Functionalization of 4,5-Dihalopyridazin-6-ones Using 1-(1,1-Dibromo-2-oxopropyl) Derivatives

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Functionalization of 4,5-dihalopyridazin-6-ones using 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones with some nucleophiles gave regioselectively only 5-halo-4-substituted-pyridazin-6-ones.

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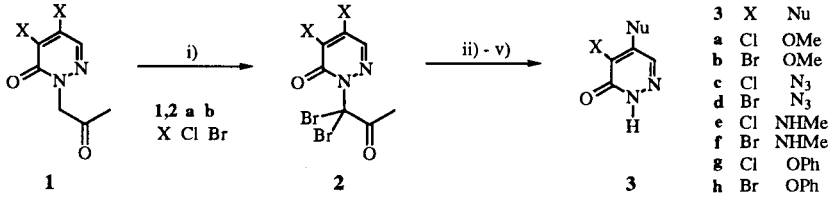
Di- or trisubstituted-pyridazin-6-ones are useful intermediates in the synthesis of pyridazine derivatives. However, the direct functionalization of pyridazin-6-ones is difficult because of the acidity for hydrogen at the N-1 position. Recently, Bryant *et al.* [1] synthesized 3-chloro-5-methoxypyridazine from 4,5-dichloropyridazin-6-one using dihydropyran as the protecting group *via* four steps. Choi, *et al.* [2] also reported the decomposition of 1-(2-oxopropyl)-4,5-dichloropyridazin-6-one and 1-(1,1-dibromo-2-oxopropyl)-4,5-dichloropyridazin-6-one with excess sodium azide or potassium carbonate to the corresponding multisubstituted pyridazin-6-one. Therefore, we attempted to investigate a regioselective functionalization of multihalopyridazin-6-ones.

The preconditions for the functionalization are the following: i) the reactivity and the regioselectivity on the ring must increase by the introduction of a protecting group at N-1 position, ii) the introduction and the removal of the protecting group must be easy under mild condition, iii) the substitution on the ring must also be faster than the cleavage of C-N bond at N-1 position. Because that the C-N bond cleavage and the introduction of 2-oxopropyl group are easy, we chose 1-(1,1-dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones as the starting materials for the functionalization.

In this paper, we report the results of the title reaction. *N*-Alkylation of 4,5-dihalopyridazin-6-ones was carried out by the Choi's method [3]. Bromination of **1** was also carried out by the reported method [2b].

First, we observed several spots on the tlc plate when **2** was allowed to react with sodium methoxide in dry methanol. For that reason, the methoxylation of **2** was performed by the Cho's method [4] using potassium carbonate-methanol. Methoxylation of **2** with potassium carbonate (about 4 equivalents) in methanol gave the corresponding 4-methoxy-5-halopyridazin-6-ones **3a** and **3b** in excellent yields. Reaction of **2** with sodium azide (about 4 equivalents) in methanol afforded selectively 4-azido derivatives **3c** and **3d** in good yields. Treatment of **2** with methylamine hydrochloride (4 equivalents) and triethylamine (8 equivalents) in methanol also yielded 4-methylamino-5-halopyridazin-6-ones **3e** and **3f**. After **2** was reacted with phenol (1 equivalent) and potassium carbonate (1 equivalent) in acetonitrile, treatment of the mixture with potassium carbonate (2 equivalents) in water gave the corresponding 4-phenoxy derivatives **3g** and **3h**.

Scheme I



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

i) Br_2, AcOH, AcONa, $CHCl_3$, room temperature.
ii) Methanol, 4 K_2CO_3, room temperature for **3a** and **3b**.
iii) 4 NaN_3, Methanol, reflux for **3c** and **3d**.
iv) 4 $MeNH_2$.HCl, 8 Et_3N, Methanol, reflux for **3e** and **3f**.
v) (1) Phenol, K_2CO_3, CH_3CN, reflux; (2) K_2CO_3, H_2O, reflux for **3g** and **3h**.

