Synthesis and Reactions of 1-(2-Oxopropyl)pyridazin-6-ones

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Oxopropylation of 4,5-dihalopyridazin-6-ones with chloroacetone afforded the corresponding 1-(2-oxopropyl) derivatives. Reaction of title compound with nucleophiles such as amines, alkoxides were investigated. In addition, selective reduction of 3-nitro-1-(2-oxopropyl)pyridazin-6-ones with iron/ammonium chloride in two phase solutions or zinc in acetic acid gave the corresponding 3-amino or 3-hydroxyimino derivatives.

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We have recently reported the synthesis of 1-(2-oxopropyl)pyridazin-6-ones as starting material for the synthesis of pyridazine acyclonucleosides [1]. In continuing studies, we have also described the reactions such as bromination, hydroxyimination and methoxylation of the title compound [2] and the synthesis of some pyridazine acyclonucleosides or thiazol-5-yl-pyridazin-6-ones [3]. Because of our interest in the selective functionalization, we investigated the convenient synthesis and the reactions of 1-(2-oxopropyl)pyridazin-6-ones with some nucleophiles.

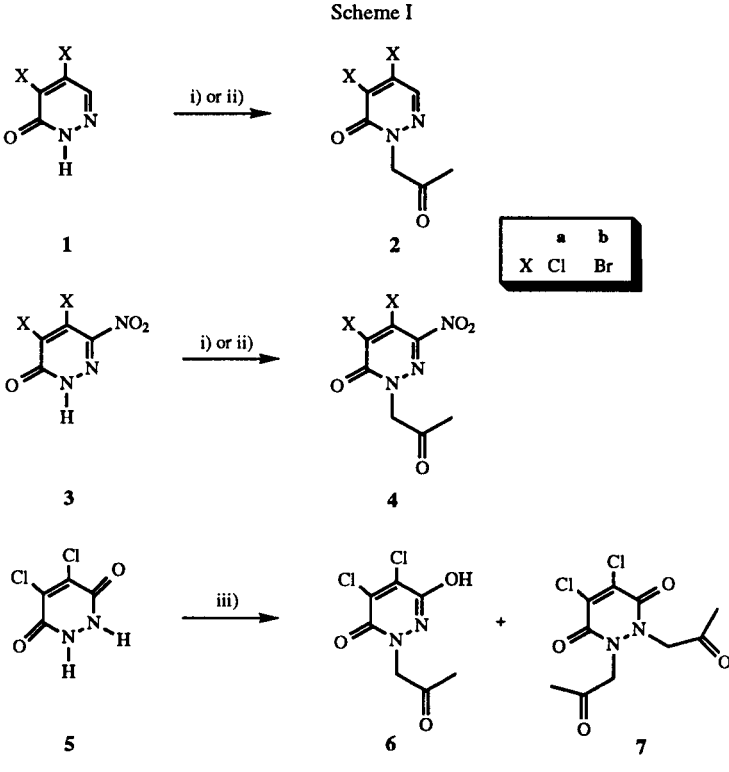
In this paper, we would like to report a convenient synthetic method and reaction results of the title compound.

In previous paper [1], we prepared 1-(2-oxopropyl)pyridazin-6-ones from pyridazin-6-ones and 4-bromoacetoacetic acid that is synthesized from diketene and bromine. Because of the instability of 4-bromoacetoacetic acid, we attempted to develop more convenient synthetic method of 1-(2-oxopropyl)pyridazin-6-ones.

Alkylation of **1** and **3** with chloroacetone in the presence of potassium carbonate at 50-60° afforded the corresponding 1-(2-oxopropyl) derivatives **2** and **4** in excellent yield, respectively. Oxopropylation of **5** with chloroacetone in the presence of potassium hydroxide and tetrabutylammonium bromide gave monooxopropyl derivative **6** in 33% yield and dioxopropyl derivative **7** in 56% yield. The structures of **2**, **4**, **6** and **7** were established by ir, nmr and elemental analyses.

