Retro-Ene Reactions. III. Alkylation of 4,5-Dichloro-1-hydroxymethylpyridazin-6-ones: Synthesis of 4,5-Dichloro-1-(ω-phthalimido and saccharin-2'-ylalkyl)pyridazin-6-ones

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Dedicated to the memory of Professor Nicholas Alexandrou

4,5-Dichloro-1-(ω-phthalimido and saccharinyl-2'-ylalkyl)pyridazin-6-ones were synthesized from 4,5-dichloro-1-hydroxymethylpyridazin-6-one and the corresponding *N*-(ω-haloalkyl)phthalimides and saccharins *via* a fragmentation of retro-ene type.

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We have recently reported the retro-ene reaction of *N*-hydroxymethyl saccharin [1] and 4,5-dichloro-1-hydroxymethylpyridazin-6-one (**2**) [2] as novel 1-O, 3-N, 5-O ene-adducts. Previously, the *N*-alkylation of these ene-adducts with some alkyl halides under basic conditions have been reported [1,2]. Because of our interest in the effect of the retro-ene fragmentation during the alkylation of 1-O, 3-N, 5-O ene-adducts, we investigated the alkylation of 4,5-dichloro-1-hydroxymethylpyridazin-6-one with some *N*-(ω-haloalkyl)heterocycles.

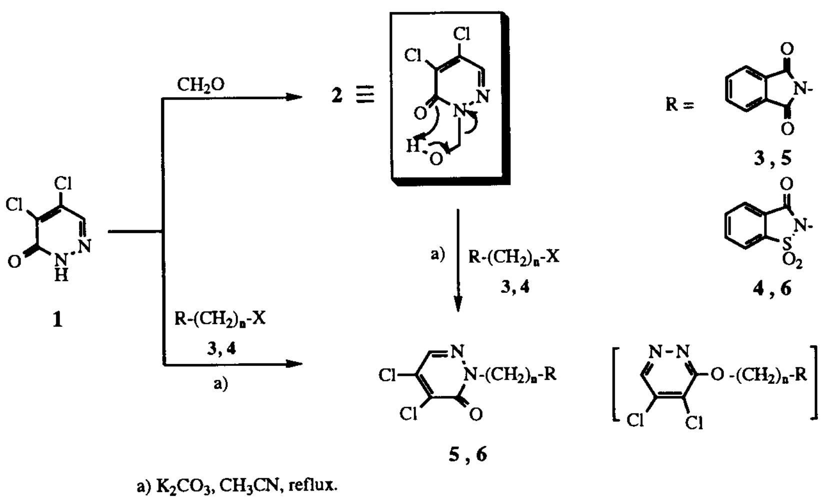
In this paper, we wish to report the synthesis of 4,5-dichloro-1-(ω-phthalimido and saccharin-2'-yl)pyridazin-6-ones **5** and **6** from 4,5-dichloro-1-hydroxymethylpyridazin-6-one (**2**) and *N*-(ω-haloalkyl)phthalimides **3** and saccharins **4** under the restricted condition *via* the fragmentation of the retro-ene type.

We attempted to synthesize *N*-(ω-haloalkyl)saccharin as the starting materials. Chlorination of *N*-hydroxymethylsaccharin [1b] with thionyl chloride in the presence of ferric chloride in chloroform afforded compound **4a** in 97% yield. Alkylation of saccharin with the corresponding α,ω-dibromoalkanes and potassium carbonate in acetonitrile yielded *N*-(ω-bromoalkyl)saccharins (**4b-4e**) in 80-90% yield [3]. The structures of compound **4** were established by ir and nmr.

Reaction of 4,5-dichloro-1-hydroxymethylpyridazin-6-one (**2**) with *N*-(ω-haloalkyl)phthalimidies **3** and saccharins **4** in the presence of potassium carbonate in acetonitrile at reflux temperature gave only the corresponding 4,5-dichloro-1-(ω-phthalimido and saccharin-2'-ylalkyl)pyridazin-6-ones **5** and **6** as *N*-alkylation products in excellent yields (the Method A).

