b]	$^1H_3$ (d_J)	$^1H_5$ (d_J)	N-CH_3 (s)	^{1}H nmr (ppm)[a] Others
3m	C	7.55	—	3.76	1.34 (t, CH_3), 3.39 (m, CH_2), 4.66 (bs, NH)
3n	C	7.39	—	3.69	1.27 (t, CH_3), 3.31 (m, CH_2), 4.89 (bs, NH)
4a	D	7.54 (2.9)	6.15 (2.9)	3.72	3.80 (s, OMe)
4b	C	7.31 (2.6)	5.69 (2.6)	3.67	2.82 (d, CH_3, J = 5.1), 4.58 (bs, NH)
4c	C	7.31 (2.6)	5.68 (2.6)	3.67	1.27 (t, CH_3), 3.12 (m, CH_2), 4.54 (bs, NH)
4d	C	7.75 (2.8)	5.98 (2.8)	3.74	7.09 (d, Ar. 2H, J = 7.9), 7.29 (t, Ar. 1H), 7.44 (t, Ar. 2H)
4e	C	7.73 (2.8)	5.95 (2.8)	3.73	3.82 (s, OMe), 6.93 (d, Ar. 2H, J = 7.8), 7.00 (d, Ar. 2H, J = 7.8)
5	D	7.55	—	3.55	6.71 (bs, NH_2)

Table 2 (continued)

Compound No.	Solvent [b]	$^1H_3$ (d_J)	$^1H_5$ (d_J)	N-CH_3 (s)	^{1}H nmr (ppm)[a] Others
6	D	7.43 (2.2)	5.57 (2.2)	3.50	6.36 (bs, NH_2)
8	D	7.69 (2.8)	6.26 (2.8)	3.56	1.33 (t, CH_3), 4.06 (q, CH_2)
10	C	7.91	—	—	2.56 (s, CH_3)

[a] Abbreviations used: Ar = Aromatic, bs = broad singlet, s = singlet, d = doublet, m = multiplet, q = quartet, J = Hz unit. The proton signals of all NH were exchangeable with deuterium oxide. [b] C = Deuteriochloroform, D = dimethyl-d_6 sulfoxide.

Table 3

^{13}C NMR Spectral Data of Compounds **2a**, **3**, **4**, **5**, **6**, **8** and **10**

Compound No.	Solvent [a]	δ (ppm)
2a	D	58.2, 106.0, 127.9, 157.5, 159.4
3a	C	41.2, 58.0, 117.0, 126.3, 155.4, 159.2
3b	C	41.4, 58.1, 108.2, 125.9, 157.3, 159.5
3c	C	41.6, 123.1, 129.8, 140.0, 158.1
3d	C	41.6, 113.9, 128.7, 142.3, 158.1
3e	C	30.3, 40.6, 107.6, 125.4, 145.2, 158.2
3f	C	31.7, 42.0, 100.7, 126.3, 148.1, 159.6
3g	C	41.2, 119.9, 120.4, 126.3, 129.7, 130.8, 153.9, 154.2, 159.2
3h	C	41.4, 111.7, 120.0, 126.3, 126.4, 129.3, 130.9, 154.2, 156.1
3i	C	40.7, 55.6, 115.3, 121.0, 128.4, 146.9, 154.1, 157.4, 158.7
3j	C	41.1, 55.9, 110.0, 115.5, 121.3, 128.5, 147.2, 156.4, 157.7, 159.2
3k	C	41.0, 108.9, 117.8, 118.7, 123.2, 130.2, 134.6, 151.6, 157.3, 158.4
3l	C	42.0, 109.9, 115.8, 118.7, 119.8, 130.8, 135.5, 154.8, 158.2, 159.7
3m	C	17.8, 40.5, 42.8, 109.8, 127.7, 146.6, 160.4
3n	C	15.6, 38.4, 40.7, 99.5, 125.3, 146.1, 158.4
4a	D	39.2, 55.6, 102.9, 132.0, 160.5, 162.0
4b	C	29.2, 39.0, 96.2, 130.7, 149.7, 162.3
4c	C	14.1, 37.7, 39.5, 97.1, 131.1, 149.0, 162.7
4d	C	40.0, 107.3, 121.2, 126.9, 130.8, 132.2, 152.9, 160.5, 162.4
4e	C	39.4, 55.6, 106.4, 115.3, 121.7, 131.6, 145.8, 157.7, 160.5, 162.0
5	C	39.2, 103.9, 129.3, 145.5, 157.2
6	D	38.2, 97.3, 130.8, 149.9, 160.9
8	D	14.4, 39.7, 64.8, 103.7, 126.3, 132.8, 160.3, 162.6
10	C	22.8, 76.0, 122.0, 132.2, 140.9, 155.0, 188.1