We also investigated the functionalization of (2-oxopropyl)pyridazin-6-ones. Reaction of 4,5-dibromo-1-(2-oxopropyl)pyridazin-6-one (**2b**) with methylamine or cyclopropylamine in the presence of triethylamine in methanol gave regioselectively the corresponding 4-alkylamino derivatives **8** (**8a** in 83% yield or **8b** in 76% yield) instead of 1-(2-alkyliminopropyl)pyridazin-6-ones. Whereas, **2b** was reacted with hydroxylamine hydrochloride under the same condition to furnish 4,5-dibromo-1-(2-hydroxyiminopropyl)pyridazin-6-one (**9**) as a mixture of the *syn* and *anti* forms in 86% yield. Although each isomer did not isolate, we could observe the two isomers in the magnetic resonance spectrum for **9**. In ketoximes, the proton signal of methyl group of the oxime carbon for *syn* form shows more up-field than it for *anti* form [2,4]. According to the intensity of proton signal for 3'-methyl in the proton magnetic resonance spectrum, the composition of two isomers is *syn:anti* = 1:2.2. Methoxylation of **9** with sodium methoxide in dry methanol also yielded **10** in 81% yield. The structures of compounds **8-10** were established by ir, nmr and elemental analyses.

Scheme I



i) Method A) $BrCH_2COCH_2COOH$, Et_3N, THF, room temperature.

ii) Method B) $ClCH_2COCH_3$, K_2CO_3, DMF, 50-60°.

iii) $ClCH_2COCH_3$, KOH, $(n\text{-}Bu)_4NBr$, Benzene.

We also attempted the direct synthesis of compound **11** from compound **2** and 4-amino-2,6-dichlorophenol. However, reaction of 4,5-dihalo-1-(2-oxopropyl)pyridazin-6-ones **2** with 4-amino-2,6-dichlorophenol in the presence of potassium carbonate in acetonitrile gave a mixture of compound **11** and the corresponding 4-(3,5-dichloro-4-hydroxyanilino)-5-halo derivatives.

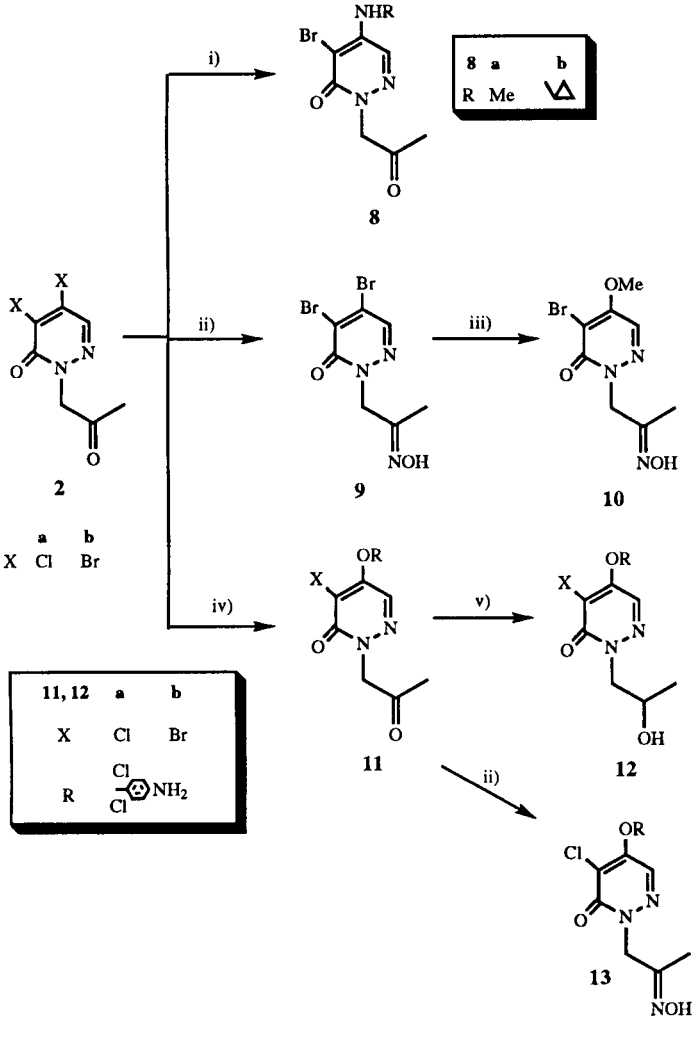
On the other hand, the formation of arylheteroaryl ethers *via* fluoride ion assisted reaction has been reported [5]. Thus, we carried out the reaction of **2** with 4-amino-2,6-dichlorophenol in the presence of potassium fluoride. This reaction also afforded two products.