On the other hand, 4,5-dichloropyridazin-6-one (**1**) was reacted with *N*-(ω-haloalkyl)phthalimides **3** and saccharins **4** under the same condition to afford the corresponding 4,5-dichloro-1-(ω-phthalimido and saccharin-2'-ylalkyl)pyridazin-6-ones **5** and **6** in excellent yields Method B). In this case, we also observed only *N*-alkylation. These products were identical with compounds **5** and **6** that were prepared by Method A.

Scheme I



a) K_2CO_3, CH_3CN, reflux.

3,4	a	b	c	d	e
n	1	2	3	4	6
x	Cl	Br	Br	Br	Br

5,6	a	b	c	d	e
n	1	2	3	4	6

The rate of the alkylation of compound **2** was faster than that of **1** under our reaction conditions. Therefore, compound **2** is a useful starting material for the alkylation of pyridazinones.

According to our previous paper [2], the alkylation of 4,5-dichloro-1-hydroxymethylpyridazin-6-one (**2**) with 1-haloalkanes under basic conditions occurs *via* two steps. In the first step, compound **2** undergoes a retro-ene fragmentation to give the 4,5-dichloropyridazin-6-one anion. The anion then reacts with 1-haloalkanes. The reaction of compound **2** with *N*-(ω-haloalkyl)heterocycles under basic conditions may also occur similarly in two steps.

Table 1

Yields, Melting Points and IR Spectral Data of Compound **5** and **6**

Compound No	Isolated Yield (%) A	B	mp (°C)	IR (KBr) C=O (cm^{-1})
5a	97	88	213-215	1722, 1675
5b	87	86	171-173	1712, 1643
5c	90	90	136-138	1720 1657
5d	93	94	137-139	1715, 1661
5e	91	89	116-117	1717, 1651
6a	92	92	190-191	1770, 1680
6b	94	88	179-180	1722, 1665
6c	90	88	134-136	1740, 1648
6d	83	96	124-125	1730, 1655
6e	93	93	106-107	1742, 1685

Table 2

^{1}H nmr Spectral Data of Compounds **5** and **6**

Compound No.	^{1}H nmr (ppm) [a] N1-CH$_2$	N2'-CH$_2$	Others
5a	5.99 (s)		7.76-7.95 (m, Ar, 4H), 7.75 (s, 1 H$_3$)
5b	4.45 (t)	4.14 (t)	7.69-7.83 (m, Ar, 4H), 7.61 (s, 1 H$_3$)
5c	4.23 (t)	3.76 (t)	7.80 (s, 1H$_3$), 7.73-7.79 (m, Ar, 4H), 2.22 (m, CH$_2$)
5d	4.22 (t)	3.72 (t)	7.81 (s, 1H$_3$), 7.74-7.83 (m, Ar, 4H), 1.87 (m, CH$_2$), 1.73 (m, CH$_2$)
5e	4.16 (t)	3.67 (t)	7.70-7.85 (m, Ar, 4H), 7.78 (s, 1H$_3$), 1.80 (m, CH$_2$), 1.68 (m, 2 CH$_2$), 1.39 (m, CH$_2$)
6a	6.15 (s)		8.03 (m, Ar, 4H), 7.90 (s, 1 H$_3$)
6b	4.60 (t)	4.20 (t)	8.07-7.82 (m, Ar, 4H), 7.86 (s, 1 H$_3$)
6c	4.26 (t)	3.83 (t)	8.07-7.78 (m, Ar, 4H), 7.84 (s, 1 H$_3$), 2.42 (m, CH$_2$)
6d	4.26 (t)	3.83 (t)	8.05-7.73 (m, Ar, 4H + 1 H$_3$), 1.94 (m, 2 CH$_2$)
6e	4.18 (t)	3.76 (t)	8.06-7.77 (m, Ar, 4H + 1 H$_3$), 1.82 (m, 2 CH$_2$), 1.44 (m, 2 CH$_2$)

[a] Solvent = deuteriochloroform. Abbreviations used: Ar = aromatic, s = singlet, t = triplet and m = multiplet.

