Retro-Ene Reaction. II. Reaction of 4,5-Dichloro-1-hydroxymethylpyridazin-6-one with Alkyl Halides and Carboxylic Acid Chlorides

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1-Alkyl-4,5-dichloropyridazin-6-ones and (4,5-dichloro-6-oxopyridazin-1-yl)methylcarboxylates were synthesized from 4,5-dichloro-1-hydroxymethylpyridazin-6-one and the corresponding alkyl halides or carboxylic acid chlorides. Also the reaction mechanisms *via* a fragmentation of retro-ene type are discussed.

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During the past two decades, a number of synthetic reports have indicated the use of retro-ene reactions [1]. We have reported the retro-ene reaction of *N*-hydroxymethylsaccharin [2]. *N*-Hydroxymethylsaccharin is a novel 1-*O*, 3-*N*, 5-*O* ene-adduct. As a part of a continuous program to study the reaction of 1-*O*, 3-*N*, 5-*O* ene-adducts, we investigated the reaction of 1-hydroxymethyl-4,5-dichloropyridazin-6-one (**2**) with alkyl halides and carboxylic acid chlorides.

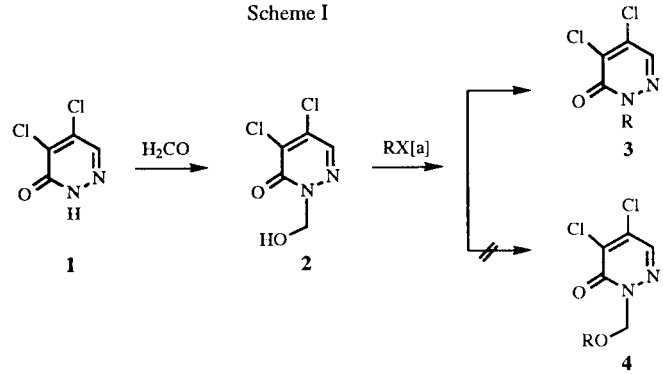
In this paper, we would like to report our observations on the title reaction.

Alkylation of **2** [3a,3b] with alkyl halides such as methyl iodide, ethyl bromide, *n*-propyl bromide, *n*-butyl chloride and 4-iodobutyl benzoate [3b] in the presence of potassium carbonate (or pyridine) in acetone (or acetonitrile) at reflux temperature for 2-4 hours gave the corresponding 1-alkylpyridazin-6-ones **3a-3e** instead of the corresponding 1-alkoxymethylpyridazin-6-ones **4** in excellent yields (Method A for **3a-3d** and Method B for **3e**). The reactions of **2** with alkyl halides in the presence of potassium carbonate in acetone at room temperature for 3 days gave the corresponding 1-alkylpyridazin-6-ones **3a-3e** as the major products and compound **1** as the minor product. In order to confirm the products, treatment of **1** with the corresponding alkyl halides and potassium carbonate at reflux temperature for 4-6 hours also provided the corresponding 1-alkylpyridazin-6-ones **3a-3e** in low yield.

It was easy to distinguish between 1-alkylpyridazin-6-ones **3** and 1-alkoxymethylpyridazin-6-ones **4** by the proton magnetic resonance spectra. The pmr spectra of compounds **3a-3e** did not show the signal as a singlet of two protons of the methylene for the -OCH_2N moiety.

On the other hand, treatment of **2** with acyl or benzoyl chlorides in the presence of potassium carbonate (or pyridine) in acetone (or acetonitrile) at reflux or room temperature furnished the corresponding esters **5a-5i** as the major products instead of the expected 1-acyl (or benzoyl) derivatives **6** and compound **1** as the minor products (the Method C). The yields of **5a-5i** were higher at room temperature than at reflux temperature, whereas the yield of **1** was higher at reflux temperature than at room temperature. However, treatment of **1** with benzoyl or acyl chlorides under the same condition did not afford 1-acyl (or benzoyl) derivatives **6**.