[a] C = Deuteriochloroform, D = dimethyl-d_6 sulfoxide.

Table 4

Elemental Analytical Data of **3**, **4**, **6**, **8** and **10**

Compound No.	Molecular Formula	Analysis(%) Calcd./Found C	H	N
3a	$C_6H_7O_2N_2Cl$	41.28	4.04	16.05
		41.07	3.76	16.07
3b	$C_6H_7O_2N_2Br$	32.90	3.22	12.79
		32.76	3.09	12.74
3c	$C_5H_4ON_5Cl$	32.36	2.17	37.74
		32.37	1.85	37.43
3d	$C_5H_4ON_5Br$	26.11	1.75	30.45
		26.27	1.88	30.22
3e	$C_6H_8N_3OCl$	41.51	4.64	24.20
		41.43	4.37	24.19
3f	$C_6H_8N_3OBr$	33.05	3.70	19.27
		33.28	3.57	19.21
3g	$C_{11}H_9N_2O_2Cl$	55.83	3.83	11.84
		55.86	3.62	11.80
3h	$C_{11}H_9N_2O_2Br$	47.00	3.23	9.97
		47.00	3.11	9.95
3i	$C_{12}H_{11}N_2O_3Cl$	54.05	4.16	10.50
		54.11	4.11	10.50
3j	$C_{12}H_{11}N_2O_3Br$	46.32	3.56	9.00
		46.34	3.55	8.94
3k	$C_{12}H_8N_3O_2Cl$	55.08	3.08	16.06
		55.12	2.97	16.10
3l	$C_{12}H_8N_3O_2Br$	47.08	2.63	13.73
		46.93	2.54	13.69
3m	$C_7H_{10}N_3OCl$	44.81	5.37	22.40
		44.76	5.23	22.43
3n	$C_7H_{10}N_3OBr$	36.23	4.34	18.11
		36.30	4.17	18.06
4a	$C_6H_8N_2O_2$	51.42	5.75	19.99
		51.41	5.74	20.07
4b	$C_6H_9N_3O$	51.79	6.52	30.20
		51.78	6.57	30.03
4c	$C_7H_{11}N_3O$	54.89	7.24	27.43
		54.65	7.13	27.14
4d	$C_{11}H_{10}N_2O_2$	65.34	4.98	13.85
		65.27	4.94	13.85
4e	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06
		61.81	5.12	12.05
5	$C_5H_6N_3OCl$	37.63	3.79	26.33
		37.85	3.60	26.16
6	$C_5H_7N_3O$	47.99	5.64	33.58
		47.76	5.71	33.67
8	$C_7H_{10}N_2O_2$	54.54	6.54	18.17
		54.55	6.55	18.24
10	$C_7H_4N_5O_2Br_2Cl$	21.94	1.05	18.29
		21.83	1.04	18.21

isomers. Thus, the functionalization of 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones under our reaction conditions may be regarded as a regiospecific substitution that yields only 5-halo-4-substituted-pyridazin-6-ones.

Finally, the difference of our results from those of Lyga's may be due to a different substituent at the N-1 position.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 or a Bruker FTNMR-DRX 500 spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed column chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. Compounds **1** [4], **2** [1] and **9** [5] were prepared by the reported methods.