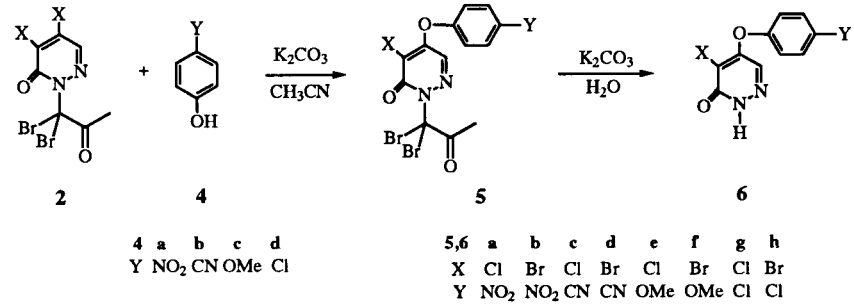
The structures of **3a-3h** were established by ir, nmr and elemental analyses.

The infrared spectra of **3a-3h** revealed the characteristic peaks of free pyridazin-6-one at the 3300-2800 cm^{-1} range and the absorption peaks of amide carbonyl at the 1650-1680 cm^{-1} range. However, we did not detect the absorption peak of carbonyl for the oxopropyl group. The

^{1}H nmr spectra of **3a-3h** showed the proton signals of NH for pyridazinone in the δ 12.53-13.43 ppm range (except for **3g**) and of one aromatic proton in the δ 7.53-8.10 ppm involving the protons of methoxy (for **3a** and **3b**), methylamino (for **3e** and **3f**) and phenyl group (**3g** and **3h**). The ^{13}C nmr spectra of **3** did not show the carbon signals of the oxopropyl group.

Because of our interest in the effect of the substituents on the phenyl ring, we attempted to synthesize **6** from **2** and *p*-substituted phenols **4** *via* two steps. Reaction of **2** with **4** in the presence of potassium carbonate in acetonitrile gave **5a-5h** in good yields. Dealkylation of **5** with potassium carbonate in water afforded compounds **6a-6h** in good yields. The structures of **5** and **6** were established by ir, nmr and elemental analyses.

Scheme II



2 **4** **5** **6**

4	**a**	**b**	**c**	**d**
Y	NO_2	CN	OMe	Cl

5,6	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
X	Cl	Br	Cl	Br	Cl	Br	Cl	Br
Y	NO_2	NO_2	CN	CN	OMe	OMe	Cl	Cl

According to our observations, the *p*-substituents on the phenyl ring and/or halogens on the pyridazine affect the rate of the substitution and the dealkylation, *i.e.*, 1) the substitution of **2** with **4a** and **4b** is easier than it was for **4c**. 2) The cleavage of the C-N bond is faster for the **5** isomers containing *p*-NO_2 or *p*-CN than for the **5** isomers containing *p*-OMe and *p*-Cl. 3) The rate of the dealkylation is faster generally for bromopyridazinones than for chloropyridazinones.

The position of substitution on the pyridazinone for **3**, **5** and **6** was proved by the further reactions of these com-

Table 1

Yields, Melting Points and Infrared Spectral Data of **2**, **3**, **5** and **6**

