# Alkylation of 4,5-Dichloropyridazin-6-one with α,ω-Dibromoalkanes or 4,5-Dichloro-1-(ω-bromoalkyl)pyridazin-6-ones



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Alkylations of 4,5-dichloropyridazin-6-one (**1**) with dibromoalkanes **2** or **3** in the presence of potassium carbonate or tetrabutylammonium bromide/potassium hydroxide were investigated under restricted condition. Reactions of **1** with **2** or **3**, except for **2b** and **3b**, in the presence of potassium carbonate or tetrabutylammonium bromide/potassium hydroxide gave only the *N*-alkylation products **3** and/or **4**. Alkylation of **1** with **2b** or **3b** in the presence of potassium carbonate yielded the *N*-alkylation products **3b** and/or **4b** and the *O*-alkylation product **5** as the main product, whereas treatment of **1** with **2b** or **3b** in the presence of tetrabutylammonium bromide/potassium hydroxide afforded selectively the *N*-alkylation products **3b** and/or **4b**.

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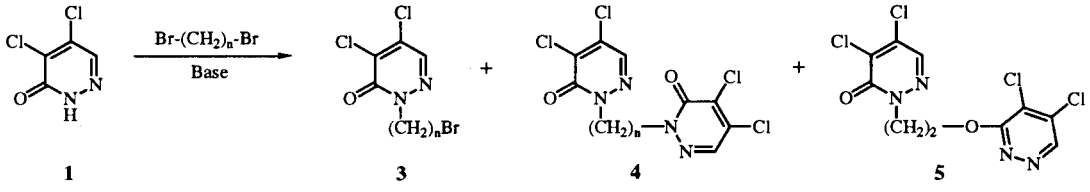
In connection with our research program for the synthesis of α,ω-bis(*N*-heteroaryl)alkanes, we attempted to prepare 4,5-dichloro-1-(ω-haloalkyl) pyridazin-6-ones from 4,5-dichloropyridazin-6-one and α,ω-dihaloalkanes.

First, when 4,5-dichloropyridazin-6-one **1** reacted with 1,1-dibromomethane (**2a**) in acetonitrile under basic condition at reflux temperature, we found the only **4a** as the *N*-alkylation product. Whereas, we detected three products **3b**, **4b** and **5** in the case of the reaction of **1** with **2b** under the same conditions.

Alkylation of pyridazin-6-ones at the N-1 position have been performed in the usual way; *i.e*, they were treated with an alkyl halide in the presence of a base [1], and in the presence of tetrabutylammonium bromide as a phase-transfer catalyst [2].

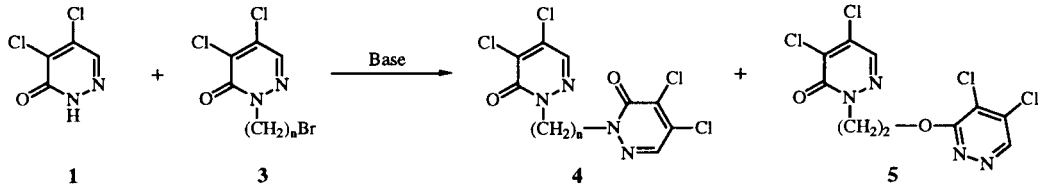
The regioselectivity of the *N/O*-alkylation for a nitrogen heterocyclic ambident anion such as 2-pyridone depends on the nature of the metal, the structure of the alkyl halide, substituents on the heterocycle, the reaction temperature and the solvent [3]. Because the pyridazin-6-one

Scheme I



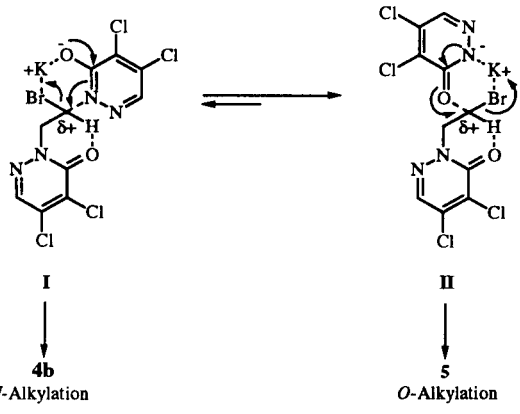

**2, 3, 4 a b c d e**
n 1 2 3 4 6

Scheme II




**3, 4 a b c d e**
n 1 2 3 4 6

Scheme III




anion is a heterocyclic amibident anion [4], the regioselectivity of the alkylation for compound **1** may also depend on the above factors. Therefore, we attempted to study on the *N/O*-alkylation of **1** with α,ω-dibromoalkanes **2** or **3** under restricted conditions.