Reaction of **2** with 4-amino-2,6-dichlorophenol in the presence of potassium fluoride and potassium carbonate gave compound **11** in good yield regio- and chemoselectively. The infrared spectra of **11** show the absorption band of the amino group. The pmr spectra of **11** detected the proton signal of NH_2 at δ 5.87 ppm. The carbon-13 nmr spectra for **11** also show the carbon signals of two carbonyls for C6 [δ 155.9 (**11a**), 157.7 (**11b**)] and for C2' [δ 198.4 (**11a**), 201.0 (**11b**)]. Reduction of **11** with sodium borohydride yielded compound **12** in good yield. Treatment of **11a** with hydroxylamine hydrochloride in the presence of triethylamine afforded the corresponding 1-(2-hydroxyimino-propyl) derivative (**13**) in 77% yield. The structures of **11-13** were established by ir, nmr and elemental analyses.

Selective reduction of compound **4b** with zinc powder in acetic acid gave 3-hydroxyamino derivative **14**, whereas chemoselective reduction of **4a** with iron/ammonium chloride in two phase solutions afforded only **15** in good yield. According to Cho's report [6], iron/ammonium chloride in two phase solutions is a good chemoselective reduction system for highly-functionalized azidopyridazin-6-ones [6]. This reduction agent may also be regarded as a good chemoseletive reduction system for highly-functionalized nitropyridazin-6-ones. Compound **15** was reacted with sodium methoxide in dry methanol to give **16** in 86% yield.

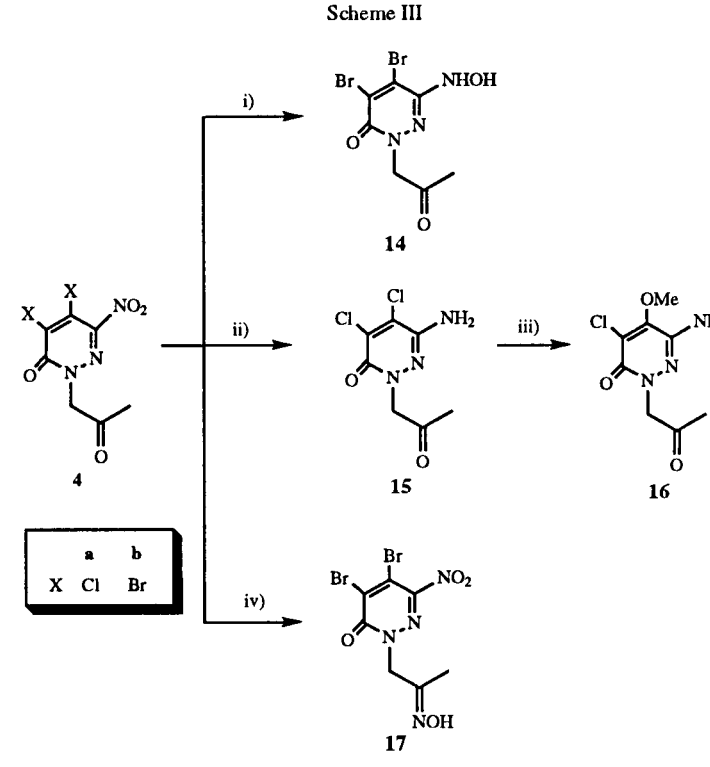
Treatment of **4b** with hydroxylamine hydrochloride in the presence of potassium hydroxide furnished 1-(2-

Scheme II



i) $MeNH_2$ (or Cyclopropylamine), Et_3N, MeOH, reflux. ii) $NH_2OH.HCl$, Et_3N, MeOH, reflux. iii) NaOMe, MeOH, room temperature iv) 4-Amino-2,6-dichlorophenol, KF, K_2CO_3, MeCN, reflux. v) $NaBH_4$, MeOH, 40-60°.