Compound No.	Isolated Yield (%)	mp (°C) (lit. mp)	IR (KBr, cm^{-1})
2a	90	124-125 (113-114) [2b]	3110, 3080, 2940, 1740, 1680, 1595, 1425, 1365, 1290, 1210, 1180, 1140
2b	90	117-118	3095, 3060, 2950, 1740, 1680, 1585, 1440, 1425, 1370, 1285, 1185
3a	91	233-235	3300, 3100, 2950, 2850, 1670, 1610, 1480, 1420, 1340, 1290
3b	87	212-213	3280, 3200, 3100, 3000, 2940, 2860, 1650, 1600, 1460, 1400, 1320, 1275, 1100
3c	77	170-172	3100, 3050, 2950, 2860, 2200, 2140, 1680, 1600, 1400, 1340, 1300, 1100
3d	84	174-175	3120, 3050, 2950, 2850, 2170, 2130, 1660, 1400, 1320, 1280
3e	70	259-261 (252-253) [6]	3290, 3150, 2840, 1660, 1620, 1460, 1430, 1410, 1350, 1310, 1070
3f	65	221-223	3300, 3140, 2950, 2850, 1675, 1660, 1610, 1460, 1300
3g	58	178-179	3150, 3050, 2950, 2850, 1660, 1610, 1590, 1490, 1395, 1320, 1260, 1200
3h	57	197	3150, 3050, 2950, 2850, 1660, 1610, 1590, 1490, 1390, 1320, 1260, 1200
5a	70	182-183	3080, 2980, 2940, 1760, 1675, 1620, 1600, 1535, 1500, 1400, 1355, 1320, 1280, 1220
5b	60	190-192	3090, 2950, 1760, 1680, 1620, 1600, 1540, 1500, 1400, 1360, 1320, 1280, 1220, 1160
5c	60	170-171	3070, 2240, 1745, 1675, 1620, 1600, 1500, 1385, 1270, 1200
5d	80	155-156	3090, 2950, 2250, 1760, 1670, 1620, 1600, 1500, 1400, 1370, 1320, 1280, 1220
5e	90	129-130	3080, 2960, 1760, 1670, 1620, 1510, 1395, 1320, 1280, 1255, 1200
5f	88	152-153	3080, 2980, 1760, 1680, 1620, 1510, 1395, 1315, 1280, 1255, 1200
5g	70	141-143	3090, 1750, 1670, 1620, 1590, 1490, 1390, 1280, 1210
5h	81	129-130	3080, 2950, 1780, 1675, 1620, 1595, 1490, 1390, 1310, 1280, 1210
6a	88	249-250	3150, 3100, 3050, 2980, 2880, 1680, 1630, 1600, 1540, 1500, 1410, 1360, 1330, 1280
6b	84	275-276	3150, 3080, 2950, 2880, 1675, 1620, 1600, 1540, 1500, 1410, 1360, 1320, 1270
6c	70	218-220	3150, 3070, 2980, 2880, 2260, 1680, 1615, 1520, 1400, 1320, 1250
6d	60	247-248	3150, 3070, 2980, 2890, 2250, 1670, 1620, 1600, 1515, 1400, 1320, 1250
6e	75	163-164	3160, 3080, 2970, 1670, 1620, 1600, 1520, 1400, 1280, 1250, 1200
6f	60	173-174	3200, 3140, 2950, 2900, 1670, 1610, 1520, 1480, 1450, 1400, 1330, 1310, 1280, 1250
6g	78	206-207	3150, 3070, 2950, 2860, 1665, 1615, 1590, 1490, 1400, 1320, 1260, 1200
6h	60	249-251	3140, 3050, 2950, 2860, 1665, 1615, 1590, 1490, 1400, 1320, 1260, 1200

Table 2

^{1}H NMR Spectral Data of Compounds **2**, **3**, **5** and **6**

Compound No.	Solvent [b]	$1H_3$ (s)	^{1}H nmr (ppm) [a] NH_1 (bs)	Others
2a	C	8.07	–	2.60 (s, CH_3)
2b	C	8.05	–	2.61 (s, CH_3)
3a	D	8.10	13.26	4.06 (s, CH_3)
3b	D	8.10	13.24	4.07 (s, CH_3)
3c	D	8.08	13.26	
3d	D	8.04	13.32	
3e	D	7.80	12.60	2.91 (d, CH_3, J = 4.9), 6.66 (q, NH)
3f	D	7.69	12.53	2.91 (d, CH_3, J = 5.0), 6.51 (q, NH)
3g	C	7.54	No Detection	7.39 (m, Ar-5H)
3h	D	7.53	13.43	7.37 (m, Ar-5H)
5a	C	7.84	–	2.66 (s, CH_3), 7.28 (d, Ar-2H, J = 2.8), 8.37 (d, Ar-2H, J = 2.8)
5b	C	7.72	–	2.66 (s, CH_3), 7.28 (d, Ar-2H, J = 2.8), 8.37 (d, Ar-2H, J = 2.8)
5c	C	7.79	–	2.65 (s, CH_3), 7.25 (d, Ar-2H, J = 2.8), 7.80 (d, Ar-2H, J = 2.8)
5d	C	7.69	–	2.64 (s, CH_3), 7.26 (d, Ar-2H, J = 2.8), 7.80 (d, Ar-2H, J = 2.8)
5e	C	7.71	–	2.59 (s, CH_3), 3.85 (s, OCH_3), 6.98 (d, Ar-2H, J = 2.8), 7.10 (d, Ar-2H, J = 2.8)
5f	C	7.61	–	2.59 (s, CH_3), 3.85 (s, OCH_3), 6.98 (d, Ar-2H, J = 2.8), 7.10 (d, Ar-2H, J = 2.8)
5g	C	7.76	–	2.64 (s, CH_3), 7.15 (d, Ar-2H, J = 2.9), 7.49 (d, Ar-2H, J = 2.8)
5h	C	7.63	–	2.61 (s, CH_3), 7.12 (d, Ar-2H, J = 2.9), 7.46 (d, Ar-2H, J = 2.9)
6a	D	7.96	13.64	7.47 (d, Ar-2H, J = 15.5), 8.32 (d, Ar-2H, J = 15.5)
6b	D	7.86	13.51	7.43 (d, Ar-2H, J = 15.9), 8.31 (d, Ar-2H, J = 16.0)
6c	D	7.90	13.60	7.43 (d, Ar-2H, J = 8.7), 7.95 (d, Ar-2H, J = 8.7)
6d	D	7.79	13.49	7.41 (d, Ar-2H, J = 8.7), 7.94 (d, Ar-2H, J = 8.7)
6e	D	7.22	13.42	3.78 (s, CH_3), 7.02 (d, Ar-2H, J = 7.8), 7.53 (d, Ar-2H, J = 7.8)
6f	D	7.43	13.34	3.78 (s, CH_3), 7.02 (d, Ar-2H, J = 9.0), 7.20 (d, Ar-2H, J = 9.0)
6g	C	7.52	12.64	7.32 (d, Ar-2H, J = 9.0), 7.45 (d, Ar-2H, J = 9.0)
6h	D	7.63	13.42	7.28 (d, Ar-2H, J = 8.9), 7.52 (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 3

