Reaction of 1-Chloromethyl-4,5-dichloropyridazin-6-one

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Received May 20, 1998

Reaction of 1-chloromethyl-4,5-dichloropyridazin-6-one with some nucleophiles such as sodium methoxide, sodium azide, 2-mercaptopyrimidine and phenol gave **2, 3, 4, 7, 8** and **10.** 5-Chloro-4-phenoxypyridazin-6-one (**10**) was also synthesized from **8** through **9**.

J. Heterocyclic Chem., **35**, 1257 (1998).

N-Hydroxymethylazinones such as 1-hydroxymethylpyridazin-6-ones and *N*-hydroxymethylsaccharin are novel 1-O, 3-N, 5-O ene-adducts and also occur easily the retro-ene fragmentation by heat and/or base [1]. Thus, 1-hydroxymethyl-4,5-dihalopyridazin-6-ones are not useful starting material for the synthesis of the corresponding 1-alkoxymethyl or aryloxymethyl derivatives.

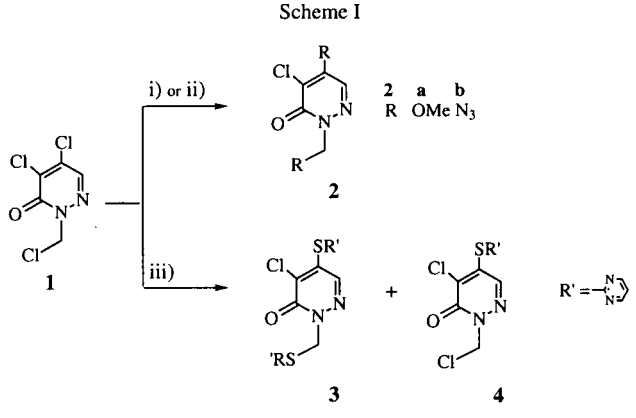
In connection with our research program for the synthesis of novel 1-substituted derivatives and for the functionalization of 4,5-dihalopyridazin-6-ones, we attempted to study the reaction of 1-chloromethyl-4,5-dichloropyridazin-6-one with some nucleophiles. In order to avoid the retro-ene fragmentation during the reaction, we chose 1-chloromethyl-4,5-dichloropyridazin-6-one as the starting materials. Compound **1** was synthesized from 1-hydroxymethyl-4,5-dichloropyridazin-6-one and dimethylchloromethyleneammonium chloride that was prepared from dry dimethylformamide and thionyl chloride [2].

In this paper, we report the results for the reaction of **1** with some nucleophiles.

According to Cho's method [3], methoxylation of **1** with potassium carbonate (2 equivalents) in methanol afforded regioselectively **2a** in good yield. Treatment of **1** with sodium azide (2 equivalents) in methanol also gave only **2b** in excellent yield. The structures of **2a** and **2b** were established by ir, nmr and elemental analyses. The infrared spectrum of **2b** shows the absorption band of the azido group at 2150 cm^{-1}. The ^1H nmr spectra of **2a** and **2b** show the proton signals of the methylene at the N-1 position (δ 5.49 for **2a** and δ 5.41 ppm for **2b**) as a singlet involving one proton at the C-3 position. In the ^1H nmr spectrum of **2a,** the proton signals of two methoxy groups were also detected.

Compound **1** was reacted with 2-mercaptopyrimidine (2 equivalents) and potassium carbonate (2 equivalents) in acetonitrile to yield **3** (36%) and **4** (6%). The ^1H nmr spectra of **3** and **4** show the proton signals of the methylene group at the N-1 position (δ 6.07 for **3**; δ 5.87 ppm for **4**) as a singlet involving one proton at the C-3 position (δ 8.00 for **3**; δ 8.08 ppm for **4**) and the aromatic protons of the pyrimidine ring.

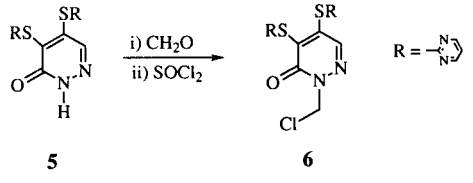
Scheme I



i) K_2CO_3 (2 equivalents), methanol. ii) NaN_3 (2 equivalents), methanol. iii) 2-Mercaptopyrimidine (2 equivalents), K_2CO_3, CH_3CN.

