Retro-Ene Reaction. V. Functionalization of 4,5-Dihalopyridazin-6-ones Using 1-Hydroxymethyl-4,5-dihalopyridazin-6-ones as 1-O, 3-N, 5-O Ene-Adducts

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Functionalization of 1-hydroxymethyl-4,5-dihalopyridazin-6-ones *via* a retro-ene reaction with some nucleophiles gave regioselectively only 5-halo-4-substitutedpyridazin-6-ones.

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In a previous paper [1], we reported the functionalization of 4,5-dihalopyridazin-6-ones using 1-(1,1-dibromo-2-oxopropyl)-5-halopyridazin-6-ones. However, 1-(1,1-dibromo-2-oxopropyl) derivatives as the starting material was synthesized from 4,5-dihalopyridazin-6-ones *via* two steps. Therefore, we attempted to investigate a convenient functionalization of 4,5-dihalopyridazin-6-ones.

The preconditions for the functionalization of 4,5-dihalopyridazin-6-ones are the following; i) the reactivity and the regioselectivity on the pyridazine ring must be increased by the introduction of a protecting group at N-1 position, ii) the introduction and the removal of the protecting group must be facile under mild conditions, and iii) the substitution on the pyridazine ring must also be faster than the cleavage of C-N bond at the N-1 position [1].

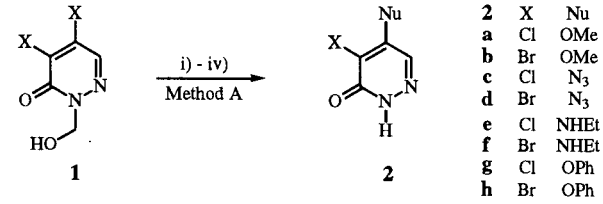
According to Kim, *et al.* [2], 1-hydroxymethylpyridazin-6-ones and *N*-hydroxymethylsaccharin as a 1-O, 3-N, 5-O ene-adduct fragment at the N-1 position *via* the retro-ene reaction to give the corresponding pyridazin-6-ones. This retro-ene reaction also is promoted by a base and/or by heat. Because the C-N bond cleavage and the introduction of 1-hydroxymethyl group are facile, we chose 1-hydroxymethyl-4,5-dihalopyridazin-6-ones as the starting materials for the functionalization.

In this paper, we report the results of the title reaction. 4,5-Dihalo-1-hydroxymethylpyridazin-6-ones were prepared by Cho's method [3].

Methoxylation of **1** with potassium carbonate/methanol [4] gave the corresponding 4-methoxy-5-halopyridazin-6-ones **2a** and **2b** in excellent yields. Azidation of **1** with sodium azide in methanol afforded selectively the 4-azido derivatives **2c** and **2d** in good yields.

Treatment of **1** with ethylamine hydrochloride (4 equivalents) and potassium carbonate (4 equivalents) in acetonitrile also yielded 4-ethylamino-5-halopyridazin-6-ones **2e** and **2f**. Reaction of **1** with phenol (1 equivalent) in the presence of potassium carbonate in acetonitrile gave the corresponding 4-phenoxy derivatives **2g** and **2h** (Method A). Whereas, treatment of **1** with excess phenol (2 equivalents) in the presence of excess potassium carbonate (2 equivalents) yielded **2g** or **2h** as the main product and **3a** or **3b** as the minor product (Method B).

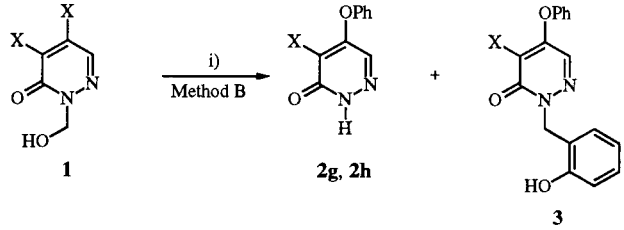
Scheme I



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

i) MeOH, K_2CO_3 (1.2 equivalents), reflux for **2a** and **2b**; ii) NaN_3 (1.2 equivalents), MeOH, reflux for **2c** and **2d**; iii) $EtNH_2$•HCl (4 equivalents), K_2CO_3 (4 equivalents), CH_3CN, reflux for **2e** and **2f**; iv) Phenol (1 equivalent), K_2CO_3 (1 equivalent), CH_3CN, reflux for **2g** and **2h**.