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

Compound No.	Solvent [a]	δ (ppm)
2a	C	23.3, 75.5, 134.8, 137.7, 138.7, 154.4, 188.6
2b	C	22.9, 62.8, 130.4, 132.7, 138.9, 254.1, 188.2
3a	D	58.2, 106.0, 127.9, 157.5, 159.4
3b	D	58.0, 105.4, 128.2, 157.8, 159.7
3c	D	119.2, 131.6, 141.1, 157.8
3d	D	111.1, 131.0, 143.4, 158.1
3e	D	30.2, 104.7, 128.0, 146.2, 158.5
3f	D	30.0, 96.3, 127.2, 147.5, 158.6
3g	C	119.7, 126.2, 130.5, 131.1, 153.8, 154.6, 160.5
3h	D	111.6, 119.1, 125.6, 130.4, 130.5, 153.8, 155.7, 159.5
5a	C	25.8, 77.4, 122.0, 124.8, 129.1, 134.2, 134.3, 147.9, 155.2, 158.5, 160.5, 191.3
5b	D	21.6, 78.6, 113.1, 120.2, 125.8, 126.7, 134.3, 145.0, 155.5, 156.9, 158.6, 187.3
5c	C	24.6, 76.5, 111.7, 119.1, 121.4, 123.2, 133.0, 133.1, 136.4, 154.2, 157.4, 157.9, 190.1
5d	C	23.6, 58.9, 110.7, 113.3, 118.0, 120.5, 131.5, 135.3, 155.5, 156.5, 156.8, 189.1
5e	C	21.9, 54.8, 75.0, 114.7, 116.6, 120.5, 129.7, 129.8, 145.3, 154.0, 155.3, 157.2, 187.3
5f	C	21.9, 54.8, 75.1, 107.4, 114.7, 120.5, 129.4, 145.3, 155.5, 156.2, 157.2, 187.3
5g	C	22.9, 23.3, 29.7, 121.3, 130.8, 132.3, 151.5, 154.0, 156.1, 188.3
5h	C	24.5, 77.1, 111.6, 123.0, 131.8, 131.9, 132.3, 133.9, 153.0, 157.8, 158.9, 190.0
6a	D	118.9, 123.0, 126.6, 132.6, 144.3, 152.3, 159.3, 159.4
6b	D	116.7, 120.0, 127.7, 133.4, 145.3, 155.5, 160.5, 160.9
6c	D	30.0, 104.9, 109.8, 118.0, 119.4, 132.2, 135.0, 157.4, 159.9
6d	D	107.4, 114.8, 118.3, 119.0, 131.7, 134.9, 154.1, 157.5, 159.4

Table 3 (continued)

Compound No	Solvent [a]	δ (ppm)
6e	D	55.7, 115.4, 121.2, 129.3, 130.3, 146.7, 154.9, 155.2, 157.7
6f	D	55.5, 115.3, 120.9, 129.5, 146.9, 156.1, 156.9, 159.4
6g	C	120.7, 130.4, 130.5, 131.3, 152.1, 153.9, 158.9, 172.9
6h	D	112.2, 120.8, 129.4, 130.2, 130.6, 152.6, 155.2, 159.4