5-Chloro-1-methyl-4-methoxypyridazin-6-one (**3a**).

Method A.

A solution of **1a** (2 g, 11.17 mmoles), potassium carbonate (23 g, 166 mmoles) and methanol (150 ml) was refluxed for 6 hours. The excess alcohol was evaporated under reduced pressure. After adding chloroform (20 ml) and water (60 ml) with stirring, the organic layer was separated by separatory funnel and evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:4, v/v) to afford **3a**.

Method B.

A mixture of **2a** (0.44 g, 2.75 mmoles), potassium carbonate (0.52 g, 3.76 mmoles), methyl iodide (0.7 g, 4.93 mmoles) and dimethylformamide (20 ml) was stirred for 4 hours at 38°. The reaction mixture was filtered. Adding chloroform (40 ml) to the filtrate, the resulting solution was washed with excess water. The organic layer was evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **3a**.

5-Bromo-1-methyl-4-methoxypyridazin-6-one (**3b**).

Method A.

A solution of **1b** (1 g, 3.73 mmoles), potassium carbonate (1.03 g, 7.45 mmoles) and methanol (20 ml) was refluxed for 5.5 hours. The excess alcohol was evaporated under reduced pressure. After adding water (30 ml) with stirring, the resulting residue was washed with water (20 ml) and dried in air to yield **3b**.

Method B.

A mixture of **2b** (0.5 g, 2.45 mmoles), potassium carbonate (0.68 g, 4.92 mmoles), methyl iodide (0.7 g, 4.93 mmoles) and dimethylformamide (10 ml) was stirred for 6 hours at 30-35°. To the reaction mixture was added chloroform (50 ml) and water (200 ml) with stirring. The organic layer was separated by separatory funnel and dried over anhydrous magnesium sulfate. The organic layer was evaporated under reduced pressure. The residue was recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to give **3b**.

5-Chloro-1-methyl-4-azidopyridazin-6-one (**3c**).

Method A.

A solution of **1a** (2 g, 11.17 mmoles), sodium azide (0.73 g, 11.23 mmoles) and methanol (15 ml) was refluxed for 24 hours.

The excess alcohol was evaporated under reduced pressure. After adding water (20 ml) with stirring, the precipitate was filtered and dried in air. The precipitates was recrystallized from chloroform/*n*-hexane (2:3, v/v) to afford **3c**.

Method B.

A mixture of **2a** (0.48 g, 3.00 mmoles), potassium carbonate (0.58 g, 4.20 mmoles) and acetone (15 ml) was stirred for 0.5 hours. After adding methyl iodide (0.593 g, 4.18 mmoles), the reaction mixture was stirred for 14 hours at 36-38°. The reaction mixture was filtered and washed with chloroform (40 ml). The resulting filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 4 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:4, v/v) to give **3c**.

5-Bromo-1-methyl-4-azidopyridazin-6-one (**3d**).

Method A.

A solution of **1b** (1 g, 3.73 mmoles), sodium azide (0.29 g, 4.46 mmoles) and methanol (15 ml) was stirred for 3 hours at room temperature. The mixture was evaporated under reduced pressure. After adding water (30 ml) with stirring, the precipitate was filtered and recrystallized from chloroform/*n*-hexane (1:2, v/v) to afford **3d**.

Method B.

A mixture of **2d** (0.5 g, 2.33 mmoles), potassium carbonate (0.64 g, 4.63 mmoles), methyl iodide (0.66 g, 4.65 mmoles) and dimethylformamide (10 ml) was stirred for 16 hours at 30-35°. After adding chloroform (50 ml) and water (100 ml), the organic layer was separated by separatory funnel and dried over anhydrous magnesium sulfate. The resulting solution was evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **3d**.

5-Chloro-1-methyl-4-(methylamino)pyridazin-6-one (**3e**).

Method A.