In order to confirm the substitution positions of two pyrimidin-2-ylsulfanyl groups, we synthesized compound **6** from compound **5** [4]. The structure of **6** was established by ir, nmr and elemental analyses. Compound **3** and **6** have the same molecular formula. However, the spectral patterns for the ir, ^1H nmr and ^{13}C nmr for **3** and **6** are different. Therefore, the suggested structure of **3** may be correct.

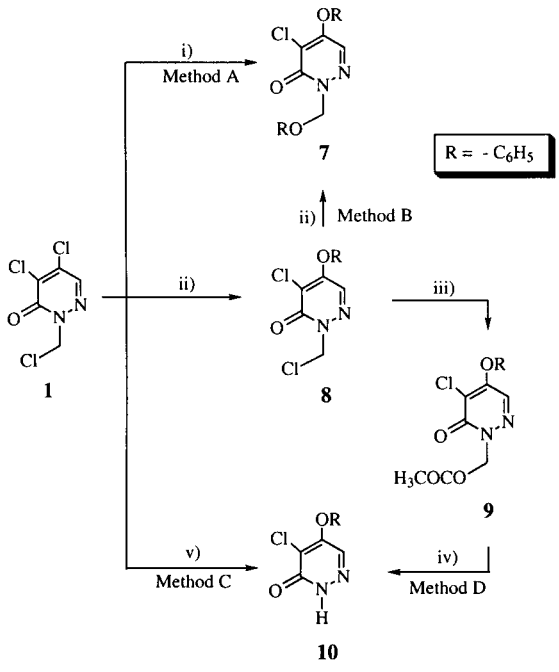
Scheme II



On the other hand, compound **1** was reacted with phenol (2 equivalents) in the presence of potassium carbonate (2 equivalents) in acetonitrile to afford **7** in quantitative yield (Method A), whereas reaction of **1** with one equivalent of phenol and potassium carbonate in acetonitrile gave the 4-phenoxy derivative **8**. Treatment of compound **8** with one equivalent of phenol and potassium carbonate also furnished compound **7** (Method B).

In connection of our research program for the functionalization, we attempted to synthesize compound **9**.

Scheme III



i) Phenol (2 equivalents), K_2CO_3, CH_3CN, reflux.
ii) Phenol (1 equivalent), K_2CO_3, CH_3CN, reflux.
iii) Acetic acid, K_2CO_3, reflux. iv) H_2O, K_2CO_3, reflux.
v) 1) Phenol (1 equivalent), K_2CO_3, CH_3CN. 2) Acetic acid, K_2CO_3, reflux.
3) H_2O, K_2CO_3, reflux.

Reaction of **8** with acetic acid in the presence of potassium carbonate afforded compound **9**. Compound **9** was treated with aqueous potassium carbonate solution and gave only 5-chloro-4-phenoxypyridazin-6-one (**10**) (Method D). Compound **10** was also synthesized from **1** by a one-pot reaction (Method C).

The structures of **7-10** were established by ir, nmr and elemental analyses. The positions of substitution for **2** and **7** were proved by the further reactions of these compounds [5]. The syntheses of **2**, **3** and **7** from **1** occur *via* two steps; *i.e.* i) the substitution of nucleophiles at the C-4 position on the ring occurs in the first step, ii) the displacement of nucleophiles at the methylene group of the N-1 position then progresses to the second step. The mechanism is proved by the synthesis of **7** from **1** through **8**, and also observed by tlc during the reaction. The synthetic mechanisms of **10** from **1** and **9** involve the retro-ene fragmentation at the final step.

Finally, compounds **1** and **9** may be regarded as the starting material for the functionalization of 4,5-dihalopyridazin-6-ones.