Table 3

^{13}C nmr Spectral Data of Compound **5** and **6**

Compound No.	^{13}C nmr (ppm) [a] N1-C	N2'-C	Carbon of	Others
5a	52.5		156.1, 166.8	124.0, 131.6, 134.7, 136.2, 137.0
5b	51.4	36.0	156.8, 168.0	123.4, 131.8, 134.1, 135.7, 136.5
5c	50.5	36.7	156.5, 168.0	25.4, 123.2, 132.2, 134.0, 134.3, 135.0, 136.0
5d	52.2	37.3	156.5, 168.3	25.4, 25.6, 123.2, 132.0, 133.9, 134.2, 135.5, 136.3
5e	52.8	37.8	156.5, 168.4	26.0, 26.3, 27.9, 28.4, 123.2, 132.1, 133.9, 134.2, 135.3, 136.2
6a	52.4		155.9, 158.0	120.6, 126.0, 126.0, 134.0, 134.5, 136.1, 136.5, 137.0, 137.5
6b	50.5	37.1	157.1, 159.0	121.1, 125.3, 126.9, 134.5, 135.0, 135.2, 136.1, 136.6, 137.4
6c	52.1	38.6	156.6, 159.0	25.3, 121.0, 125.2, 127.3, 134.3, 134.4, 134.8, 135.6, 136.6 137. 6
6d	52.1	38.6	156.6, 159.0	25.3, 25.3, 120.9, 125.2, 127.3, 134.3, 134.3, 134.8, 135.6, 136.4, 137. 6
6e	52.8	39.2	156.5, 158.9	25.9, 26.3, 27.9, 28.2, 120.9, 125.1, 127.4, 134.2, 134.3, 134.7, 135.4, 136.3, 137.6

[a] Solvent = deuteriochloroform.

Table 4

Analytical Data of Compounds **5** and **6**

Compound No.	Molecular Formula	Analysis (%) Calcd./Found C	H	N
5a	$C_{13}H_7N_3O_3Cl_2$	48.17	2.18	12.96
		48.23	2.30	12.62
5b	$C_{14}H_9N_3O_3Cl_2$	49.73	2.68	12.43
		49.90	2.78	12.51
5c	$C_{15}H_{11}N_3O_3Cl_2$	51.08	3.06	11.73
		51.28	3.18	11.79
5d	$C_{16}H_{13}N_3O_3Cl_2$	52.48	3.58	11.47
		52.76	3.48	11.24
5e	$C_{18}H_{17}N_3O_3Cl_2$	54.84	4.35	10.66
		54.90	4.47	10.68
6a	$C_{12}H_7N_3O_4SCl_2$	40.02	1.96	11.67
		39.87	1.87	11.45
6b	$C_{13}H_9N_3O_4SCl_2$	41.73	2.42	11.23
		41.48	2.32	11.09
6c	$C_{14}H_{11}N_3O_4SCl_2$	43.31	2.86	10.82
		43.29	2.78	10.78
6d	$C_{15}H_{13}N_3O_4SCl_2$	44.79	3.26	10.45
		44.64	3.19	10.35
6e	$C_{17}H_{17}N_3O_4SCl_2$	47.45	3.98	9.77
		47.39	3.80	9.65

The regioselectivity of the alkylation for a heterocyclic ambident anion such as 2-pyridone depends on the nature of the metal, the structure of the alkyl halide, substituents on the heterocycle, and the solvent [4]. Because the pyridazin-6-one anion is a heterocyclic ambident anion [5], the regioselectivity of the alkylation for compound **2** may also depend on the above factors. In addition, if the alkylation occurs in the initial stage of the retro-ene fragmentation of 1-hydroxymethylpyridazin-6-one, the regioselectivity of *N*/*O*-alkylation may depend on the rate of departure of formaldehyde as the leaving group under our restricted conditions. However, we observed only *N*-alkylation in our reaction systems.