Scheme III



i) Zn, AcOH, room temperature ii) Fe, NH_4Cl, $CHCl_3$, H_2O, room temperature iii) NaOMe, MeOH, room temperature iv) $NH_2OH.HCl$, MeOH, KOH, room temperature

Table 1

Yields, Melting Points and IR Spectral Data of 1-(2-Oxopropyl)pyridazin-6-ones

Compound No.	Isolated Yield (%)	mp (°C) (lit mp)	ir (KBr, cm^{-1})
2a	63 (A) [a] 86 (B)	139-140 (136-137) [1]	3082, 3010, 2958, 1740, 1680, 1596, 1378, 1360, 1240, 1192, 1150, 1042
2b	85 (A) 92 (B)	167-168	3100, 3060, 2990, 1750, 1660, 1580, 1376, 1358, 1240, 1190, 1153, 1040
4a	80 (A) 93 (B)	94-95 (93-94) [1]	2998, 2950, 1744, 1690-, 1582, 1550, 1376, 1186, 1014
4b	82 (A) 90 (B)	136-137	2990, 2946, 1740, 1682, 1564, 1538, 1492, 1370, 1342, 1286, 1180, 1150
6	33	203-204	3450, 3158, 3040, 2992, 2900, 1732, 1684, 1600, 1432, 1398, 1186, 1072
7	56	137-138	3020, 2872, 1748, 1678, 1604, 1456, 1412, 1346, 1198, 1032
8a	83	167-168	3326, 3088, 2948, 1736, 1650, 1532, 1464, 1440, 1392, 1360, 1332, 1238, 1180, 1092
8b	76	132-133	3390, 3100, 3016, 2950, 1740, 1668, 1626, 1450, 1404, 1360, 1196, 1038
9	86	124-125	3260, 3086, 3014, 2942, 1670, 1648, 1570, 1372, 1208, 1146, 1026
10	81	109-110	3350, 3101, 3018, 2930, 1656, 1604, 1480, 1326, 1270, 1232, 1116
11a	75	245-246	3490, 3368, 3256, 3092, 2974, 1746, 1668, 1610, 1492, 1280, 1240, 1192
11b	91	251-252	3480, 3362, 3250, 3098, 3000, 2958, 1734, 1652, 1604, 1480, 1232
12a	80	189-190	3400, 3248, 3100, 2998, 2950, 1658, 1490, 1276, 1100
12b	85	202-203	3380, 3220, 3088, 2972, 2934, 1650, 1608, 1480, 1400, 1312, 1260, 1228, 1064
13	77	235-256	3350, 3100, 3018, 2930, 1658, 1604, 1480, 1400, 1326, 1270
14	82	165-166	3298, 3024, 2932, 2846, 1740, 1642, 1572, 1470, 1406, 1194, 1026
15	89	167-168	3442, 3348, 3230, 3000, 2958, 1738, 1680, 1652, 1596, 1470, 1358, 1192, 1044
16	86	160-161	3420, 3346, 3218, 2994, 2950, 1738, 1632, 1570, 1488, 1370, 1192, 1160
17	84	137-138	3350, 3101, 3018, 2930, 1656, 1604, 1480, 1326, 1270, 1232, 1116

[a] A = Method A, B = Method B.

Table 2

^{1}H NMR Spectral Data of 1-(2-Oxopropyl)pyridazin-6-ones

Compound No.	Solvent [b]	^{1}H nmr (ppm) [a] $2H_{1'}$(s)	$3H_{3'}$(s)	$1H_3$(s)	Others
2a	C	5.00	2.31	7.83	
2b	D	4.12	2.22	8.05	
4a	C	4.99	2.29		
4b	D	5.00	2.30		
6	D+C	4.87	2.20		12.82 (bs, OH)
7	C	4.74 4.79	2.22		
8a	C+D	4.89	2.20	7.63	3.03 (d, 3H, J = 5.1), 5.00 (bs, NH)
8b	C	4.92	2.23	7.92	0.73 (q, 2H), 0.94 (q, 2H), 2.65 (m, 1H), 5.10 (bs, NH)
9	C+D	5.07	1.69	7.94	10.66 (bs, OH) for *syn* isomer
		4.84	1.84	7.91	10.65 (bs, OH) for *anti* isomer
10	D	4.82	1.77	7.80	4.03 (s, 3H), 10.85 (bs, OH)

Table 2 (continued)