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

Table 4

Elemental Analytical Data of **3**, **5** and **6**

Compound No.	Molecular Formula	Analysis (%) Calcd/Found		
		C	H	N
3a	$C_5H_5O_2N_2Cl$	37.40	3.14	17.45
		37.53	2.95	17.32
3b	$C_5H_5O_2N_2Br$	29.29	2.46	13.66
		29.02	2.24	13.39
3c	$C_4H_2ON_5Cl$	28.01	1.18	40.82
		28.05	1.24	40.56
3d	$C_4H_2ON_5Br$	22.24	0.93	32.42
		22.14	0.94	32.06
3e	$C_5H_6N_3OCl$	37.63	3.79	26.33
		37.62	3.68	26.03
3f	$C_5H_6N_3OBr$	29.43	2.96	20.60
		29.21	2.72	20.50
3g	$C_{10}H_7N_2O_2Cl$	53.95	3.17	12.58
		53.76	3.12	12.79
3h	$C_{10}H_7N_2O_2Br$	44.97	2.64	10.49
		44.70	2.37	10.47
5a	$C_{13}H_8N_3O_5Br_2Cl$	32.43	1.67	8.73
		32.35	1.42	8.66
5b	$C_{13}H_8N_3O_5Br_3$	29.69	1.53	7.99
		29.71	1.57	7.89
5c	$C_{14}H_8N_3O_3ClBr_2$	36.44	1.75	9.11
		36.25	1.75	9.20
5d	$C_{14}H_8N_3O_3Br_3$	33.24	1.59	8.31
		33.09	1.62	8.39
5e	$C_{14}H_{11}N_2O_4ClBr_2$	36.04	2.38	6.00
		36.07	2.36	6.10
5f	$C_{14}H_{11}N_2O_4Br_3$	32.91	2.17	5.48
		32.64	2.17	5.54
5g	$C_{13}H_8N_2O_3Cl_2Br_2$	33.16	1.71	5.95
		33.09	1.73	6.03
5h	$C_{13}H_8N_2O_3Br_3Cl$	30.30	1.56	5.44
		30.02	1.58	5.50
6a	$C_{10}H_6N_3O_4Cl$	44.88	2.26	15.70
		44.73	2.29	15.43
6b	$C_{10}H_6N_3O_4Br$	38.49	1.94	13.46
		38.21	1.96	13.30
6c	$C_{11}H_6N_3O_2Cl$	53.35	2.44	16.97
		53.07	2.40	16.67
6d	$C_{11}H_6N_3O_2Br$	45.23	2.07	14.39
		44.83	2.06	14.18
6e	$C_{11}H_9N_2O_3Cl$	52.29	3.59	11.09
		52.12	3.57	10.89
6f	$C_{11}H_9N_2O_3Br$	44.47	3.05	9.43
		44.26	2.92	9.36
6g	$C_{10}H_6N_2O_2Cl_2$	46.72	2.35	10.90
		46.73	2.30	10.80
6h	$C_{10}H_6N_2O_2BrCl$	39.83	2.01	9.29
		39.82	2.03	9.02

pounds [5]. This functionalization is easy and regioselective. According to the observation during the reaction by tlc, the functionalization occur *via* two steps, *i.e.*, the replacement of halogens by nucleophiles occurs in the first step, and C-N bond at the N-1 position of the pyridazinone then cleave in the second step.

Finally, compounds **2** as the starting materials may be regarded to as satisfying the preconditions for the functionalization of the 4,5-dihalopyridazin-6-ones.

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 on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

1-(1,1-Dibromo-2-oxopropyl)-4,5-dihalopyridazin-6-ones (**2**).

A mixture of **1** (119.43 mmoles), sodium acetate (250.81 mmoles, 20.58 g), acetic acid (250.81 mmoles, 15.06 g) and chloroform (120 ml) was stirred for 20 minutes at room temperature. Bromine (250.81 mmoles, 12.92 ml) was added to the mixture. The reaction mixture was stirred for 48 hours at 20° and washed with excess water. The organic solution was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (20 x 2 cm). The column was eluted with chloroform. Fractions involving the product were combined and evaporated under reduced pressure. The residue was recrystallized from carbon tetrachloride to give compound **2**.