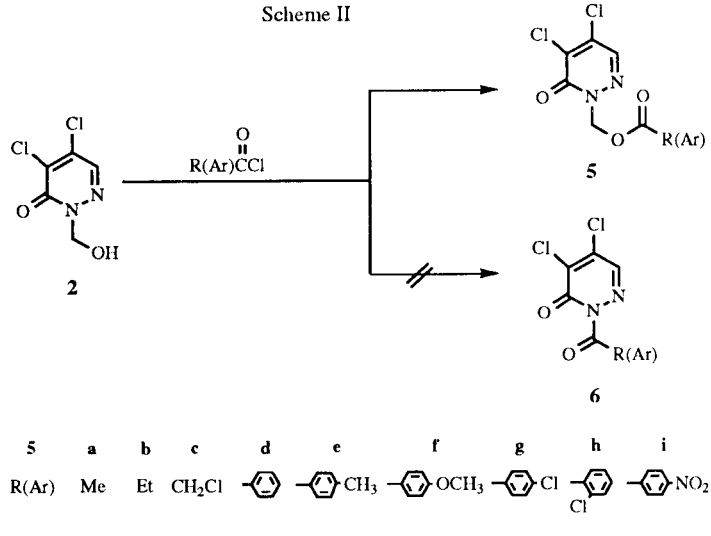
Scheme I



3	a	b	c	d	e
R	Me	Et	*n*-Pr	*n*-Bu	$C_6H_5COO(CH_2)_4$-

[a] X: I for **3a** and **3e**; Br for **3b** and **3c**; Cl for **3d**

Scheme II



5	a	b	c	d	e	f	g	h	i
R(Ar)	Me	Et	CH_2Cl	C_6H_5	$C_6H_5CH_3$	$C_6H_5OCH_3$	C_6H_5Cl	$C_6H_3Cl_2$	$C_6H_5NO_2$

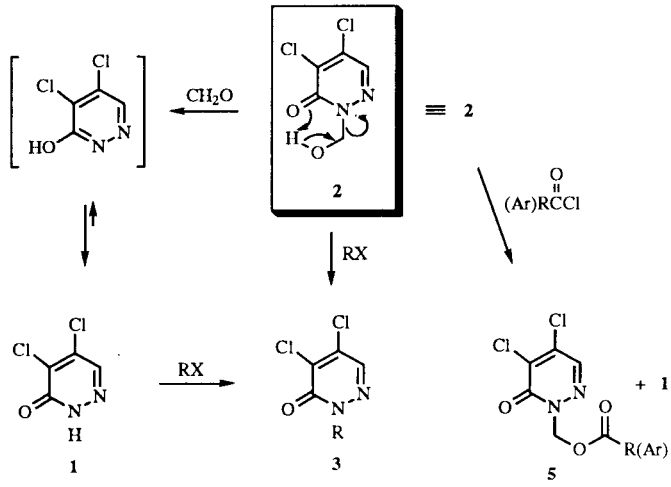
The proton signal as a singlet of two protons for the methylene group of N-CH_2-O was detected by the pmr spectra for compounds **5a-5i** at δ 6.0-6.3 ppm. The infrared spectra of compounds **5a-5i** also showed absorption bands of the carbonyl and the C-O bond for the esters at 1720-1790 cm^{-1} and 1190-1280 cm^{-1}, respectively.

It has already been reported by us [2a,2b] that the reaction of the 1-*O*, 3-*N*, 5-*O* ene adduct such as *N*-hydroxymethylsaccharin occurs *via* a fragmentation of the retro-ene type in which facile carbon-nitrogen cleavage occurs and the leaving enophile is formaldehyde. The second step is the formation step of a new carbon-nitrogen bond.

In order to provide evidence of a mechanism for the results of reaction **2** with alkyl halides or carboxylic acid chlorides under basic condition, we attempted to convert **2** to **1**. Treatment of compound **2** with potassium carbonate in acetone at reflux temperature during a short period yielded compound **1** in quantitative yield (Method D). Reaction of compound **2** with potassium carbonate in acetone at room temperature for 1 day also gave compound **1** in good yield. The conversion rate of compound **2** to **1** under basic conditions was faster at higher temperature than at lower temperature.

In conclusion, compound **2** was subject to a fragmentation of the retro-ene type at the first step. Then formation of a new nitrogen-carbon bond at the second step to yield the corresponding 1-alkylpyridazin-6-ones **3a-3e** was observed when compound **2** was allowed to react with alkyl halides in the presence of base at reflux temperature.

Scheme III



1 3 5

Table 1

Physical and Analytical Data of 1-Alkylpyridazin-6-ones **3a-3e**

Compound No.	Yield (%) [a]	mp °C [b]	Molecular Formula	Analysis (%), Calcd./Found C	H	N
3a	95	87-88	$C_5H_4N_2OCl_2$	33.55	2.25	15.65
		[c]		33.76	2.21	15.55
3b	89	49-50	$C_6H_6N_2OCl_2$	37.33	3.13	14.51
		[d]		37.52	3.30	14.70
3c	90	liquid	$C_7H_8N_2OCl_2$	40.61	3.89	13.53
				40.81	4.01	13.74
3d	92	liquid	$C_8H_{10}N_2OCl_2$	43.46	4.56	12.67
		[d]		43.58	4.68	12.84
3e	82	79-80	$C_{15}H_{14}N_2O_3Cl_2$	52.81	4.14	8.21
				52.73	4.25	8.22

[a] Isolated yield for Method A for **3a-3d** and Method B for **3e**. [b] Recrystallization solvent: *n*-hexane for **3a-3d** or diethyl ether for **3e**. [c] Lit [3a] mp 89-90°. [d] Lit [4] mp 49-51° for **3b**; liquid for **3d**.