In this paper, we wish to report the results of the title reaction under the restricted conditions.

We carried out the alkylation of **1** (1 equivalent) under the following two conditions; i) α,ω-dibromoalkane **2** or 1-(ω-bromoalkyl)-4,5-dichloropyridazin-6-ones **3** (1.8 equivalents) and potassium carbonate (1.8 equivalents) in acetonitrile at 82±2°, or ii) α,ω-dibromoalkanes **2** or 1-(ω-bromoalkyl)-4,5-dichloropyridazin-6-ones **3** (1.8 equivalents), tetrabutylammonium bromide (1.8 equivalents) and potassium hydroxide (1.8 equivalents) in benzene at 56±2°.

Table 1

Reaction Conditions and Results of 4,5-Dichloropyridazin-6-one (**1**) with α,ω-Dibromoalkanes

| Entry | $Br(CH_2)_nBr$ | Method | Time | Product Ratio (%) [c] (Isolated Yield %) | | | |
|---|---|---|---|---|---|---|---|
| | n | [a] | (hours) [b] | **3** | **4** | **5** | Total N/O [c] |
| 1 | 1 | A | 9 | — | 100 (96) | — | 1:0 |
| 2 | 1 | B | 6 | — | 100 (97) | — | 1:0 |
| 3 | 2 | A | 5 | 36.4 (30) | 1.2 | 62.4 (59) | 1:1.7 |
| 4 | 2 | B | 2 | 93.1 (90) | 6.9 | — | 1:0 |
| 5 | 3 | A | 6 | 80.8 (76) | 19.2 (16) | — | 1:0 |
| 6 | 3 | B | 3 | 99.8 (96) | 0.2 | — | 1:0 |
| 7 | 4 | A | 4 | 97.8 (95) | 2.2 | — | 1:0 |
| 8 | 4 | B | 1 | 95.1 (92) | 4.9 | — | 1:0 |
| 9 | 6 | A | 5 | 96.0 (94) | 4.0 | — | 1:0 |
| 10 | 6 | B | 2 | 66.2 (61) | 33.8 (31) | — | 1:0 |

[a] Method A: Solvent = Acetonitrile, Base = potassium carbonate, Reaction temperature = 82 ± 2°,Mole ratio of the reactants: **1**/$Br(CH_2)_nBr$/ Base = 1:1.8:1.8; Method B: Solvent = Benzene, Base = tetrabutylammonium bromide/potassium hydroxide, Reaction temperature = 56 ± 2°, Mole ratio of the reactants: **1**/$Br(CH_2)_nBr$/Base = 1:1.8:1.8. [b] Completed alkylation time. [c] Determination by gc.

Table 2

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

| Entry | 4,5-Dichloropyridazin-1-yl$(CH_2)_nBr$ (**3**) | Method | Time | Product Ratio (%) [c] (Isolated Yield, %) | | |
|---|---|---|---|---|---|---|
| | n | [a] | (hours)[b] | **4** | **5** | Total N/O[c] |
| 1 | 1 | A | 1 | 100 (96) | — | 1:0 |
| 2 | 1 | B | 12 | 100 (95) | — | 1:0 |

Table 2 (continued)

| Entry | 4,5-Dichloropyridazin-1-yl($CH_2$)$_n$Br (3) n | Method [a] | Time (hours)[b] | Product Ratio (%) [c] (Isolated Yield, %) 4 | 5 | Total N/O[c] |
|---|---|---|---|---|---|---|
| 3 | 2 | A | 12 | 3.9 | 96.1 (93) | 1:24.6 |
| 4 | 2 | B | 1 | 100 (93) | — | 1:0 |
| 5 | 3 | A | 6 | 100 (92) | — | 1:0 |
| 6 | 4 | A | 6 | 100 (93) | — | 1:0 |
| 7 | 6 | A | 1 | 100 (96) | — | 1:0 |

[a] Method A: Solvent = acetonitrile, base = potassium carbonate, Reaction temperature = 82 ± 2°, Molar ratio of the reactants: 1/4,5-Dichloropyridazin-1-yl($CH_2$)$_n$Br/base = 1:1.8:1.8; Method B: Solvent = benzene, base = tetrabutylammonium bromide/potassium hydroxide, Reaction temperature = 56 ± 2°, Mole ratio of the reactants: 1/4,5-Dichloropyridazin-1-yl($CH_2$)$_n$Br/base = 1:1.8:1.8. [b] Completed alkylation time. [c] Determination by gc.