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

A methanol solution (30 ml) containing potassium carbonate (3.21 g, 23.23 mmoles) was stirred for 10 minutes at room temperature. After adding **2a** (2 g, 5.28 mmoles), the mixture was stirred for 22 hours at 22°. The reaction mixture was acidified to *p*H 5 using diluted aqueous hydrochloric acid [concentrated hydrochloric acid (1 ml)/water (20 ml)]. The mixture was coevaporated with silica gel (2 g) under reduced pressure and applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with ether. Fractions containing the product were

combined and evaporated under reduced pressure. The residue was recrystallized from methanol/water (1:2, v/v) to give **3a**.

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

A mixture of methanol (15 ml), potassium carbonate (1.15 g, 8.32 mmoles) and **2b** (1 g, 2.14 mmoles) was stirred for 64 hours at 16°. The reaction mixture was evaporated under reduced pressure. After adding water (20 ml), the resulting mixture was acidified to *p*H 5 using aqueous hydrochloric acid [concentrated hydrochloric acid (1 ml)/water (20 ml)]. The mixture was coevaporated with silica gel (2 g) under 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 **3b**.

4-Azido-5-chloropyridazin-6-one (**3c**).

A solution of **2a** (1 g, 2.64 mmoles), sodium azide (0.8 g, 10.56 mmoles) and methanol (20 ml) was refluxed for 2 hours. The mixture was coevaporated with silica gel (1.4 g) under reduced pressure and applied to the top of an open-bed silica gel column (2 x 6 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 ethyl acetate/*n*-hexane (1:2, v/v) to yield **3c**.

4-Azido-5-bromopyridazin-6-one (**3d**).

A solution of **2b** (1 g, 2.14 mmoles), sodium azide (0.61 g, 9.41 mmoles) and methanol (15 ml) was refluxed for 1 hour. The mixture was evaporated under reduced pressure. The residue was recrystallized from water to afford **3d**.

5-Chloro-4-methylaminopyridazin-6-one (**3e**).

A mixture of triethylamine (3.2 ml, 21.65 mmoles), methylamine hydrochloride (0.73 g, 10.82 mmoles) and methanol (15 ml) was stirred for minutes at room temperature. After adding **2a** (1 g, 2.64 mmoles), the reaction mixture was refluxed for 17 hours. The solvent was evaporated under reduced pressure. The residue was triturated in *n*-hexane (100 ml) and filtered. The product was extracted with methanol (40 ml), coevaporated with silica gel (2 g) and applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with ethyl acetate. Fractions involving the product were combined and evaporated under reduced pressure. The crude product was recrystallized from methanol to furnish **3e**.

5-Bromo-4-methylaminopyridazin-6-one (**3f**).

A mixture of triethylamine (2.39 ml, 17.11 mmoles), methylamine hydrochloride (0.58 g, 8.52 mmoles) and methanol (15 ml) was stirred for 5 minutes at room temperature. After adding **2b** (1 g, 2.14 mmoles), the reaction mixture was refluxed for 1.5 hours. The solvent was evaporated under reduced pressure. The residue was triturated in ethyl acetate (100 ml) and filtered. The filtrate was coevaporated with silica gel (1.4 g) 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 involving the product were combined and evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate to give **3f**.

5-Halo-4-phenoxypyridazin-6-one **3g** and **3h.**

A mixture of phenol (0.25 g, 2.64 mmoles), potassium carbonate (0.4 g, 2.9 mmoles) and acetonitrile (15 ml) was stirred for 5 minutes at room temperature. After adding **2** (2.64 mmoles), the reaction mixture was refluxed for 1 hour (for **3h**) or 2 hours (for **3g**). The solvent was evaporated under reduced pressure. After adding potassium carbonate (0.4 g, 2.9 mmoles) and water (25 ml), the mixture was refluxed for 0.5 hour (for **3h**) or 1 hour (for **3g**). The mixture was cooled to room temperature and neutralized using diluted aqueous hydrochloric acid. The resulting crystals were filtered and dried in air to give **3g** or **3h**.

1-(1,1-Dibromo-2-oxopropyl)-5-chloro-4-(4-nitrophenoxy)pyridazin-6-one (**5a**).