A solution of **1a** (1 g, 5.58 mmoles), methylamine hydrochloride (0.46 g, 6.81 mmoles), triethylamine (1.03 ml, 7.38 mmoles) and methanol (15 ml) was refluxed for 7 hours. The mixture was evaporated under reduced pressure. After adding chloroform (10 ml) and diethyl ether (20 ml) with stirring, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/*n*-hexane (1:4, v/v) to afford **3e**.

Method B.

A mixture of **2e** (0.1 g, 0.63 mmole), potassium carbonate (0.1 g, 0.72 mmole), methyl iodide (0.114 g, 0.80 mmole) and dimethylformamide (3 ml) was stirred for 22 hours at 38-40°. After adding chloroform (30 ml) and water (30 ml) with stirring, the organic layer was separated by separatory funnel and evaporated under reduced pressure to give **3e**.

5-Bromo-1-methyl-4-(methyamino)pyridazin-6-one (**3f**).

Method A.

A solution of **1b** (1 g, 3.74 mmoles), methylamine hydrochloride (0.33 g, 4.88 mmoles), triethylamine (0.68 ml, 4.88 mmoles) and methanol (20 ml) was refluxed for 48 hours. The mixture was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to afford **3f**.

Method B.

A mixture of **2f** (0.17 g, 0.84 mmole), potassium carbonate (0.16 g, 1.16 mmoles) and acetone (15 ml) was stirred for 0.5 hours at room temperature. Adding methyl iodide (0.23 g, 1.61 mmoles), the mixture was stirred for 24 hours at 35°. The reaction mixture was filtered and washed with chloroform (30 ml). The combined filtrate was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 4 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:4, v/v) to give **3f**.

5-Chloro-1-methyl-4-phenoxypyridazin-6-one (**3g**).

Method A.

A solution of **1a** (0.5 g, 2.79 mmoles), potassium carbonate (0.46 g, 3.33 mmoles), phenol (0.32 g, 3.40 mmoles) and acetonitrile (15 ml) was refluxed for 24 hours. The mixture was evaporated under reduced pressure. After adding chloroform/water (1:2, v/v, 120 ml) with stirring, the organic layer was separated by separatory funnel, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was washed with diethyl ether to afford **3g**.

Method B.

A mixture of **2g** (1.5 g, 6.76 mmoles), potassium carbonate (2.49 g, 18 mmoles), methyl iodide (2.56 g, 18 mmoles) and dimethylformamide (15 ml) was stirred for 60 hours at 30-35°. Adding chloroform/water (1:2, v/v, 150 ml) with stirring, the organic layer was separated by separatory funnel and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The residue was triturated in water. The resulting crystal was filtered and dried in air to give **3g**.

5-Bromo-1-methyl-4-phenoxypyridazin-6-one (**3h**).

Method A.

A solution of **1b** (0.5 g, 1.87 mmoles), potassium carbonate (0.31 g, 2.24 mmoles), phenol (0.21 g, 2.23 mmoles) and acetonitrile (15 ml) was refluxed for 24 hours. The solvent was evaporated under reduced pressure. After adding chloroform/water (1:1, v/v, 100 ml) with stirring, the organic layer was separated by separatory funnel, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:3, v/v) to afford **3h**.

Method B.

A mixture of **2h** (0.5 g, 1.88 mmoles), potassium carbonate (0.52 g, 3.76 mmoles), methyl iodide (0.53 g, 3.73 mmoles) and dimethylformamide (10 ml) was stirred for 13 hours at 30-35°. Adding water (50 ml) to the solution, the resulting mixture was filtered. Chloroform (50 ml) was added, and the organic layer was separated by separatory funnel and evaporated under reduced pressure to give **3h**.

5-Chloro-1-methyl-4-(4-methoxyphenoxy)pyridazin-6-one (**3i**).

Method A.

A solution of **1a** (1 g, 5.59 mmoles), potassium carbonate (1.54 g, 11 mmoles), 4-methoxyphenol (1.37 g, 11 mmoles) and acetonitrile (20 ml) was refluxed for 7 hours. After cooling to room temperature, the mixture was filtered, and evaporated under reduced pressure. The resulting residue was washed with diethyl ether (10 ml) and dried in air to afford **3i**.