Table 3

Melting Points and Spectral Data of 4,5-Dichloro-1-(ω-bromoalkyl)pyridazin-6-ones **3**

| Compound No. | mp (°C) | ir (KBr) C=O ($cm^{-1}$) | $^1$H nmr (ppm) [b] Solvent [a] | $NCH_2$ | $CH_2Br$ | Others | $^{13}$C nmr (ppm) |
|---|---|---|---|---|---|---|---|
| **3a** | 74-75 | 1660 | C | 5.84 (s) | | 7.87 (s, H3) | 45.1<br>136.4<br>137.1<br>137.2<br>155.2 |
| **3b** | 76-77 | 1660 | C | 4.58 (t) | 3.73 (t) | 7.83 (s, H3) | 27.2<br>53.6<br>134.3<br>135.8<br>136.7<br>156.3 |
| **3c** | 74-76 | 1690 | D | 4.31 (t) | 3.48 (t) | 2.30 (m, 2H),<br>7.95(s, H3) | 29.6<br>30.9<br>51.6<br>134.4<br>135.8<br>136.6<br>156.6 |
| **3d** | 72-74 | 1670 | C | 4.22 (t) | 3.43 (t) | 1.94 (m, 4H),<br>7.79 (s, H3) | 26.5<br>29.2<br>32.6<br>51.5<br>133.9<br>135.3<br>136.1<br>156.2 |
| **3e** | liquid | 1680 | C | 4.18 (t) | 3.40 (t) | 1.43 (m, 4H),<br>1.85 (m, 4H),<br>7.78 (s, H3) | 25.6<br>27.6<br>27.8<br>32.4<br>33.5<br>52.7<br>134.1<br>135.3<br>136.2<br>156.5 |

[a] Solvents: C = Deuteriochloroform, D = DMSO-$d_6$ . [b] Abbreviations used: s = singlet, t = triplet, m = multiplet.

Table 4

Melting Points and Spectral Data of Compound **4** and **5**

| Compound No. | mp (°C) | ir (KBr) C=O ($cm^{-1}$) | Solvent [a] | $^1$H nmr (ppm) [b] $NCH_2$ | Others | $^{13}$C nmr (ppm) |
|---|---|---|---|---|---|---|
| **4a** | 241-242 | 1680 | C | 6.32 (s) | 8.06 (s, $2H_{3+3'}$) | 69.4<br>138.9<br>141.6<br>141.9<br>160.8 |
| **4b** | 210-211 | 1660 | C | 4.61 (s) | 7.68 (s, $2H_{3+3'}$) | 50.9<br>134.2<br>135.9<br>136.7<br>156.8 |
| **4c** | 158-160 | 1645 | C | 4.25 (t) | 2.34 (m, 2H),<br>7.77 (s, $2H_{3+3'}$) | 26.6<br>49.9<br>134.2<br>135.7<br>136.4<br>156.5 |
| **4d** | 164-165 | 1650 | D | 4.12 (t) | 1.75 (m, 4H),<br>8.12 (s, $2H_{3+3'}$) | 24.4<br>51.4<br>132.8<br>135.5<br>135.7<br>155.6 |
| **4e** | 111-112 | 1651 | C | 4.14 (t) | 1.36 (m, 4H),<br>1.76 (m, 4H),<br>7.75 (s, $2H_{3+3'}$) | 26.0<br>27.8<br>52.7<br>134.2<br>135.3<br>136.2<br>156.5 |
| **5** | 151-152 | 1682<br>1240<br>(C-O) | C | 4.64 (t) | 3.76 (t, $OCH_2$)<br>7.87 (s, $H_3$)<br>8.01 (s, $H_{3'}$) | 27.0<br>54.0<br>126.8<br>131.4<br>131.8<br>134.3<br>139.3<br>142.1<br>154.3<br>157.3 |

[a] Solvent: C = Deuteriochloroform, D = DMSO-$d_6$. [b] Abbreviations used: s = singlet, t = triplet, m = multiplet.

Alkylation of compound **1** with 1,1-dibromomethane (**2a**) in the presence of potassium carbonate or tetrabutylammonium bromide/potassium hydroxide gave only **4a** in quantitative yield. Reaction of **1** with 1,2-dibromoethane (**2b**) in the presence of potassium carbonate afforded **3b** (36%), **4b** (1.2%) and **5** (62%), whereas treatment of **1** with 1,3-dibromopropane (**2c**) in the presence of tetrabutylammonium bromide/potassium hydroxide yielded **3c** (93%) and **4c** (6.9%). Alkylation of **1** with 1,4-dibromobutane (**2d**) in the presence of potassium carbonate also afforded **3d** (80.8%) and **4d** (19%), whereas treatment of **1** with **2d** in the presence of tetrabutylammonium bromide/potassium hydroxide gave **3d** (100%) and **4d** (0.2%) as *N*-alkylation products. In addition, reaction of **1** with 1,6-dibromohexane (**2e**) in the presence of potassium carbonate afforded **3e** (96%) and **4e** (4.0%). Alkylation of **1** with **2e** in the presence of tetrabutylammonium bromide/potassium hydroxide yielded the corresponding **3e** (66%) and **4e** (34%).