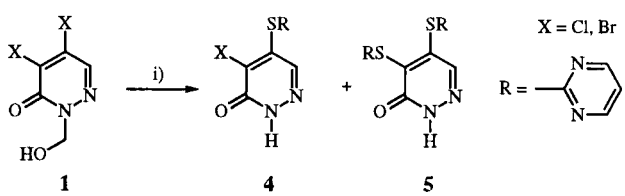
Scheme II



i) Phenol (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN, reflux.

On the other hand, reaction of **1a** with 2-mercaptopyrimidine (2 equivalents) in the presence of potassium carbonate (2 equivalents) afforded **4** in 32% yield and **5** in 60% yield, whereas treatment of **1b** with 2-mercaptopyrimidine under the same condition gave only **5** in 90% yield.

Scheme III

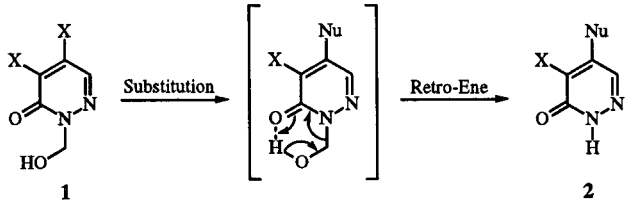


i) 2-Mercaptopyrimidine (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN, room temperature.

The structures of **2-5** were established by ir, nmr and elemental analyses. The infrared spectra of **2**, **4** and **5** revealed the characteristic peaks of the free pyridazin-6-one in the 3300-2900 cm^{-1} range and the absorption peaks of the amide carbonyl at the 1640-1680 cm^{-1} range. However, we did not detect the absorption peak of the OH group except for **3**. The ^1H nmr spectra of **2**, **4** and **5** showed the proton signals for the NH for pyridazinone in the δ 12.42-13.59 ppm range (except for **2g**) and of one aromatic proton in the δ 7.42-8.20 ppm involving the protons of methoxy (for **2a** and **2b**), ethylamino (for **2e** and **2f**) and the phenyl group (**2g** and **2h**). The infrared spectra of **3** showed the absorption peaks of the phenolic OH and the carbonyl group. However, we did not detect the absorption peak of the NH group. The proton magnetic resonance spectra of **3** showed the signals of the protons for the phenolic OH at δ 9.12 ppm (**3a**) or δ 9.14 ppm (**3b**) and for methylene at the N-1 position (δ 5.32 for **3a**; δ 5.33 for **3b**). The proton magnetic resonance spectra of **3** revealed the characteristic pattern of the proton signals for an *ortho*-disubstituted benzene.

The position of substitution on the pyridazinone for **2**, **3** and **4** was proved by additional reactions of these compounds [5]. Our functionalization may be regarded as a reaction *via* two steps; *i.e.*, the replacement of halogens by nucleophiles occurs in the first step, and then fragmentation at the N-1 position occurs by the retro-ene reaction.

Scheme IV



1 2

On the other hand, the formation of **3** is unusual in our system. It has been reported that the reaction of *N*-hydroxymethylpyrrolidinone with acetanilide in sulfuric acid gave 2-(pyrrolidinon-1-ylmethyl)acetanilide as the main product and also 4-(pyrrolidino-1-ylmethyl)acetanilide [6]. Katritzky, *et al.* [7] reported the reaction of 1-(hydroxymethyl)benzotriazole with ketones *via* the corresponding immonium cation to give monosubstituted Mannich products. Therefore, the reaction of **1** with phenol under our conditions may be regarded to occur by two different mechanisms; *i.e.*, 1) the fragmentation *via* the retro-ene reaction to give **2g** or **2h**, 2) the Mannich condensation *via* the immonium intermediate to give **3**.