Compound No.	Solvent [b]	^{1}H nmr (ppm) [a] $2H_{1'}$(s)	$3H_{3'}$(s)	$1H_3$(s)	Others
11a	D	5.08	2.21	7.65	5.87 (bs, NH_2), 6.73 (s, Ar, 2H)
11b	D	5.08	2.21	7.53	5.87 (bs, NH_2), 6.74 (s, Ar, H)
12a	D	4.00 (m, $3H_{1'+2'}$)	1.07 (d, J = 5.5)	7.57	4.86 (d, OH, J = 4.4), 5.86 (bs, NH_2) 6.73 (s, Ar, 2H)
12b	D	4.02 (m, $3H_{1'+2'}$)	1.06 (d, J = 5.4)	7.44	4.86 (d, OH, J = 5.4), 5.86 (s, NH_2) 6.73 (s, Ar, 2H)
13	D	4.80	1.74	7.63	5.86 (s, NH_2), 6.73 (s, Ar, 2H), 10.83 (s, OH)
14	D	4.81	2.20		8.63 (bs, OH), 8.88 (bs, NH)
15	D	4.82	2.17		6.27 (bs, NH_2)
16	C	4.73	2.18		4.10 (s, OCH_3), 5.64 (bs, NH_2)
17	D	4.83	1.80		10.95 (bs, OH)

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

Table 3

^{13}C NMR Spectral Data of 1-(2-Oxopropyl)pyridazin-6-ones

Compound No.	Solvent [a]	^{13}C nmr (ppm) C_6=O	C_2=O (or =N)	$C_{1'}$	$C_{3'}$	Others
2a	C	150.3	192.6	55.2	21.1	128.2, 129.9, 130.7
2b	C	150.6	192.8	55.5	21.2	124.47, 125.1, 131.8
4a	C	155.2	197.2	61.5	27.1	130.0, 138.2, 140.6
4b	D	155.3	199.9	61.9	27.2	122.9, 134.4, 146.5
6	D+C	154.7	200.3	70.1	24.8	129.5, 135.6, 146.5
7	C	155.1	199.3	60.6	26.1	131.0, 137.2, 145.5
			201.7	71.7	27.2	
8a	C+D	156.2	200.1	59.7	28.7	26.0, 95.7, 125.0, 145.8
8b	C	157.6	201.0	60.9	27.3	8.1, 24.6, 99.2, 127.1, 147.0
9	C+D	155.3 (155.5)	148.9 (149.1)	49.7 (54.7)	11.1 (15.9)	129.0, 129.6, 136.3 for syn (129.1), (129.8), (136.6) for anti
10	D	152.8 (157.3)	149.8 (152.8)	54.8	12.0	57.1, 113.2 (115.7), 127.2 (127.5) 133.0
11a	D	155.9	198.4	59.6	25.5	111.9, 114.6, 125.7, 126.0, 132.0, 147.0, 151.7
11b	D	157.7	201.0	61.4	27.2	107.5, 113.2, 127.2, 127.7, 133.3, 148.9, 155.2
12a	D	157.6	20.8	59.1	63.6	113.1, 115.7, 126.7, 127.4, 133.2, 148.8, 152.8
12b	D	158.1	20.9	59.3	63.6	107.6, 113.2, 126.5, 127.5, 133.4, 148.8, 154.8
13	D	157.3	149.9	54.9	12.0	113.1, 115.7, 127.3, 127.4, 133.1, 148.8, 153.0
14	D	154.3	201.0	61.5	27.2	124.2, 131.5, 146.6
15	D	153.4	201.1	60.7	27.1	129.8, 134.0, 145.0
16	C	156.0	199.7	59.0	25.6	119.0, 122.0, 143.7, 148.1
17	D	154.4	149.5	55.8	12.1	122.4, 134.5, 146.2

[a] C = Deuteriochloroform, D = DMSO-d_6.

hydroxyiminopropyl) derivative **17** in 84% yield. The structures of **14-17** were established by ir, nmr and elemental analyses. The position of substitution on the pyridazine for **8**, **10**, **11** and **16** was proved by the further reactions of these compounds [7].