Further experiments including the functionalization and other transformation of the products 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 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

Table 1

Yields, Melting Points and Infrared Spectral Data of **1-10**

Compound No.	Isolated Yield (%)	mp (°C) (lit mp)	IR (potassium bromide, cm^{-1})
1	95	70-71 (70-71)[6]	3450, 2955, 2400, 1680, 1600, 1440, 1300, 1240, 1120, 980, 940, 760
2a	84	107-108	3090, 2980, 1660, 1620, 1400, 1320, 1300, 1180, 1100, 920, 770
2b	96	92-93	3060, 2950, 2150, 1640, 1600, 1410, 1330, 1220, 1140
3	36	120-121	3110, 3070, 3025, 2960, 1668, 1560, 1385, 1180, 960, 764
4	6	106-108	3100, 3050, 1680, 1580, 1400, 1180, 980, 760
6	38	147-148	3080, 3010, 2950, 1680, 1570, 1400, 1300, 1190, 980, 942, 820, 780, 760, 720
7	98 [a] 69 [b]	75-77	3100, 3050, 2900, 1680, 1600, 1500, 1400, 1280, 1240, 1050, 1030, 760
8	63	95-96	3100, 3050, 2830, 1680, 1600, 1410, 1320, 1240, 760
9	98	124-125	3100, 3000, 1780, 1760, 1690, 1610, 1510, 1410, 1340, 1300, 1230, 1150
10	64 [c] 62 [d]	178-179 (178-179) [4]	3350, 3230, 3150, 3050, 2960, 2900, 1660, 1600, 1500, 1400, 1280, 1100, 780

[a] Method A. [b] Method B. [c] Method C. [d] Method D.

Table 2

^{1}H Nmr Spectral Data of Compounds **1-10**

Compound No.	Solvent [b]	^{1}H NMR (ppm) [a] $1H_3$	N-CH_2 (s)	Others
1	C	7.88 (s)	5.83	—
2a	C	7.89 (s)	5.49	3.47 (s, OCH_3), 4.11 (s, OCH_3)
2b	C	7.68 (s)	5.41	—
3	C	8.00 (s)	6.07	7.05 (t, Ar, 1H), 7.16 (t, Ar, 1H), 8.57 (d, Ar, 2H, J = 7.2), 8.59 (d, Ar, 2H, J = 6.4)
4	C	8.08 (s)	5.87	7.22 (t, Ar, 1H), 8.62 (d, Ar, 2H, J = 6.8)
6	C	8.12 (s)	5.85	7.06 (t, Ar, 1H), 7.17 (t, Ar, 1H), 8.49 (d, Ar, 2H, J = 4.5), 8.59 (d, Ar, 2H, J = 4.5)
7	C	7.52 (s)	6.05	7.53-6.08 (m, Ar, 10H)
8	C	7.54 (s)	5.85	7.47-7.10 (m, Ar, 5H)
9	C	8.10 (s)	6.04	2.12 (s, CH_3), 7.05 (t, 1H), 7.16 (t, Ar, 2H), 8.49 (d, Ar, 1H, J = 4.8), 8.59 (d, Ar, 1H, J = 4.0)
10	C	7.54 (s)	—	7.26-7.48 (m, Ar, 4H), NH (no detection)

[a] Abbreviations used: Ar = Aromatic, bs = broad singlet, s = singlet, d = doublet, m = multiplet, q = quartet, J = Hz unit. [b] C = Deuteriochloroform.

Table 3

^{13}C NMR Spectral Data of Compounds **2-10**

Compound No.	Solvent [a]	^{13}C nmr (ppm) C=O [b]	N-CH_2	Others
1	C	155.6	58.4	134.9, 137.2, 137.3
2a	C	159.2	81.9	57.8, 57.9, 116.9, 127.1, 155.1
2b	C	157.3	66.4	122.9, 130.8, 140.1
3	C	170.0	52.3	117.4, 118.7, 135.7, 137.9, 138.5, 156.1, 157.5, 158.1, 168.0
4	C	167.9	58.8	119.1, 136.1, 136.9, 137.9, 139.6, 155.6, 158.4
6	C	169.3	59.2	118.5, 119.2, 137.3, 140.0, 143.9, 157.4, 158.1, 158.5, 168.9
7	C	159.3	116.7	120.4, 120.7, 123.2, 126.9, 130.3, 131.0, 131.2, 154.0, 154.3, 157.2
8	C	157.9	58.5	119.9, 126.6, 130.8, 131.4, 153.5, 153.9
9	C	158.5	73.4	20.6, 53.2, 63.0, 119.7, 121.0, 126.2, 130.5, 130.7, 153.7, 169.5
10	C	160.5	—	119.7, 126.2, 130.5, 131.1, 153.8, 154.6

[a] C = Deuteriochloroform. [b] Carbonyl at C-6 position on the pyridazine ring.