Finally, compound **1** as a 1-O, 3-N, 5-O ene-adduct may be regarded to satisfy the preconditions for the functionalization of 4,5-dihalopyridazin-6-ones. Our method is also regioselective and more convenient than that using 1-(1,1-dibromo-2-oxopropyl)-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 silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

5-Halo-4-methoxypyridazin-6-ones **2a** and **2b**.

A mixture of **1** (10 mmoles), potassium carbonate (12 mmoles) and methanol (40 ml) was refluxed for 25-27 hours. The solvent was evaporated under reduced pressure, and the residue was then poured into water (50 ml). The aqueous solution was neutralized with aqueous hydrochloric acid (7.4%) with stirring. The resulting crystals were filtered and recrystallized from ethanol to give **2a** or **2b** in excellent yields.

Scheme V

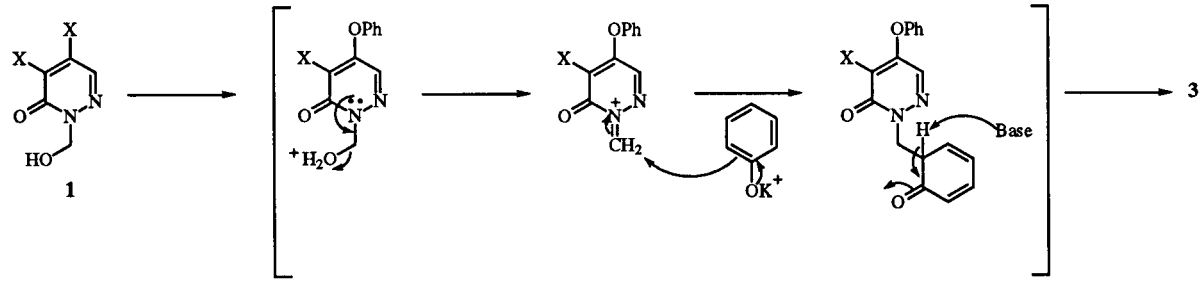


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Table 1

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

Compound No.	Method	Isolated Yield (%)	mp (°C) (lit mp)	IR (Potassium Bromide, cm^{-1})
2a	A	82	232-233 (233-235) [1]	3300, 3100, 2950, 2850, 1660, 1600, 1470, 1410, 1280, 1120, 950, 900
2b	A	94	213-214 (212-213) [1]	3280, 3200, 3100, 3000, 2940, 2850, 1650, 1610, 1400, 1280, 1100, 960, 890
2c	A	89	172-173 (170-172) [1]	3300, 3100, 3050, 2950, 2860, 2200, 2150, 1665, 1620, 1410, 1350, 1310, 1100
2d	A	90	173-175 (174-175) [1]	3300, 3120, 3050, 2950, 2200, 2150, 1660, 1610, 1410, 1340, 1300, 1070
2e	A	46	203-204 (198-200) [8]	3350, 3150-2950, 1680, 1660, 1620, 1460, 1350, 1320, 1030
2f	A	40	197-198	3350, 3000-2900, 1660, 1620, 1450, 1340, 1300, 1020, 560
2g	A	53	178-179	3300, 3140, 2950, 1680, 1620, 1600, 1500,
	B	36	(178-179) [1]	1400, 1280, 1100, 780
2h	A	57	195-196	3150, 3050, 2950, 2850, 1660, 1600, 1500,
	B	36	(197) [1]	1410, 1280
3a	B	6	140-142	3150-3050, 1640, 1620, 1600, 1580, 1500, 1400, 1220, 1160, 760
3b	B	20	157-158	3200-3300, 1640, 1600, 1500, 1220, 760
4a		32	222 dec	3200-2900, 1680, 1580, 1400, 1180, 1080
5		60 [a] 90 [b]	174-175	3200-2900, 1640, 1570, 1400, 1180

[a] From **1a**; [b] From **1b**.

