Retro-Ene Reactions IV. Alkylation of 4,5-Dichloro-1-hydroxymethylpyridazin-6-one with α,ω-Dibromoalkanes or 4,5-Dichloro-1-(ω-bromoalkyl)pyridazin-6-ones

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Alkylation of 4,5-dichloro-1-hydroxymethylpyridazin-6-one (**1**) with α,ω-dibromoalkanes **2** or ω-bromoalkylpyridazin-6-ones **3** *via* a fragmentation of the retro-ene type under the two restricted conditions was investigated.

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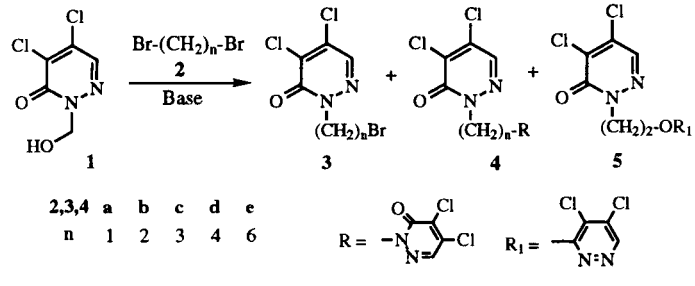
In a previous paper, we reported the alkylation of 4,5-dichloropyridazin-6-one with α,ω-dibromoalkanes or 4,5-dichloro-1-(ω-alkyl)pyridazin-6-ones [1]. 4,5-Dichloro-1-hydroxymethylpyridazin-6-one (**1**) is a novel 1-O, 3-N, 5-O ene-adduct [2]. Previously, the *N*-alkylation of this ene-adduct with some alkyl halides or carboxylic acid halides under basic conditions [3] and with *N*-(ω-haloalkyl)heterocycles [4] have been reported. These reactions also occur *via* the fragmentation of the retro-ene type [3,4]. Because of our interest in the effect on the retro-ene fragmentation during the alkylation of 1-O, 3-N, 5-O ene adduct with α,ω-dihaloalkanes or *N*-(ω-haloalkyl)heterocycles, we investigated the alkylation of 4,5-dichloro-1-hydroxy-methylpyridazin-6-one (**1**) with α,ω-dibromoalkanes **2** or 4,5-dichloro-1-(ω-alkyl)pyridazin-6-ones **3** under two restricted conditions.

In this paper, we would like to report the results of the title reaction.

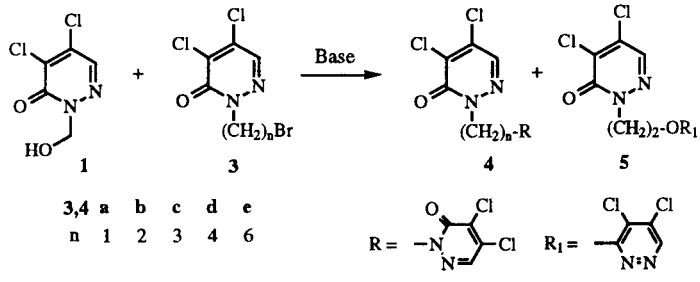
We carried out the alkylation of **1** (1 equivalent) under the following two conditions; i) bromides **2** or **3** (1.8 equivalents) and potassium carbonate (1.8 equivalents) in acetonitrile at 82 ±2°, or ii) bromides **2** or **3** (1.8 equivalents) and tetrabutylammonium bromide, $(n\text{-Bu})_4N^+ Br^-$, (1.8 equivalents) and potassium hydroxide (1.8 equivalents) in benzene at 56 ±2°.

Scheme I



Alkylation of compound **1** with 1,1-dibromomethane (**2a**) in the presence of potassium carbonate or tetra-*n*-butylammonium bromide/potassium hydroxide afforded only **4a** as the *N*-alkylation product in quantitative yield. Reaction of **1** with 1,2-dibromoethane in the presence of potassium carbonate gave **5** (75%) as the major product and **4b** (25%) as the minor product, whereas treatment of **1** with **2b** in the presence of tetra-*n*-butylammonium bromide/potassium hydroxide yielded **3b** (95%) and **4b** (5%). These results are different from that of the alkylation of 4,5-dichloropyridazin-6-one with **2b** under the same conditions. Using potassium carbonate in the case of **2b**, the regioselectivity of the *N/O*-alkylation for **1** is 1:3, whereas for 4,5-dichloropyridazin-6-one it is 1:1.7 [1]. However, we did not detect **3b** in the reaction of **1** with α,ω-dibromoethane in the presence of potassium carbonate.