A mixture of **4a** (0.37 g, 2.64 mmoles), potassium carbonate (0.37 g, 2.64 mmoles) and acetonitrile (15 ml) was stirred for 1.5 hours at room temperature. After adding **2a** (1 g, 2.64 mmoles), the resulting solution was stirred for 1.5 hours at room temperature. The reaction mixture was filtered and washed with chloroform (30 ml). The combined filtrate was evaporated under reduced pressure. The crude product was recrystallized from chloroform/methanol (1:3, v/v) to give **5a**.

1-(1,1-Dibromo-2-oxopropyl)-5-bromo-4-(4-nitrophenoxy)pyridazin-6-one (**5b**).

A mixture of **4a** (0.6 g, 4.28 mmoles), potassium carbonate (0.65 g, 4.7 mmoles) and acetonitrile (20 ml) was stirred for 0.5 hours at room temperature. After adding **2b** (2 g, 4.7 mmoles), the resulting solution was stirred for 5 hours at room temperature. The reaction mixture was filtered and washed with chloroform (30 ml). The combined filtrate was evaporated under reduced pressure. The crude products were recrystallized from chloroform/methanol (1:6, v/v) to give **5b**.

1-(1,1-Dibromo-2-oxopropyl)-5-chloro-4-(4-cyanophenoxy)-pyridazin-6-one (**5c**).

A mixture of **4b** (0.33 g, 2.64 mmoles), potassium carbonate (0.44 g, 3.17 mmoles) and acetonitrile (15 ml) was stirred for 2 hours at room temperature. After adding **2a** (1 g, 2.64 mmoles), the resulting solution was stirred for 2 hours at room temperature. 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 (2.5 x 10 cm). The column was eluted with chloroform/*n*-hexane (9:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure to give **5c**.

1-(1,1-Dibromo-2-oxopropyl)-5-bromo-4-(4-cyanophenoxy)-pyridazin-6-one (**5d**).

A solution of **4b** (0.54 g, 4.27 mmoles), potassium carbonate (0.6 g, 4.28 mmoles) and acetonitrile (20 ml) was stirred for 1.5 hours at room temperature. After adding **2b** (2 g, 4.27 mmoles), the resulting solution was stirred for 1.5 hours at room temperature. The reaction mixture was filtered and washed with acetonitrile (30 ml). The combined filtrate was evaporated under reduced pressure. The crude product was recrysatallized from chloroform/methanol (1:5, v/v) to give first **5d**. The resulting filtrate was evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:2, v/v) to afford second **5d**. The total yield of **5d** is 80% (1.72 g).

1-(1,1-Dibromo-2-oxopropyl)-5-chloro-4-(4-methoxyphenoxy)-pyridazin-6-one (**5e**).

A mixture of **4c** (0.33 g, 2.64 mmoles), potassium carbonate (0.44 g, 3.17 mmoles) and acetonitrile (15 ml) was stirred for 40

minutes at room temperature. After adding **2a** (1 g, 2.64 mmoles), the resulting solution was stirred for 12 hours at room temperature. 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 5 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized from chloroform/methanol/*n*-hexane (1:3:1, v/v/v) to give **5e**.

1-(1,1-Dibromo-2-oxopropyl)-5-bromo-4-(4-methoxyphenoxy)-pyridazin-6-one (**5f**).

A mixture of **4c** (0.53 g, 4.28 mmoles), potassium carbonate (0.65 g, 4.7 mmoles) and acetonitrile (20 ml) was stirred for 0.5 hours at room temperature. After adding **2b** (2 g, 4.28 mmoles), the resulting solution was stirred for 15 hours at room temperature. The reaction mixture was evaporated under reduced pressure, then triturated in water (30 ml) and filtered. The resulting residue was applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give **5f**.

1-(1,1-Dibromo-2-oxopropyl)-5-chloro-4-(4-chlorophenoxy)-pyridazin-6-one (**5g**).

A mixture of **4d** (0.34 g, 2.64 mmoles), potassium carbonate (0.44 g, 3.17 mmoles) and acetonitrile (15 ml) was stirred for 20 minutes at room temperature. After adding **2a** (1 g, 2.64 mmoles), the resulting solution was stirred for 2 hours at room temperature. The reaction mixture was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with chloroform/*n*-hexane (9:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **5g**.

1-(1,1-Dibromo-2-oxopropyl)-5-bromo-4-(4-chlorophenoxy)-pyridazin-6-one (**5h**).