Table 2

^1H NMR Spectral Data of Compounds **2-5**

Compound No.	Solvent [b]	^1H nmr (ppm) [a] $1H_3$ (s)	NH_1 (bs)	Others
2a	D	8.10	13.26	4.06 (s, CH_3)
2b	D	8.10	13.24	4.07 (s, CH_3)
2c	D	8.08	13.26	—
2d	D	8.04	13.32	—
2e	C	7.63	12.42	1.32 (t, CH_3), 3.41 (quin, CH_2, 5.19 (bs, NH)
2f	C	7.42	12.42	1.12 (t, CH_3), 3.21 (quin, CH_2), 4.98 (bs, NH)
2g	C	7.54	No Detection	7.26-7.48 (m, Ar, 4H)
2h	D	7.53	13.43	7.23-7.51 (m, Ar, 4H)
3a	C	7.55	—	5.32 (s, CH_2), 6.83-7.47 (m, Ar, 9H), 9.12 (bs, OH)
3b	C	7.45	—	5.33 (s, CH_2), 6.83-7.48 (m, Ar, 9H), 9.14 (bs, OH)
4a	D	8.14	13.59	7.42 (t, Ar, 1H). 8.74 (d, Ar, 2H, J = 4.5)
5	D	8.20	13.40	7.30 (t, Ar, 1H), 7.40 (t, Ar, 1H), 8.60 (d, Ar, 2H, J = 8), 8.70 (d, Ar, 2H, J = 8.0)

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

Table 3

Elemental Analytical Data of **2-5**

Compound No.	Molecular Formula	Analysis(%) Calcd/Found C	H	N	S
2a	$C_5H_5O_2N_2Cl$	37.40	3.14	17.45	
		37.55	3.00	17.36	
2b	$C_5H_5O_2N_2Br$	29.29	2.46	13.66	
		29.22	2.54	13.49	
2c	$C_4H_2ON_5Cl$	28.01	1.18	40.82	
		28.15	1.34	40.67	
2d	$C_4H_2ON_5Br$	22.24	0.93	32.42	
		22.04	0.97	32.36	
2e	$C_6H_8N_3OCl$	41.51	4.64	24.20	
		39.34	4.45	22.17	
2f	$C_6H_8N_3OBr$	33.05	3.70	19.27	
		32.27	3.55	19.10	
2g	$C_{10}H_7N_2O_2Cl$	53.95	3.17	12.58	
		53.73	3.32	12.67	
2h	$C_{10}H_7N_2O_2Br$	44.97	2.64	10.49	
		44.78	2.57	10.55	
3a	$C_{17}H_{13}N_2O_3Cl$	62.11	3.99	8.52	
		61.95	3.97	8.48	
3b	$C_{17}H_{13}N_2O_3Br$	54.71	3.51	7.51	
		54.86	3.54	7.49	
4a	$C_8H_5N_4OSCl$	39.93	2.09	23.28	13.32
		39.72	2.07	23.07	13.34
5	$C_{12}H_8N_6OS_2$	45.56	2.55	26.57	20.27
		45.71	2.66	26.46	20.41

4-Azido-5-halopyridazin-6-ones **2c** and **2d**.

A solution of **1** (5.13 mmoles), sodium azide (0.4 g, 6.15 mmoles) and methanol (20 ml) was refluxed for 4 hours for **1a** or 2 hours for **1b**. The solvent was evaporated under reduced pressure, and the residue was then poured into water (50 ml) with stirring. The resulting crystals were filtered and dried in air to give **2c** or **2d** in excellent yields.

5-Halo-4-ethylaminopyridazin-6-ones **2e** and **2f**.

A mixture of **1** (3.52 mmoles), ethylamine hydrochloride (1.15 g, 14.09 mmoles), potassium carbonate (1.95 g, 14.09 mmoles) and acetonitrile (20 ml) was refluxed for 14 hours for **1b** or for 19 hours for **1a**. The solvent was evaporated under reduced pressure, and the residue was then poured into water/chloroform (30/30 ml/ml). The organic layer was separated and dried over anhydrous magnesium sulfate. The solution was coevaporated with silica gel (2 g) under reduced pressure, and then applied to the top of an open-bed silica gel column (3 x 12 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate/*n*-hexane for **2e** or from diethyl ether for **2f** to give **2e** or **2f** in excellent yields.