Method B.

A mixture of **2i** (0.51 g, 2.02 mmoles), potassium carbonate (0.34 g, 2.44 mmoles), methyl iodide (0.35 g, 2.44 mmoles) and dimethylformamide (5 ml) was stirred for 12 hours at 38-40°. After adding chloroform (30 ml), the reaction mixture was filtered and evaporated under reduced pressure. Adding ice water (50 ml), the resulting precipitate was filtered and dried in air to give **3i**.

5-Bromo-1-methyl-4-(4-methoxyphenoxy)pyridazin-6-one (**3j**).

Method A.

A solution of **1b** (1 g, 3.73 mmoles), potassium carbonate (0.62 g, 4.48 mmoles), 4-methoxyphenol (0.51 g, 4.11 mmoles) and acetonitrile (20 ml) was refluxed for 24 hours. After cooling to room temperature, the mixture was filtered and washed with acetone (30 ml). The filtrate was evaporated under reduced pressure. The residue was recrystallized from methanol to afford **3j**.

Method B.

A mixture of **2j** (0.16 g, 0.54 mmoles), potassium carbonate (0.11 g, 0.8 mmoles), methyl iodide (0.114 g, 0.8 mmoles) and acetone (20 ml) was stirred for 3 hours at 37°. The reaction mixture was filtered, evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 4 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **3j**.

5-Chloro-1-methyl-4-(4-cyanophenoxy)pyridazin-6-one (**3k**).

Method A.

A solution of **1a** (0.95 g, 5.31 mmoles), potassium carbonate (0.88 g, 6.37 mmoles), 4-cyanophenol (0.67 g, 5.62 mmoles) and acetonitrile (20 ml) was refluxed for 6 hours. After cooling to room temperature, the mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was recrystallized from chloroform/methanol/*n*-hexane (3:15:10, v/v/v) to afford **3k**.

Method B.

A mixture of **2k** (0.29 g, 1.17 mmoles), potassium carbonate (0.24 g, 1.75 mmoles), methyl iodide (0.25 g, 1.77 mmoles) and acetone (15 ml) was stirred for 10 hours at 37°. The reaction mixture was filtered, evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 4 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:4, v/v) to give **3k**.

5-Bromo-1-methyl-4-(4-cyanophenoxy)pyridazin-6-one (**3l**).

Method A.

A solution of **1b** (1 g, 3.73 mmoles), potassium carbonate (0.62 g, 4.49 mmoles), 4-cyanophenol (0.53 g, 4.45 mmoles) and acetonitrile (20 ml) was refluxed for 6.5 hours. After cooling to room temperature, the mixture was filtered and washed with chloroform (30 ml). The filtrate was evaporated under reduced pressure. The residue was dissolved in acetone (20 ml) and filtered. The resulting filtrate was evaporated under reduced pressure and dried in air to afford **3l**.

Method B.

A mixture of **2l** (0.234 g, 0.80 mmole), potassium carbonate (0.22 g, 1.6 mmoles), methyl iodide (0.524 g, 3.69 mmoles) and acetone (20 ml) was stirred for 16 hours at 37°. The reaction mixture was filtered, evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 4 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give **3l**.

5-Chloro-1-methyl-4-(ethylamino)pyridazin-6-one (**3m**)

Method A.

A solution of **1a** (1 g, 5.59 mmoles), ethylamine hydrochloride (0.68 g, 8.34 mmoles), triethylamine (0.9 g, 8.89 mmoles) and methanol (20 ml) was refluxed for 32 hours. After cooling to room temperature, the solution was evaporated under reduced pressure. After adding water (50 ml), the mixture was neutralized by aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water (1:20, v/v)]. The product was extracted with ethyl acetate (100 ml x 3). The extract was coevaporated with silica gel (1.5 g) and applied to the top of an open-bed silica gel column (2.5 x 10). The column was eluted with chloroform/diethyl ether (19:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from diethyl ether to afford **3m**.