The alkylation of **1** with α,ω-dibromoalkanes **2** using tetrabutylammonium bromide/potassium hydroxide is faster than it using potassium carbonate. When compound **1** was reacted with **2**, except for **2b** in the presence of potassium carbonate, we observed only *N*-alkylation. Whereas, *O*-alkylation occurred predominantly in the case of the alkylation of **1** with **2b** in the presence of potassium carbonate. The ratio of *N*/*O*-alkylation of **1** with **2b** is 1:1.7.

Table 5
Elemental Analytical Data of Compounds 3, 4 and 5

| Compound No. | Molecular Formula | Calcd./Found (%) C | H | N |
|---|---|---|---|---|
| **3a** | $C_5H_3N_2OCl_2Br$ | 23.29 | 1.17 | 10.86 |
| | | 23.42 | 1.19 | 10.96 |
| **3b** | $C_6H_5N_2OCl_2Br$ | 26.50 | 1.85 | 10.30 |
| | | 26.67 | 1.81 | 10.52 |
| **3c** | $C_7H_7N_2OCl_2Br$ | 29.40 | 2.47 | 9.80 |
| | | 29.63 | 2.44 | 9.97 |
| **3d** | $C_8H_9N_2OCl_2Br$ | 32.03 | 3.02 | 9.34 |
| | | 31.92 | 2.98 | 9.36 |
| **3e** | $C_{10}H_{13}N_2OCl_2Br$ | 36.61 | 3.99 | 8.54 |
| | | 36.93 | 3.95 | 8.67 |
| **4a** | $C_9H_4N_4O_2Cl_4$ | 31.61 | 1.18 | 16.38 |
| | | 30.80 | 1.22 | 16.18 |
| **4b** | $C_{10}H_6N_4O_2Cl_4$ | 33.74 | 1.70 | 15.74 |
| | | 33.45 | 1.66 | 15.88 |
| **4c** | $C_{11}H_8N_4O_2Cl_4$ | 35.71 | 2.18 | 15.14 |
| | | 35.35 | 2.13 | 15.17 |
| **4d** | $C_{12}H_{10}N_4O_2Cl_4$ | 37.53 | 2.62 | 14.59 |
| | | 37.36 | 2.51 | 14.70 |
| **4e** | $C_{14}H_{14}N_4O_2Cl_4$ | 40.80 | 3.42 | 13.60 |
| | | 40.44 | 3.37 | 13.61 |
| **5** | $C_{10}H_6N_4O_2Cl_4$ | 33.74 | 1.70 | 15.74 |
| | | 33.47 | 1.62 | 15.72 |

During the experiment, we also observed first the spot of compound **3**, and then the spots of compounds **4** and **5** on the tlc plate. For that reason, we thought that these reactions occurred through two steps; a first alkylation of **1** with α,ω-dibromoalkanes **2** produced compound **3**, and it was then alkylated with an anion of **1** in the second step to yield compounds **4** or **5** under our reaction conditions.

In order to provide evidence of a mechanism for the results of reaction of **1** with α,ω-dibromoalkanes **2**, we also studied on the alkylation of **1** with compound **3** under the same conditions. Alkylation of **1** with compound **3**, except for **3b** in potassium carbonate, under our conditions yielded only the *N*-alkylation product **4** in excellent yield. Whereas, reaction of **1** with **3b** in the presence of potassium carbonate gave **4b** (3.9%) as the *N*-alkylation product and **5** (96%) as the *O*-alkylation product. The ratio of *N/O*-alkylation of **1** with **3b** is about 1:25.

*O*- and *N*-alkylation of **1** with **2b** or **3b** in the presence of potassium carbonate can account for the mechanism in Scheme III. The electron density on oxygen of the carbonyl group is higher than that of nitrogen at the 1-position in a free anion of 4,5-dichloropyridazin-6-one [5]. Potassium ion may be located in the proximity of oxygen in the potassium salt. However, structure **II** is more favorable structurally than structure **I** in the transition state. Thus, *O*-alkylation occurs predominantly in the case of the alkylation of **1** with **2b** or **3b** in the presence of potassium carbonate. It may be regarded that the structures of the transition state for other compounds **2** and **3** do not affect the regioselectivity for the alkylation of **1** in the presence of potassium carbonate.