Table 4

Elemental Analytical Data of **2-10**

Compound No.	Molecular Formula	Analysis (%) Calcd./Found C	H	N	S
1	$C_5H_3N_2OCl_3$	28.14	1.42	13.12	
		28.32	1.56	3.34	
2a	$C_7H_9O_3N_2Cl$	41.09	4.43	13.69	
		41.34	4.56	13.78	
2b	$C_5H_3ON_8Cl$	26.50	1.33	49.45	
		26.77	1.55	49.76	
3	$C_{13}H_9ON_6S_2Cl$	42.80	2.49	23.04	17.58
		42.90	2.76	23.34	17.87
4	$C_9H_6OSN_4Cl_2$	37.39	2.09	19.38	11.09
		37.45	2.27	19.49	11.32
6	$C_{13}H_9ON_6S_2Cl$	42.80	2.49	23.04	17.58
		42.89	2.53	23.11	17.80
7	$C_{17}H_{13}N_2O_3Cl$	62.11	3.99	8.52	
		62.33	3.97	8.69	
8	$C_{11}H_8N_2O_2Cl_2$	48.73	2.97	10.33	
		48.98	2.88	10.53	

Table 4 (continued)

Compound No	Molecular Formula	Analysis (%) Calcd./Found C	H	N	S
		37.45	2.27	19.49	11.32
9	$C_{13}H_{11}N_2O_4Cl$	52.98	3.76	9.51	
		53.03	3.89	9.66	
10	$C_{10}H_7N_2O_2Cl$	53.95	3.17	12.58	
		53.76	3.12	12.79	

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.

1-Chloromethyl-4,5-dichloropyridazin-6-one (**1**).

A mixture of thionyl chloride (8.58 g, 72 mmoles, d = 1.638), dry dimethylformamide (5.26 g, 72 mmoles, d = 0.94) and dry chloroform (35 ml) was stirred for 10 minutes at room temperature. 1-Hydroxymethyl-4,5-dichloropyridazin-6-one (7.03 g, 36

mmoles) was added to the reaction mixture. The resulting solution was stirred for 20 minutes at room temperature. The mixture was poured into water (150 ml) with stirring. The organic layer was separated and washed with excess water. The solvent was evaporated under reduced pressure. The residue was triturated into water (200 ml). The resulting crystals were filtered and dried in air to give **1** in 95% (7.3 g) yield.

5-Chloro-1-(methoxymethyl)-4-methoxypyridazin-6-one (**2a**).

A mixture of **1a** (2 g, 9.37 mmoles), potassium carbonate (2.59 g, 18 mmoles) and methanol (20 ml) was refluxed for 1 hour. After cooling to room temperature, the mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was recrystallized from methanol/water (1:1, v/v) to give **2a**.

5-Chloro-1-(azidomethyl)-4-azidopyridazin-6-one (**2b**).

A mixture of **1a** (2 g, 9.37 mmoles), sodium azide (1.22 g, 18.74 mmoles) and methanol (15 ml) was refluxed for 2 hours. After evaporating the solvent under reduced pressure, the residue was dissolved in chloroform (40 ml) and filtered. The filtrate was evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:2, v/v) to give **2b**.

5-Chloro-1-(pyrimidin-2-ylsulfanylmethyl)-4-(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**3**) and 5-Chloro-1-(chloromethyl)-4-(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**4**).

A mixture of **1a** (2 g, 9.37 mmoles), potassium carbonate (2.59 g, 18.74 mmoles), 2-mercaptopyrimidine (2.02 g, 18.74 mmoles) and acetonitrile (25 ml) was refluxed for 3 hours. After cooling to room temperature, the mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column. First, the column was eluted with chloroform. The chloroform fractions were combined and evaporated under reduced pressure to give **4** in 6% (0.15 g) yield. The column was then eluted with ethyl acetate/*n*-hexane (1:1, v/v). These fractions were combined and evaporated under reduced pressure to give **3** in 36% (1.16 g) yield.