Method B.

A mixture of **2m** (1.1 g, 6.36 mmoles), potassium carbonate (1.74 g, 12.6 mmoles), methyl iodide (1.79 g, 12.61 mmoles) and dimethylformamide (15 ml) was stirred for 48 hours at 30-35°. After adding ethyl acetate/water (1:2, v/v, 150 ml), the organic layer was separated by separatory funnel, washed with water (30 ml) and dried over anhydrous magnesium sulfate. The resulting solution was coevaporated with silica gel (1 g) under reduced pressure and applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1:9, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/*n*-hexane (1:1, v/v) to give **3m**.

5-Bromo-1-methyl-4-(ethylamino)pyridazin-6-one (**3n**).

Method A.

A solution of **1b** (1.5 g, 5.6 mmoles), ethylamine hydrochloride (0.91 g, 11 mmoles), triethylamine (1.13 g, 11 mmoles) and methanol (40 ml) was refluxed for 48 hours. The mixture was evaporated under reduced pressure. After adding water (50 ml), the mixture was neutralized using aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water (1 ml/20 ml)]. The product was extracted with ethyl acetate (100 ml x 3). The solution was coevaporated with silica gel (2 g) and applied to the top of an open-bed silica gel column (2.5 x 12 cm). The column was eluted with chloroform/diethyl ether (19:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from diethyl ether to afford **3n**.

Method B.

A mixture of **2n** (1.1 g, 5.07 mmoles), potassium carbonate (1.27 g, 9.2 mmoles), methyl iodide (1.31 g, 9.23 mmoles) and dimethylformamide (10 ml) was stirred for 40 hours at room temperature. After adding ethyl acetate/water (1:2, v/v, 120 ml) with stirring, the organic layer was separated by separatory funnel and dried over anhydrous magnesium sulfate. The solution was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with chloroform/diethyl ether (19:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/*n*-hexane (1:3, v/v) to give **3n**.

1-Methyl-4-methoxypyridazin-6-one (**4a**).

Method C.

A mixture of Pd/C (0.44 g for **3a**; 0.2 g for **3b**), **3** (5.75 mmoles for **3a**; 2.05 mmoles for **3b**), aqueous sodium hydroxide (10%, 3 ml for **3a**; 2 ml for **3b**) and methanol (15-25 ml) was stirred for 2-3 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with chloroform or methanol (40 ml). The solution was evaporated under reduced pressure. The residue was dissolved in water (10-15 ml) and neutralized using aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water = 1 ml/20 ml)]. The product was extracted with chloroform (30-50 ml). The resulting solution was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **4a**.

Method F.

A mixture of **3k** or **3l** (1.97 mmoles), Pd/C (0.2 g), aqueous sodium hydroxide (10%, 2 ml) and methanol (25 ml) was stirred for 14 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the resin was washed with methanol (20 ml) and chloroform (40 ml). The resulting solution was evaporated under reduced pressure. The residue was dissolved in water (10 ml) and neutralized using aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water = 1 ml/20 ml)]. The resulting solution was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with chloroform/ethyl acetate (10:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure to afford **4a**.

1-Methyl-4-(methyamino)pyridazin-6-one (**4b**).

A mixture of Pd/C (0.3 g), **3e** (or **3f** 2.89 mmoles), aqueous sodium hydroxide (10%, 2 ml) and ethanol (25 ml) was stirred for 2-3 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with chloroform (30 ml) and ethanol (20 ml). The solution was evaporated under reduced pressure. The residue was dissolved in water (10-15 ml) and neutralized using aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water = 1 ml/20 ml)]. The product was extracted with chloroform (60 ml). The resulting solution was evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:4, v/v) to give **4b**.

1-Methyl-4-(ethylamino)pyridazin-6-one (**4c**).