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 spectrometer with

Table 4
Elemental Analytical Data of 1-(2-Oxopropyl)pyridazin-6-ones

Compound No.	Molecular Formula	Analysis (%) Calcd./Found C	H	N
2a	$C_7H_6O_2N_2Cl_2$	38.19	2.75	12.73
		38.32	2.80	12.60
2b	$C_7H_6O_2N_2Br_2$	27.28	1.96	9.10
		27.25	2.05	9.15
4a	$C_7H_5O_4N_3Cl_2$	31.70	1.90	15.85
		31.73	1.96	16.00
4b	$C_7H_5O_4N_3Br_2$	23.81	1.43	11.91
		23.85	1.66	11.95
6	$C_7H_6N_2O_3Cl_2$	35.60	2.56	11.87
		35.67	2.86	11.78
7	$C_{10}H_{10}N_2O_4Cl_2$	41.10	3.45	9.59
		41.04	3.76	9.77
8a	$C_8H_{10}N_3O_2Br$	37.07	3.89	16.22
		37.10	3.90	16.10
8b	$C_{10}H_{12}N_3O_2Br$	42.10	4.24	14.74
		42.12	4.45	14.80
9	$C_7H_7N_3O_2Br_2$	26.02	2.18	13.01
		25.96	2.30	13.01
10	$C_8H_{10}N_3O_3Br$	34.91	3.66	15.28
		34.95	3.86	15.65
11a	$C_{13}H_{10}N_3O_3Cl_3$	43.22	2.79	11.64
		43.24	2.90	11.70
11b	$C_{13}H_{10}N_3O_3Cl_2Br$	38.53	2.49	10.37
		38.74	2.56	10.42
12a	$C_{13}H_{12}N_3O_3Cl_3$	42.98	3.33	11.57
		42.99	3.23	11.55
12b	$C_{13}H_{12}N_3O_3Cl_2Br$	38.33	2.97	10.32
		38.34	3.01	10.43
13	$C_{13}H_{11}N_4O_3Cl_3$	41.49	2.95	14.90
		41.57	3.10	14.65
14	$C_7H_7N_3O_3Br_2$	24.79	2.08	12.40
		24.82	2.18	12.47
15	$C_7H_7N_3O_2Cl_2$	35.75	3.00	17.88
		35.78	3.21	17.88
16	$C_8H_{10}N_3O_3Cl$	41.55	4.36	18.18
		41.67	4.65	18.46
17	$C_7H_6N_4O_4Br_2$	22.83	1.64	15.23
		22.90	1.89	15.11

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.

4,5-Dihalo-1-(2-oxopropyl)pyridazin-6-ones **2** and 4,5-Dihalo-3-nitro-1-(2-oxopropyl)pyridazin-6-ones **4**.

Method A [1].

A mixture of **1** or **3** (58 mmoles), 4-bromoacetoacetic acid [1] (77 mmoles), triethylamine (or potassium carbonate, 80 mmoles) and tetrahydrofuran (50 ml) was stirred for 2 hours at room temperature. After adding concentrated hydrochloride (5 ml), the solvent was evaporated under reduced pressure. The resulting residue was dissolved in chloroform (100 ml). The chloroform solution was washed with water (100 ml x 5) and dried over anhydrous magnesium sulfate. After evaporating the solvent, the resulting residue was applied to the top of an open-bed silica gel column (3 x 20 cm). The column was eluted with chloroform. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure to give **2** and **4**, respectively.

Method B.

A mixture of **1** or **3** (18.2 mmoles), chloroacetone (18.4 mmoles), anhydrous potassium carbonate (18.4 mmoles) and dimethylformamide (50 ml) was stirred for 2 hours at 50-60°. After cooling to room temperature, the reaction mixture was poured into the mixture of chloroform (100 ml) and water (500 ml) with stirring. The organic layer was separated and dried over anhydrous magnesium sulfate. After evaporating the solvent, the resulting residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure to give **2** and **4**, respectively.

4,5-Dichloro-1-(2-oxopropyl)pyridazin-6-one (**6**) and 4,5-dichloro-1-di(2-oxopropyl)pyridazin-6-one (**7**).