1-Chloromethyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**6**).

A mixture of **5** [4] (0.6 g, 1.9 mmoles) and formalin solution (20 ml, 35%) was refluxed for 3 hours. After cooling to room temperature, the mixture was poured into ice water (20 ml) with stirring. The product was extracted with ethyl acetate (20 ml x 2). The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated under reduced pressure. The residue was reacted with thionyl chloride (7 ml) for 15 minutes at room temperature. The reaction mixture was poured into chloroform/water (50 ml/150 ml) with stirring. The organic layer was separated and washed with excess water and evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.8 x 4 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The resulting powder was recrystallized from chloroform/*n*-hexane (1:1, v/v) to give **6** in 38% (0.26 g) yield.

5-Chloro-1-phenoxymethyl-4-phenoxypyridazin-6-one (**7**).

Method A.

A mixture of **1a** (3 g, 14.05 mmoles), potassium carbonate (3.88 g, 28.11 mmoles), phenol (2.65 g, 28.11 mmoles) and acetonitrile (15 ml) was refluxed for 3 hours. After evaporating the solvent under reduced pressure, the residue was triturated in water (50 ml). The resulting crystal was filtered, washed with *n*-hexane (30 ml) and dried in air to give **7** in 98% (4.56 g) yield.

Method B.

A solution of **8** (0.74 g, 2.73 mmoles), phenol (0.26 g, 2.73 mmoles), potassium carbonate (0.38 g, 2.79 mmoles) and acetonitrile (20 ml) was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform/water (1:3, v/v; 100 ml) with stirring. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was recrystallized from ether/*n*-hexane (1:2, v/v) to give **7** in 69% (0.62 g) yield.

5-Chloro-1-chloromethyl-4-phenoxypyridazin-6-one (**8**).

A mixture of **1a** (2 g, 9.37 mmoles), potassium carbonate (1.29 g, 9.37 mmoles), phenol (0.88 g, 9.37 mmoles) and acetonitrile (30 ml) was refluxed for 6 hours. After evaporating the solvent under reduced pressure, the residue was triturated in water (60 ml)/chloroform (20 ml) with stirring. The organic layer was separated and evaporated under reduced pressure. The resulting crystal was recrystallized from chloroform/*n*-hexane (1:4, v/v) to give **8** in 63% (1.46 g) yield.

1-(Acetyloxymethyl)-5-chloro-4-phenoxypyridazin-6-one (**9**).

A mixture of **8** (1 g, 3.69 mmoles), potassium carbonate (1.02 g, 7.38 mmoles) and acetic acid (15 ml) was refluxed for 6 hours. After evaporating the solvent under reduced pressure, the residue was triturated in water (70 ml)/chloroform (15 ml) with stirring. The organic layer was separated and evaporated under reduced pressure. The resulting crystal was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give **9** in 60% (0.66 g) yield.

5-Chloro-4-phenoxypyridazin-6-one (**10**).

Method C.

A mixture of **1a** (2 g, 9.37 mmoles), potassium carbonate (1.29 g, 9.37 mmoles), phenol (0.88 g, 9.37 mmoles) and acetonitrile (20 ml) was refluxed for 1 hour. After evaporating the solvent under reduced pressure, acetic acid (10 ml) and potassium carbonate (1.29 g) was added, and the mixture was then refluxed for 1 hour. After cooling to the room temperature, the mixture was neutralized using diluted hydrochloric acid [concentrated-hydrochloric acid (1 ml)/water (20 ml)] with stirring. The resulting crystals were filtered, washed with water (25 ml) and then diethyl ether (20 ml) and dried in air to give **10** in 64% (1.34 g) yield.

Method D.

A mixture of **9** (0.3 g, 1.02 mmoles), potassium carbonate (0.28 g, 2.04 mmoles) and water (5 ml) was refluxed for 20 minutes. After cooling to room temperature, the resulting crystals were filtered and dried in air to give **10** in 62% (0.11 g) yield.

Acknowledgment.

This work was supported by Korean Ministry of Education through Research Fund, 1997 (BSRI-97-3441).

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