A mixture of **4d** (0.55 g, 4.28 mmoles), potassium carbonate (0.65 g, 4.7 mmoles) and acetonitrile (15 ml) was stirred for 0.5 hours at room temperature. After adding **2b** (1 g, 2.64 mmoles), the resulting solution was stirred for 4.5 hours at room temperature. The reaction mixture was filtered and washed with chloroform (30 ml). The combined filtrate was evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **5h** as white crystal.

5-Halo-4-(4-nitrophenoxy)pyridazin-6-ones **6a** and **6b.**

A mixture of **5a** or **5b** (0.56 mmole), potassium carbonate (3.17 mmoles) and water (15 ml) was refluxed for 1 hour (for **5b**) or 2 hours (for **5a**). After cooling to room temperature, the mixture was neutralized using diluted aqueous hydrochloric acid (concentrated hydrochloric acid/water = 1:20, v/v). The resulting crystals were filtered and dried in air to give **6a** or **6b**.

5-Halo-4-(4-cyanophenoxy)pyridazin-6-ones **6c** and **6d.**

A mixture of **5c** or **5d** (0.55 mmole), potassium carbonate (3.17 mmoles) and water (20 ml) was refluxed for 1 hour (for **5c**) or 2 hours (for **5d**). After cooling to room temperature, the mixture was neutralized using diluted aqueous hydrochloric acid (concentrated hydrochloric acid/water = 1:20, v/v). The resulting crystals were filtered, washed with water (40 ml) and dried in air. The crude product was dissolved in methanol (50 ml). The solution was coevaporated with silica gel (2.4 g) under reduced pressure and applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **6c** or **6d**.

5-Halo-4-(4-methoxyphenoxy)pyridazin-6-ones **6e** and **6f.**

A mixture of **5e** or **5f** (1.08 mmoles), potassium carbonate (3.62 mmoles) and water (15 ml) was refluxed for 5 hours (for **5f**) or 10 hours (for **5e**). After cooling to room temperature, the mixture was neutralized using diluted aqueous hydrochloric acid (concentrated hydrochloric acid/water = 1:20, v/v). The resulting crystals were filtered and dried in air. The crude product was dissolved in chloroform (10 ml) and applied to the top of an open-bed silica gel column (2 x 6 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **6e** or **6f**.

5-Chloro-4-(4-chlorophenoxy)pyridazin-6-one (**6g**).

A mixture of **5g** (0.5 g, 1.11 mmoles), potassium carbonate (0.18 g, 1.33 mmoles) and water (15 ml) was refluxed for 10 hours. After cooling to room temperature, the mixture was neutralized using diluted aqueous hydrochloric acid (concentrated hydrochloric acid/water = 1:20, v/v). The resulting crystals were filtered and recrystallized from methanol/water (1:2, v/v) to give **6g**.

5-Bromo-4-(4-chlorophenoxy)pyridazin-6-one (**6h**).

A mixture of **5h** (1 g, 1.95 mmoles), potassium carbonate (1 g, 7.24 mmoles) and water (15 ml) was refluxed for 4 hours. After cooling to room temperature, the mixture was neutralized using diluted aqueous hydrochloric acid (concentrated hydrochloric acid/water = 1:20, v/v). The resulting crystals were filtered and applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with chloroform (100 ml) and then ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give **6h**.

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REFERENCES AND NOTES

[1] R. D. Bryant, F. A. Kunng and M. S. South, *J. Heterocyclic Chem.*, **32**, 1473 (1995).

[2a] S. Y. Choi, S. G. Lee and Y. J. Yoon, *J. Heterocyclic Chem.*, **28**, 1235 (1991); [b] S. Y. Choi, S. C. Shin and Y. J. Yoon, *J. Heterocyclic Chem.*, **28**, 385 (1991).

[3] W. Y. Choi, S. D. Cho, S. K. Kim and Y. J. Yoon, *J. Heterocyclic Chem.*, **34**, 1307 (1997).

[4] S. D. Cho, W. Y. Choi and Y. J. Yoon, *J. Heterocyclic Chem.*, **33**, 1579 (1996).

[5] D. H. Kweon, Y. J. Kang, H. A. Chung and Y. J. Yoon, These results will be published elsewhere.

[6] K. Dury, *Angew. Chem., Int. Ed. Engl.*, **4**, 292 (1964).