A mixture of **5** (5.0 g, 27.7 mmoles), chloroacetone (5.58 g, 60.7 mmoles), tetrabutylammonium bromide (2.96 g, 9.2 mmoles), potassium hydroxide (1.55 g, 27.7 mmoles) and benzene (150 ml) was refluxed for 8 hours with stirring. After cooling in ice bath, the resulting residue was filtered and washed with chloroform (50 ml). The first filtrate and chloroform solution were combined. The combined solution was evaporated under reduced pressure. The resulting product was applied to the top of an open-bed silica gel column (2.5 x 12 cm). The column was eluted with chloroform/diethyl ether (20:1, v/v). The fractions containing compound **7** (detection using tlc, Rf = 0.75, developing solvent, chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure. The resulting solid was recrystallized from diethyl ether/*n*-hexane (1:1, v/v) to give **7** in 56% (4.5 g) yield. The fractions containing compound **6** (detection using tlc, Rf = 0.45, developing solvent, chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure. The resulting solid was recrystallized from diethyl ether/*n*-hexane (1:1, v/v) to give **6** in 33% (2.16 g) yield.

5-Bromo-4-methylamino-1-(2-oxopropyl)pyridazin-6-one (**8a**).

A solution of **2b** (2.0 g, 6.5 mmoles), methylamine hydrochloride (0.5 g, 7.41 mmoles), triethylamine (1.5 g, 14.8 mmoles) and methanol (30 ml) was refluxed for 13 hours. After cooling to room temperature, the solvent was removed on a rotary evaporator and the residue was triturated into chloroform with stirring. The salt was filtered and the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform/diethyl ether (8:2, v/v). Fractions containing the product were combined and the solvent removed on a rotary evaporator to give **8a** in 83% (1.39 g) yield.

5-Bromo-4-cyclopropylamino-1-(2-oxopropyl)pyridazin-6-one (**8b**).

A mixture of **2b** (2.0 g, 7.0 mmoles), cyclopropylamine (0.42 g, 7.36 mmoles), triethylamine (0.72 g, 7.1 mmoles) and methanol (30 ml) was refluxed for 8 hours. After cooling to

room temperature, the solvent was removed on a rotary evaporator and the residue was triturated into chloroform (10 ml) and water (20 ml) with stirring. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator and the residue was recrystallized from diethyl ether to give **8b** as yellow crystals in 76% (1.5 g) yield.

4,5-Dibromo-1-(2-hydroxyimino)pyridazin-6-one (**9**).

A mixture of **2b** (2.0 g, 7.0 mmoles), hydroxylamine hydrochloride (0.5 g, 7.1 mmoles), triethylamine (1.45 g, 14.2 mmoles) and methanol (30 ml) was refluxed for 6 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform (30 ml) and water (20 ml). The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator and the resulting residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with chloroform/diethyl ether (7:3, v/v). Fractions containing the product were combined and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from diethyl ether to give **9** as mixture of *syn* and *anti* isomers in 86% (1.94 g) yield.

5-Bromo-4-methoxy-1-(2-hydroxyimino)pyridazin-6-one (**10**).

A solution of **9** (4.0 g, 12.4 mmoles), sodium methoxide (0.78 g, 14.4 mmoles) and dry methanol (80 ml) was refluxed for 12 hours. After cooling to room temperature, the solvent was removed on a rotary evaporator. The residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm) and the column was eluted with chloroform. Fractions containing the product were combined and the solvent was evaporated under reduced pressure to give **10** in 81% (2.76 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-(2-oxopropyl)-pyridazin-6-one (**11a**).

A mixture of **2a** (4.0 g, 18.2 mmoles), 4-amino-2,6-dichlorophenol (3.2 g, 18.1 mmoles), potassium carbonate (3.0 g, 21.7 mmoles) and acetonitrile (100 ml) was refluxed for 4 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3.5 x 5 cm) and the column was eluted with ethyl acetate/methylene chloride (1:10, v/v). Fractions containing the product were combined and the solvent was removed on a rotary evaporator. The resulting solid was washed with diethyl ether (100 ml) to give **11a** in 75% (4.93 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-bromo-1-(2-oxopropyl)-pyridazin-6-one (**11b**).

A solution of **2b** (4.0 g, 12.99 mmoles), 4-amino-2,6-dichlorophenol (2.3 g, 13 mmoles), potassium carbonate (2.0 g, 14.5 mmoles) and acetonitrile (60 ml) was refluxed for 10 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was triturated in water (200 ml) with stirring and the solid was filtered. This solid was applied to the top of an open-bed silica gel column (2.5 x 8 cm) and the column was eluted with ethyl acetate/chloroform (10:1, v/v). Fractions containing the product were combined and the solvent was removed on a rotary evaporator to give **11b** in 91% (4.8 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-(2-hydroxy-propyl)pyridazin-6-one (**12a**).