Finally, the retro-ene fragmentation and the structure of *N*-(ω-haloalkyl)heterocycles **3** and **4** do not have an effect on the regioselectivity of the alkylation of compound **2** in our reaction system.

It was easy to distinguish between *N*- and *O*-alkyl products by infrared and ^{13}C nmr spectra. The infrared spectra of **5** and **6** showed the absorption bands of two carbonyl groups at 1708-1718 (for the phthalimide of **5**) or 1722-1770 (for the saccharin of **6**), and 1643-1685 cm^{-1} (for the pyridazin-6-one of **5** and **6**), respectively. In the ^{13}C nmr spectra of **5** and **6**, the signals of two carbonyl carbons were detected at δ 155.7-157.1 and δ 158.6-168.3 ppm. The ^{13}C nmr spectra of **5** and **6** also showed the signals of the carbons at δ 50.5-52.5 ppm (for the carbon attached to nitrogen of pyridazine) and δ 36.0-38.6 ppm (for the carbon attached to the nitrogen of phthalimide or saccharin) involving other carbon signals. The proton magnetic resonance spectra showed the proton signals as singlet or triplet at δ 4.15-6.15 ppm (for the proton of methylene attached to pyridazine) and at δ 3.68-4.20 ppm (for the proton of methylene attached to phthalimide or saccharin) involving signals for other methylene and aromatic protons. The molecular formulas of compound **5** and **6** were established by elemental analysis.

Further experiments including kinetics, alkylation and synthetic applications of some 1-O 3-N, 5-O retro-ene adducts including compound **2** are under way 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 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 with silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. *N*-(ω-Haloalkyl)-phthalimide (**3**) was purchased from Aldrich Chemical Company.

Reaction of 4,5-Dichloro-1-hydroxymethylpyridazin-6-one (**2**) with *N*-(ω-Haloalkyl)phthalimides **3** and Saccharins **4**.

Method A.

A mixture of compound **2** [6] (1.54 mmoles), *N*-(ω-haloalkyl)phthalimides **3** and saccharins **4** (2.78 mmoles), potassium carbonate (92.78 mmoles) and acetonitrile (50 ml) was refluxed for 0.5-2.5 hours. 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 column (10 x 2 cm). the column was eluted with chloroform. Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give compounds **5** in 85-97% yields and **6** in 83-94% yields, respectively. Recrystallization of a small sample from chloroform/*n*-hexane (1:1, v/v) yielded white crystals.

Reaction of 4,5-Dichloropyridazin-6-one (**1**) with *N*-(ω-Haloalkyl)phthalimides (**3**) and saccharins (**4**).

Method B.

A mixture of compound **1** [7] (0.61 mmole), *N*-(ω-haloalkyl)phthalimides **3** and saccharins **4** (1.11 mmoles), potassium carbonate (1.11 mmoles) and acetonitrile (20 ml) was refluxed for 1-4 hours. 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 column (10 x 2 cm). The column was eluted with chloroform. Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give compounds **5** in 86-94% yields and compounds **6** in 88-92% yields, respectively. Recrystallization of a small sample from chloroform/*n*-hexane (1:1, v/v) yielded white crystals.

Synthesis of *N*-Chloromethylsaccharin (**4a**)

A mixture of *N*-hydroxymethylsaccharin [1b] (3 g, 15.4 mmoles), ferric chloride (3 g, 18.5 mmoles), thionyl chloride (1.34 ml, 18.5 mmoles) and chloroform (50 ml) was refluxed for 0.5-1 hours. After cooling to room temperature, the mixture was filtered using Celite. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (10 x 2.5 cm). The column was eluted with chloroform (or methylene chloride). Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give compound **4a** in 97% yield. Recrystallization of a small sample from *n*-hexane yielded white crystals,. mp 146-147°; ir (potassium bromide) 3010, 3045, 2960,1762, 1600, 1465, 1340, 1330, 1300, 1256, 1195 cm^{-1}; ^1H nmr (deuteriochloroform) δ 5.58 (s, NCH_2), 7.89-8.15 ppm (m, aromatic 4H); ^{13}C nmr (deuteriochloroform) δ 45.3, 121.3, 125.7, 126.3, 134.8, 135.7, 137.5, 157.5 ppm.