On the other hand, alkylation of **1** with **2** or **3** in the presence of tetrabutylammonium bromide/potassium hydroxide may occur selectively only to give *N*-alkylation because of steric hindrance of the tetrabutylammonium group.

Finally, the counter ion and the structure of alkyl halides affect the regioselectivity of *N/O*-alkylation of compound **1** in our reaction system.

The structures of compound **3**, **4** and **5** were established by ir, nmr and elemental analysis. It was easy to distinguish between compound **4b** and **5** by ir and nmr. The infrared spectrum of **4b** showed an absorption band of one carbonyl group, whereas the ir of **5** detected the absorption bands of one carbonyl group and a C-O bond. The proton magnetic resonance spectrum of **4b** also showed one proton signal of 2($NCH_2$) as singlet at δ 4.61 ppm, whereas the nmr of **5** showed two proton signals as triplets at δ 3.76 ($OCH_2$) and at δ 4.64 ($NCH_2$), respectively. The $^{13}C$ nmr of **4b** showed five carbon signals, whereas the $^{13}C$ of **5** showed ten carbon signals because of the different chemical environment of the two pyridazine rings.

Additional chemical transformations of the novel compounds, along with an evaluation of their biological properties, are currently under investigation in our laboratory.

## 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 chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectra were obtained on a Hitachi 270-50 spectrophotometer. 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 a slurries with the elusion solvent. The reaction temperature for 56 ± 2° was controlled using a jacket-flask with acetone in the outer flask.

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** (12.12 mmoles) [6], α,ω-dibromoalkanes **2** or, 4,5-dichloro-1-(ω-bromoalkyl)pyridazin-6-ones **3** [7] (21.82 mmoles), potassium carbonate (21.82 mmoles) and acetonitrile (50 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 the same conditions, and the products of each reaction were also isolated by the above method. Recrystallization of a small sample from *n*-hexane/chloroform yielded analytical samples.

Method B.

A mixture of **1** (6.06 mmoles), α,ω-dibromoalkanes **2** or 4,5-Dichloro-1-(ω-bromoalkyl)pyridazin-6-ones (**3**) (10.91 mmoles), tetrabutylammonium bromide (10.91 mmoles), potassium hydroxide (10.91 mmoles) and benzene (30 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.

Synthesis of 1-(ω-Bromomethyl)-4,5-dichloropyridazin-6-one **3a**.

A mixture of 1-(hydroxymethyl)-4,5-dichloropyridazin-6-one (0.5 g, 2.56 mmoles) [8], thionyl bromide (0.35 ml, 4.61 mmoles) and *N,N*-dimethylformamide (10 ml) was refluxed for 4 hours. After cooling to room temperature, chloroform (50 ml) was added to the reaction mixture. The organic layer was washed with excess water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. *n*-Hexane (10 ml) was then added to the resulting residue with stirring. The crystals were filtered and dried in air to give compound **3a** as white crystals in 94% (0.62 g) yield.

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REFERENCES AND NOTES

[1a] J. A. King, and F. H. McMillan, *J. Am. Chem. Soc.*, **74**, 3222 (1952); [b] Y. Nitta, F. Yoneda, T. Ohtaka, and T. Kato, *Chem. Pharm. Bull.*, **12**, 69 (1964); [c] H. M. Holava, and R. A. Partyka, *J. Med. Chem.*, **14**, 262 (1971)

[2] T. Yamada, and M. Ohki, *Synthesis*, 631 (1981)

[3a] D. L. Comins, and G. Jianhua, *Tetrahedron Letters.*, **35**, 2819 (1994); [b] N. M. Chung, and H. Tieckelmann, *J. Org. Chem.*, **35**, 2517 (1970); [c] S. K. Kim, S. D. Cho, J. K. Moon, and Y. J. Yoon, *J. Heterocyclic Chem.*, **33**, 615 (1996).

[4] N. Kornblumn, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955)

[5] The electron charge densities of N-1 (-0.2176) and 0-6 (-0.4183) for a free anion of 4,5-dichloropyridazin-6-one were calculated using MOPAC 6.0 AMI Hamiltonian program.

[6] D. T. Mowry, *J. Am. Chem. Soc.*, **75**, 1909 (1953)

[7] Compound **3**, except for **3a**, was synthesized by the Method B.

[8] S. D. Cho, J. W. Chung, W. Y. Choi, S. K. Kim, and Y. J. Yoon, *J. Heterocyclic Chem.*, **31**, 1199 (1994).