A mixture of **11a** (2.7 g, 7.48 mmoles), sodium borohydride (0.31 g, 8.1 mmoles) and methanol (30-50 ml) was stirred for 4 hours at 40-50°. The solvent was removed on a rotary evaporator. The residue was triturated in water (150 ml) with stirring. The resulting solid was filtered and dried in air to give **12a** in 80% (2.17 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-bromo-1-(2-hydroxy-propyl)pyridazin-6-one (**12b**).

A mixture of **11b** (3 g, 7.41 mmoles), sodium borohydride (0.31 g, 8.1 mmoles) and methanol (40-50 ml) was stirred for 4 hours at 40-50°. The solvent was removed on a rotary evaporator. The residue was triturated in water (150 ml) with stirring. The resulting solid was filtered and dried in air to give **12b** in 85% (2.56 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-(2-hydroxyimino-propyl)pyridazin-6-one (**13**).

A mixture of **11a** (2.0 g, 5.5 mmoles), hydroxylamine hydrochloride (1.02 g, 14.8 mmoles), potassium hydroxide (0.95 g, 17 mmoles) and methanol (50 ml) was refluxed for 3 hours. After cooling to room temperature, the solvent was removed on a rotary evaporator. The residue was triturated in water (100 ml). The resulting solid was filtered, washed with water (50 ml x 4) and dried in air to give **13** in 77% (1.59 g) yield.

4,5-Dibromo-3-hydroxyamino-1-(2-oxopropyl)pyridazin-6-one (**14**).

A mixture of **4b** (1.5 g, 4.25 mmoles), zinc powder (0.5 g, 7.8 mmoles) and acetic acid (15 ml) was stirred for 30 hours at room temperature. Acetic acid was removed on a rotary evaporator. The residue was triturated in *n*-hexane (50 ml) with stirring. The resulting solid was filtered and the solid was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with chloroform/methanol (10:0.5, v/v). Fractions containing the product were combined and the solvent was evaporated under reduced pressure. The resulting crystals were recyrstallized from diethyl ether/chloroform (1:1, v/v) to afford **14** in 82% (1.18 g) yield.

3-Amino-4,5-dichloro-1-(2-oxopropyl)pyridazin-6-one (**15**).

A mixture of **4a** (2.84 g, 11.3 mmoles), ammonium chloride (2.4 g, 45.3 mmoles), iron powder (3 g, 53.6 mmoles), chloroform (30 ml) and water (30 ml) was stirred for 16 hours at room temperature. The mixture was filtered using Celite-545 and washed with chloroform (60 ml). The organic layer was separated by separatory funnel and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator. The resulting solid was recrystllized from diethyl ether/*n*-hexane (1:1, v/v) to give **15** as yellow crystals in 89% (2.36 g) yield.

3-Amino-5-chloro-4-methoxy-1-(2-oxopropyl)pyridazin-6-one (**16**).

A mixture of **15** (2.82 g, 12 mmoles), sodium methoxide (0.78 g, 14.4 mmoles) and dry methanol (80 ml) was stirred for 12 hours at room temperature. The mixture was filtered and the residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform. Fractions containing the product were combined and the solvent was evaporated under reduced pressure to give **16** in 86% (2.38 g) yield.

4,5-Dibromo-3-nitro-1-(2-hydroxyimino)pyridazin-6-one (**17**).

A solution of **4b** (2.0 g, 5.67 mmoles), hydroxylamine hydrochloride (0.43 g, 6.2 mmoles), potassium hydroxide

(0.35 g, 6.2 mmoles) and methanol (30 ml) was refluxed for 10 hours. After cooling to room temperature, the solvent was removed on a rotary evaporator. The residue was triturated in acetone (20 ml) and the resulting precipitate was filtered. The filtrate was poured into a mixture of chloroform (10 ml) and water (20 ml) with stirring. The organic layer was separated by separatory funnel and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting solid was recrystallized from carbon tetrachloride to furnish **17** as yellow crystals in 84% (1.75 g) yield.

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