Scheme II



Reaction of **1** with **2c-2e** under our two conditions gave only *N*-alkylation products such as **3c-3e** as the major products and **4c-4e** as the minor products. However, the corresponding α,ω-dipyridazinylalkanes **4c-4e** gave a higher yield using tetra-*n*-butylammonium bromide/potassium hydroxide than using potassium carbonate.

During the alkylation of **1** with **2**, we observed first the spot from compound **3**, and then the spots from compounds **4** and **5** on tlc plates. Therefore, these reactions are identical mechanistically with that of 4,5-dichloropyridazin-6-one with **2** under the same conditions [1].

In order to provide evidence of a mechanism, we also studied the reaction of **1** with 1-(ω-bromoalkyl)pyridazin-6-

Table 1

Reaction Conditions and Results of **1** with α,ω-Dibromoalkanes **2**

Entry	$Br(CH_2)_nBr$ **2** n	Method [a]	Time (hr)[b]	Product Ratio (%) [c] (Isolated Yield %) **3**	**4**	**5**	Total N/O[c]
1	1	A	5	–	100 (90)	–	1:0
2	1	B	11	–	100 (91)	–	1:0
3	2	A	14	–	25 (23)	75 (72)	1:3
4	2	B	1	95 (91)	5	–	1:0
5	3	A	1	99 (96)	1	–	1:0
6	3	B	3	97 (94)	3	–	1:0
7	4	A	1	96 (93)	4	–	1:0
8	4	B	1	93 (90)	7	–	1:0
9	6	A	1	99 (94)	1	–	1:0
10	6	B	1	66 (60)	34 (29)	–	1:0

[a] Method A: Solvent = Acetonitrile, Base = K_2CO_3, Reaction temperature = 82 ±2°, Mole ratio of the reactants: **1/2**/Base = 1:1.8:1.8; Method B: Solvent = Benzene, Base= $(n\text{-}Bu)_4N^+$ Br^-/KOH, Reaction temperature = 56 ±2°, Mole ratio of the reactants: **1/2**/Base = 1:1.8:1.8. [b] Completed alkylation time. [c] Determination by gc.

Table 2

Reaction Conditions and Results of **1** with 1-(ω-Bromoalkyl)-4,5-dichloropyridazin-6-ones **3**

Entry	**3** [a] n	Method [b]	Time (hours) [c]	Product Ratio (%) [d] (Isolated Yield,%) **4**	**5**	Total N/O [d]
1	1	A	3	100 (91)	–	1:0
2	1	B	2	100 (89)	–	1:0
3	2	A	3	–	100 (92)	0:1
4	2	B	1	100 (89)	–	1:0
5	3	A	1	100 (95)	–	1:0
6	4	A	1	100 (90)	–	1:0
7	6	A	2	100 (94)	–	1:0

[a] 1-[ω-$Br(CH_2)_n$]-4,5-dichloropyridazin-6-one. [b] Method A: Solvent = Acetonitrile, Base = K_2CO_3, Reaction temperature = 82 ±2°, Mole ratio of the reactants: **1/3**/ Base = 1:1.8:1.8; Method B: Solvent = Benzene, Base = $(n\text{-}Bu)_4N^+$ Br^-/KOH, Reaction temperature = 56 ±2°, Mole ratio of the reactants: **1/3**/ Base = 1:1.8:1.8. [c] Completed alkylation time. [d] Determination by gc.