5-Halo-4-phenoxypyridazin-6-ones **2g** and **2h**.

Method A.

A mixture of **1** (2.56 mmoles), phenol (0.24 g, 2.56 mmoles), potassium carbonate (0.35 g, 2.56 mmoles) and acetonitrile (20 ml) was refluxed for 4 hours for **1a** or for 7 hours for **1b**. The workup was carried out as follows: For **2g** the solvent was evaporated under reduced pressure, and the residue was then poured into water (30 ml). The aqueous solution was neutralized by aqueous hydrochloric acid (7.4%) with stirring. The resulting crystals were filtered and dried in air to give **2g**. For **2h** the solvent was evaporated under reduced pressure. The residue was poured into water/chloroform (1:1, v/v, 100 ml) with stirring. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated and the resulting 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. The resulting crystals were recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **2h**.

5-Chloro-4-phenoxypyridazin-6-one (**2g**) and 5-Chloro-1-(2-hydroxybenzyl)-4-phenoxypyridazin-6-one (**3a**).

Method B.

A mixture of **1a** (2 g, 10 mmoles), phenol (1.93 g, 20 mmoles), potassium carbonate (2.83 g, 20 mmoles) and acetonitrile (50 ml) was refluxed for 7 hours. The solvent was evaporated under reduced pressure. The residue was poured into water (30 ml). The solution was acidified using diluted hydrochloric acid (7.4%) to *p*H 6-7. The resulting crystals were filtered and dissolved in chloroform. The solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with chloroform. Fractions with Rf = 0.93 (chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from diethyl ether/*n*-hexane (1:3, v/v) to give **3a** in 6% (0.2 g) yield. Fractions with Rf = 0.23 (chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure to give **2g** in 36% (0.81 g) yield.

5-Bromo-4-phenoxypyridazin-6-one (**2h**) and 5-Bromo-1-(2-hydroxybenzyl)-4-phenoxypyridazin-6-one (**3b**).

Method B.

A mixture of **1b** (1.5 g, 5.28 mmoles), phenol (0.99 g, 10 mmoles), potassium carbonate (1.46 g, 10 mmoles) and acetonitrile (50 ml) was refluxed for 20 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 (2 x 7 cm). The column was eluted with chloroform. Fractions with Rf = 0.89 (chloroform/diethyl ether = 19:1, v/v) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to give **3b** in 20% (0.4 g) yield. Fractions with Rf = 0.2 (chloroform/diethyl ether = 19:1, v/v) were combined and evaporated under reduced pressure to give **2h** in 36% (0.51 g) yield.

5-Chloro-4-(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**4a**) and 4,5-Di(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**5**) from **1a**.

A mixture of **1a** (0.5 g, 2.11 mmoles), 2-mercaptopyrimidine (0.47 g, 4.22 mmoles), potassium carbonate (0.58 g, 4.22 mmoles) and acetonitrile (20 ml) was refluxed for 24 hours. After cooling to room temperature, the reaction mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 12 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions with Rf = 0.72 (ethyl acetate) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from diethyl ether to give **4a** in 32% (0.18 g) yield. Fractions with Rf = 0.4 (ethyl acetate) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate to afford **5** in 60% (0.4 g) yield.

4,5-Di(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**5**) from **1b**.

A mixture of **1b** (0.5 g, 1.76 mmoles), 2-mercaptopyrimidine (0.4 g, 3.52 mmoles), potassium carbonate (0.49 g, 3.52 mmoles) and acetonitrile (20 ml) was refluxed for 20 hours. After cooling to room temperature, the reaction mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 12 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate to afford **5** as yellow crystal in 90% (0.51 g) yield.

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