Synthesis of *N*-(ω-Bromoalkyl)saccharins (**4b-4e**)

A mixture of saccharin (54.59 mmoles), α,ω-dibromoalkanes (98.26 mmoles), potassium carbonate (98.26 mmoles) and acetonitrile (30 ml) was refluxed for 4-5 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of a open-bed silica gel column (10 x 2 cm). The column was eluted with chloroform/*n*-hexane (1:1, v/v). Fractions containing *N*-(ω-haloalkyl)saccharins (**4b-4e**) were combined, and the solvent was evaporated under reduced pressure to give compounds **4b-4e** in 80-90% yield. Recrystallization of a small sample from $CHCl_3$/n-hexane (1:1, v/v) yielded white crystals.

Compound **4b**: mp 100-102°; ir (potassium bromide): 3110, 3060, 3010, 2990, 1750, 1604, 1475, 1350, 1304, 1262, 1230, 1180 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.66 (t, CH_2Br), 4.16 (t, NCH_2), 7.86-8.10 ppm (m, aromatic 4H); ^{13}C nmr (deuteriochloroform): δ 27.0, 39.8, 121.1, 125.4, 126.9, 134.6, 135.1, 137.3, 158.5 ppm.

Compound **4c**: mp 89-91°; ir (potassium bromide): 3100, 3020, 2980, 1740, 1605, 1462, 1330, 1310, 1270, 1240, 1180 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (m, CH_2), 3.51 (t, CH_2Br), 3.95 (t, NCH_2), 7.85-8.08 ppm (m, aromatic 4H); ^{13}C nmr (deuteriochloroform): δ 29.8, 31.2, 37.8, 121.0, 123.3, 125.2, 127.1, 134.5, 134.9, 137.5, 159.0 ppm.

Compound **4d**: mp 54-55°; ir (potassium bromide): 3105, 3050, 2990, 1740, 1600, 1470, 1340, 1310, 1270, 1185 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.01 (m, $2CH_2$), 3.46 (t, CH_2Br), 3.83 (t, NCH_2), 7.84-8.05 ppm (m, aromatic 4H); ^{13}C nmr (deuteriochloroform): δ 27.1, 29.7, 32.7, 38.4, 121.0, 125.2, 127.3, 134.4, 134.9, 13.6, 159.9 ppm.

Compound **4e**: mp 69-70°; ir (potassium bromide): 3100, 2980, 2800, 1750, 1610, 1480, 1340, 1320, 1280, 1200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (m, $2CH_2$), 1.87 (m, $2CH_2$), 3.40 (t, CH_2Br), 3.78 (t, NCH_2), 7.80-8.07 ppm (m, aromatic 4H); ^{13}C nmr (deuteriochloroform): δ 25.9, 27.5, 28.1, 32.5, 33.6, 39.2, 120.8, 125.1, 127.4, 134.2, 134.6, 137.7, 158.9 ppm.

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REFERENCES AND NOTES

[1a] S. K. Kim, J. G. Moon, S. Y. Choi, S. D. Cho and Y. J. Yoon, *J. Heterocyclic Chem.*, **30**, 353 (1993); [b] S. Y. Cho, S. G. Lee, Y. J. Yoon and K. W. Kim, *J. Heterocyclic Chem.*, **26**, 1073 (1989).

[2] S. K. Kim, S. D. Cho, D. H. Kweon, S. G. Lee, J. W. Chung, S. C. Shin and Y. J. Yoon, *J. Heterocyclic Chem.*, **33**, (1996) in press.

[3] In this case, disaccharinylalkanes as an impurity was also detected.

[4a] D. L. Comins and G. Jianhua, *Tetrahedron Letters*, **35**, 2819 (1994); [b] N. M. Chung and H. Tieckelmann, *J. Org. Chem.*, **35** (8), 2517 (1970).

[5] N. Korblum, R. A. similey, R. K. Blackwood and D. C. Inffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

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

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