Table 3

Melting Points and Elemental Analytical Data of Compound **3**, **4** and **5**

Compound No.	mp (°C) (lit [1])	Molecular Formula	Calcd./Found (%) C	H	N
3a	75-76 (74-75)	$C_5H_3N_2OCl_2Br$	23.29 23.32	1.17 1.20	10.86 10.88
3b	76-77 (76-77)	$C_6H_5N_2OCl_2Br$	26.50 26.65	1.85 1.90	10.30 10.53
3c	75-76 (74-76)	$C_7H_7N_2OCl_2Br$	29.40 29.53	2.47 2.52	9.80 9.88
3d	73-74 (72-74)	$C_8H_9N_2OCl_2Br$	32.03 31.77	3.02 2.98	9.34 9.44
3e	liquid (liquid)	$C_{10}H_{13}N_2OCl_2Br$	36.61 36.88	3.99 4.00	8.54 8.78
4a	241-242 (241-242)	$C_9H_4N_4O_2Cl_4$	31.61 31.87	1.18 1.31	16.38 16.47
4b	210-211 (210-211)	$C_{10}H_6N_4O_2Cl_4$	33.74 33.56	1.70 1.57	15.74 15.68
4c	159-160 (158-160)	$C_{11}H_8N_4O_2Cl_4$	35.71 35.36	2.18 2.10	15.14 15.19
4d	164-165 (164-165)	$C_{12}H_{10}N_4O_2Cl_4$	37.53 37.44	2.62 2.45	14.59 14.70
4e	110-112 (111-112)	$C_{14}H_{14}N_4O2Cl_4$	40.80 40.56	3.42 3.29	13.60 13.52
5	152-153 (151-152)	$C_{10}H_6N_4O_2Cl_4$	33.74 33.52	1.70 1.59	15.74 15.57

ones under the two conditions. Alkylation of **1** with **3**, except for **3b** using potassium carbonate, under the two conditions afforded only the corresponding α,ω-dipyridazinylalkanes **4** (except for **4b**) as *N*-alkylation products in excellent yields. Whereas, reaction of **1** with **3b** in the presence of potassium carbonate gave only the *O*-alkylation product **5b** in excellent yield. Because of the stability of the transition state [1], *O*-alkylation occurs predominantly in the case of **1** with **2b** or **3b** in the presence of potassium carbonate.

Compound **3**, **4** and **5** were identical with authenthic samples. The structures of products **3**, **4** and **5** were also established by ir and nmr. These spectral data and melting points were identical with the reported data [1].

Finally, the retro-ene fragmentation of **1** does not have an effect on the regioselectivity of the alkylation of 1-hydroxymethylpyridazin-6-one under our conditions. However, the structure of the 1-(ω-bromoalkyl)pyridazin-6-ones and the counter ion affects the regioselectivity of the *N/O*-alkylation of compound **1** in our reaction system. In addition, the rate of alkylation is generally faster for the 1-hydroxypyridazin-6-ones than for pyridazin-6-ones in our system.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed with a Perkin Elmer 240C. A mixture of *N/O*-alkylation products was analyzed on a Hewlett Packard HP 5890A gas chromatograph equipped methyl silicon gum capillary HP-1 column (d = 0.53 mm, l = 5 m). 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. The reaction temperature for 56 ±2° was controlled using a jacketed flask employing acetone in the outer flask. Compound **3a** was prepared according to Kim's method [1].

Alkylation of **1** with α,ω-Dibromoalkanes **2** and 4,5-Dichloro-1-(ω-bromoalkyl)pyridazin-6-ones **3**.

Method A.

A mixture of **1** (5.13 mmoles) [5], α,ω-dibromoalkanes **2** or, 4,5-dichloro-1-(ω-bromoalkyl)pyridazin-6-ones **3** [6] (9.23 mmoles), potassium carbonate (9.23 mmoles) and acetonitirle (30 ml) was refluxed (at 82 ±2°) with stirring until the alkylations were completed. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open bed silica gel (10 x 2 cm). The column was eluted with chloroform until the products were eluted completely. Fractions containing the products were combined. Samples of the mixture were taken and subjected to gc analysis. Each experiment was repeated under same condition, and the products of each reaction were also isolated by above method. Recrystallization of a small sample from *n*-hexane/chloroform yielded analytical samples. Infrared and nuclear magnetic resonance spectral data of each compound were identical with the reported data [1].

Method B.

A mixture of **1** (10.26 mmoles), α,ω-dibromoalkanes **2** or 4,5-dichloro-1-(ω-bromoalkyl)pyridazin-6-ones **3** (18.47 mmoles), tetra-*n*-butylammonium bromide (18.47 mmoles), potassium hydroxide (18.47 mmoles) and benzene (35 ml) was stirred at 56 ±2° until the alkylations were completed. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open bed silica gel (10 x 2 cm). The column was eluted with chloroform until the products were eluted completely. Fractions containing the products were combined. Samples of the mixture were taken and subjected to gc analysis. Each experiment was also repeated under same condition, and the products of each reaction were isolated by above method. Recrystallization of a small sample from *n*-hexane/chloroform yielded analytical samples. Infrared and nuclear magnetic resonance spectral data of each compound were identical with the reported data [1].

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[6] Compound **3**, except for **3a**, was synthesized according to Kim's Method [1].