Table 2

Physical and Analytical Data of Esters **5a-5i**

Compound No.	Yield (%) [a]	mp °C [b]	Molecular Formula	Analysis (%), Calcd./Found C	H	N
5a	73	88-89	$C_7H_6N_2O_3Cl_2$	35.47	2.55	11.82
		[c]		35.67	2.37	11.77
5b	83	55-56	$C_8H_8N_2O_3Cl_2$	38.27	3.21	11.16
				38.30	2.98	10.88
5c	86	83-84	$C_7H_5N_2O_3Cl_3$	30.97	1.86	10.32
				30.93	2.01	10.30
5d	81	103-104	$C_{12}H_8N_2O_3Cl_2$	48.19	2.70	9.37
		[c]		48.43	2.45	9.21
5e	86	133-134	$C_{13}H_{10}N_2O_3Cl_2$	49.86	3.22	8.95
				49.62	3.52	9.12
5f	85	124-125	$C_{13}H_{10}N_2O_4Cl_2$	47.44	3.06	8.51
				47.21	2.85	8.36

Table 2 (continued)

Compound No.	Yield (%) [a]	mp °C [b]	Molecular Formula	Analysis (%), Calcd./Found C	H	N
5g	78	190-192	$C_{12}H_7N_2O_3Cl_3$	43.21 43.44	2.12 1.97	8.40 8.26
5h	88	138-139	$C_{12}H_7N_2O_3Cl_3$	43.21 43.33	2.12 1.98	8.40 8.16
5i	79	235-236	$C_{12}H_7N_3O_5Cl_2$	41.89 41.79	2.05 2.26	12.21 12.16

[a] Isolated yield of the Method C at room temperature. [b] Recrystallization solvent; water for **5a-5c**; *n*-hexane/chloroform (1:1, v/v) for **5d-5i**. [c] Lit [4] mp 87-89° for **5a**; mp 97-99° for **5d**.

Table 3

Spectral Data of 1-Alkylpyridazin-6-ones **3a-3e**

Compound No.	^{1}H NMR (Solvent)	δ (ppm)	IR (cm^{-1}) (Potassium bromide disk)
	[a]	[b]	
3a	C	3.7 (s, CH_3), 7.7 (s, $1H_3$)	3100, 3000, 2980, 1650, 1600
3b	C	1.3 (t, CH_3), 4.2 (q, CH_2), 7.7 (s, $1H_3$)	3100, 3050, 2950, 1650,1600
3c	C	1.0 (t, CH_3), 1.3-2.4 (m, CH_2), 4.1 (t, CH_2), 7.6 (s, $1H_3$)	3100, 2950, 1680, 1580
3d	C	1.0 (t, CH_3), 1.1-2.3 (m, $2CH_2$), 4.1 (t, CH_2), 7.7 (s, $1H_3$)	3100, 2950, 2850, 1690, 1580
3e	D	1.7-2.4 (m, $2H_{2'}$+$2H_{3'}$), 4.0-4.2 (m, $2H_{1'}$+$2H_{4'}$), 7.3-8.0 (m, Bz-H), 8.2 (s, $1H_3$)	3080, 2960, 2880, 1716,1664, 1280

[a] C = Deuteriochloroform, D = DMSO-d_6; [b] Abbreviations used: Bz = benzoyl, s = siglet, t = triplet, q = quatet, m = multiplet.