A mixture of Pd/C (0.2 g), **3m** (or **3n**, 2.19 mmoles), aqueous sodium hydroxide (10%, 2 ml) and ethanol (25 ml) was stirred for 2-3 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the resin was washed with ethanol (40 ml). The solution was evaporated under reduced pressure. The residue was dissolved in chloroform (50 ml) and filtered. The solution was evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **4c**.

1-Methyl-4-phenoxypyridazin-6-one (**4d**).

A mixture of Pd/C (0.2 g), **3g** (or **3h** 1.28 mmoles) and ethanol (20 ml) was stirred for 3-5 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with ethanol (30 ml). The solution was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **4d**.

1-Methyl-4-(4-methoxyphenoxy)pyridazin-6-one (**4e**).

A mixture of Pd/C (0.2 g), **3i** (or **3j**, 1.88 mmoles for **3a**; 2.05 mmoles for **3b**), aqueous sodium hydroxide (10%, 1 ml) and ethanol (20 ml) was stirred for 2-3 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with chloroform (40 ml). The solution was evaporated under reduced pressure. The residue was dissolved in water (20 ml). And the precipitate was filtered and recrystallized from chloroform/*n*-hexane (1:5, v/v) to give **4e**.

1-Methyl-4-aminopyridazin-6-one (**6**) and 1-Methyl-4-amino-5-chloropyridazin-6-one (**5**).

Method D.

A mixture of Pd/C (0.2 g), **3c** (0.59 g, 3.19 mmoles) and ethanol (15 ml) was stirred for 22 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with ethanol (30 ml). The solution was evaporated under reduced pressure. The residue was neutralized using aqueous sodium hydroxide (10%). The resulting solution was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 8 cm). The column was eluted with ethyl acetate. Fractions containing **5** were combined and evaporated under reduced pressure to give **5** in 36% (0.18 g) yield. Fractions containing **6** were also combined and evaporated under reduced pressure to give **6** in 38% (0.15 g) yield.

1-Methyl-4-aminopyridazin-6-one (**6**).

Method E.

A mixture of Pd/C (0.4 g), **3c** (or **3d**, 2 mmoles) and ethanol (25 ml) was stirred for 17 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with ethanol (20 ml). The solution was evaporated under reduced pressure. After adding water (10 ml), the residue was neutralized using aqueous sodium hydroxide (10%). The resulting solution

was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **6** in quantitative yield.

4-Ethoxy-1-methylpyridazin-6-one (**8**).

Method F.

A mixture of **3k** or **3l** (1.15 mmoles), Pd/C (0.2 g), aqueous sodium hydroxide (10%, 1 ml) and ethanol (20 ml) was stirred for 96 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the resin was washed with chloroform (40 ml). The resulting solution was evaporated under reduced pressure. The residue was dissolved in water (25 ml) and neutralized using aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water = 1 ml/20 ml)]. The product was extracted with chloroform (50 ml). The resulting solution was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 6 cm). The column was eluted with diethyl ether. Fractions containing the product were combined and evaporated under reduced pressure to afford **8**.

4-Azido-5-chloro-1-(1,1-dibromo-2-oxopropyl)pyridazin-6-one (**10**).

A solution of **9** (1 g, 2.64 mmoles), sodium azide (0.21 g, 3.17 mmoles) and methanol (10 ml) was stirred for 1 hour at room temperature. The mixture was evaporated under reduced pressure. The residue was dissolved in water (20 ml). The resulting precipitate was filtered and dried in air to give **10** in 96% (0.98 g) yield.

5-Chloro-4-methoxypyridazin-6-one (**2a**).

A mixture of **10** (1.5 g, 3.99 mmoles), Pd/C (0.3 g), aqueous sodium hydroxide (10%, 6 ml) and methanol (50 ml) was stirred for 3 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the resin was washed with methanol (30 ml). The resulting solution was evaporated under reduced pressure. The residue was dissolved in water (20 ml) and neutralized using aqueous diluted hydrochloric acid [concentrated hydrochloric acid/water = 1 ml/20 ml)]. The resulting precipitate was filtered and dried in air to afford **2a** in 74% (0.47 g) yield. This product was identical with an authentic sample.

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