Table 4

Spectral Data of Esters **5a-5i**

Compound No.	^{1}H NMR δ (ppm) [a]	IR (cm^{-1}) (Potassium bromide disk)
5a	2.0 (s, CH_3), 6.0 (s, CH_2), 7.8 (s, $1H_3$)	3100, 1750, 1690, 1600,1250
5b	1.1 (t, CH_3), 2.3 (q, CH_2), 6.0 (s, CH_2), 7.8 (s, $1H_3$)	3100, 2950, 1760, 1680, 1600, 1220
5c	4.1 (s, CH_2Cl), 6.1 (s, CH_2), 7.8 (s, $1H_3$)	3100, 3000, 2950, 1750, 1680, 1590, 1190
5d	6.3 (s, CH_2), 7.2-8.2 (m, Bz-5H + $1H_3$)	3010, 3000, 2950, 1720, 1680, 1580, 1260
5e	2.3 (s, CH_3), 6.2 (s, CH_2), 7.1-8.0 (m, Bz-4H +$1H_3$)	3100, 3010, 2900, 1740, 1680, 1610, 1280
5f	3.8 (s, OCH_3), 6.3 (s, CH_2), 6.7-7.8 (m, Bz-4H + $1H_3$)	3100, 3010, 2980, 1740, 1700, 1610, 1260
5g	6.2 (s, CH_2), 7.1-8.0 (m, Bz-4H +$1H_3$)	3100, 3010, 2980, 1760, 1710, 1620, 1240
5h	6.2 (s, CH_2), 7.2-8.2 (m, Bz-4H +$1H_3$)	3100, 3010, 2980, 1750, 1700, 1600, 1280
5i	6.3 (s, CH_2), 7.7-8.2 (m, Bz-4H + $1H_3$)	3160, 3100, 3010, 2980, 1760, 1680, 1580, 1540, 1350, 1280

[a] Solvent = Deuteriochloroform; Abbreviations used: Bz = benzoyl, s = singlet, t = triplet, q = quatet, m = multiplet.

Reaction of **2** with carboxylic acid chlorides under basic conditions did not afford 1-acyl (or benzoyl) pyridazin-6-ones **6** because compound **1** did not react with acyl (or benzoyl) chlorides under our reaction conditions.

Finally, 1-hydroxymethylpyridazin-6-one (**2**) as a new 1-*O*, 3-*N*, 5-*O* retro-ene adduct easily undergoes a fragmentation of the retro-ene type under mild conditions. The retro-ene fragmentation of **2** may be regarded as a heat and/or a base promoted retro-ene type reaction.

Further work including kinetics and synthetic applications of some 1-*O*, 3-*N*, 5-*O* retro-ene adduct including compound **2** are under way in our laboratory. Additional findings in exploring the alkylations leading to dipyridazinylalkanes will be presented elsewhere.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Proton magnetic resonance

spectra were obtained on a Bruker 80 MHz spectrometer with chemical shift values reported in δ units (part per milion) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a LECO Micro Carbon Hydrogen Determinator (CHN-800).

Synthesis of 1-Alkyl-4,5-dichloropyridazin-6-ones **3a-3e**.

Method A.

A mixture of **2** [3a,3b] (5.1 mmoles), alkyl halides (7.7 mmoles), potassium carbonate (15.5 mmoles) and acetonitrile (or acetone) was refluxed for 4-5 hours. After cooling to room temperature and then adding diethyl ether (200 ml), the mixture was poured into cold water (250 ml) with stirring. The resulting precipitate was filtered. The ether layer was separated using a separatory funnel and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the corresponding 1-alkylpyridazin-6-ones **3a-3d**.

Method B.

A mixture of **2** (2 g, 1.1 mmoles), potassium carbonate (1 g, 7.24 mmoles), 4-iodobutyl benzoate [3b] (3.12 g, 1.2 mmoles) and tetrahydrofuran (20 ml) was refluxed for 2 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to an open-bed silica gel column (1.5 x 8 cm). The column was eluted with *n*-hexane/dichloromethane (2:10, v/v). The fractions containing the product (detection using tlc) were combined, and the solvent was evaporated under reduced pressure to give compound **3e**. The crude product was recrystallized from diethyl ether to give pure **3e**.

Synthesis of (4,5-Dichloro-6-oxopyridazin-1-yl)methyl Carboxylates **5a-5i**.

Method C.

A mixture of **2** (7.7 mmoles), carboxylic acid chlorides (7.7 mmoles), potassium carbonate (or pyridine, 7.7 mmoles) and dry acetone (15-20 ml) was stirred for 6-10 hours at room (or reflux) temperature. The reaction mixture was poured into cold water (200 ml) with stirring. The resulting precipitate was filtered, washed with cold water (200 ml x 3) and dried in air to give the corresponding esters **5a-5i**.

Synthesis of 4,5-Dichloropyridazin-6-one (**1**) from Compound **2**.

Method D.

A mixture of **2** (2 g, 1.1 mmoles), potassium carbonate (0.18 g, 1.3 mmoles) and acetonitrile (20 ml) was refluxed for 2 hours. After cooling to room temperature, the mixture was filtered. The solvent was evaporated under reduced pressure to give crude **1** in quantitative yield. The crude product was recrystallized from ethanol/water (1:1, v/v) to give pure product **1**. The product was identical with an authentic sample.

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