Concurrent Alkylation-Methoxylation of 4,5-Dihalopyridazin-6-ones and Synthesis of 5-Halo-4-hydroxypyridazin-6-ones

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Received May 10, 1996

1-Alkyl-5-halo-4-methoxypyridazin-6-ones were synthesized from 1-alkyl-4,5-dihalopyridazin-6-ones by the concurrent alkylation-methoxylation. 1-Alkyl-5-halo-4-hydroxypyridazin-6-ones were also prepared.

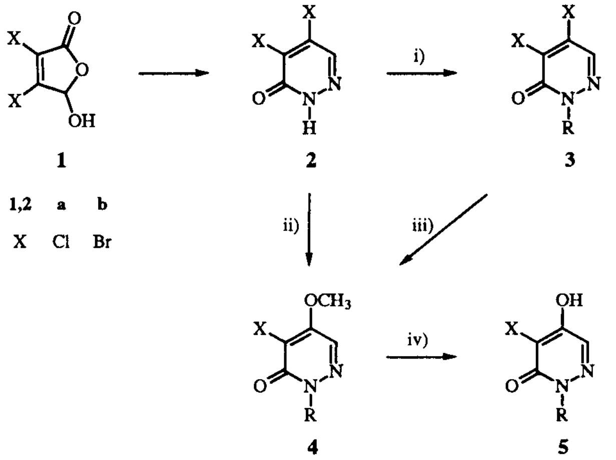
J. Heterocyclic Chem., **33**, 1579 (1996).

In connection with our research program for the multicyclic pyridazine derivatives such as pyridazinooxazine, we attempted to synthesize some 1-alkyl-5-halo-4-hydroxypyridazin-6-ones **5** from the corresponding 4-methoxy derivatives 4.

Dury [1] reported the synthetic methods of 1-substituted-4-(or 5-)hydroxy(or dihydroxy)pyridazin-6-ones from the corresponding 4,5-dichloro- or 4-(or 4,5-)-mono-(or di-)alkoxypyridazin-6-ones by hydroxylation or hydrolysis. Recently, Bryant *et al.* [2] also reported the methoxylation of 4,5-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)pyridazin-6-one in potassium hydroxide-methanol mixture.

On the other hand, Yoon, *et al.* [3] and Askura, *et al.* [4] reported *O*-debenzoylation and/or methoxylation of some tribenzoylated nucleosides in potassium cyanide-methanol system. Dury [1] also reported the synthesis of the corresponding 4,5-diphenoxy derivatives from 1-alkyl-4,5-dichloropyridazin-6-ones and potassium carbonate in phenol. However, we observed several spots on the tlc plate when 1-alkyl-4,5-dihalopyridazin-6-ones **3** were reacted with potassium hydroxide or potassium cyanide in methanol at reflux temperature. Therefore, we investigated a simple synthetic method of 1-alkyl-5-halo-4-methoxypyridazin-6-ones **4** as a useful starting material for the synthesis of **5** from 4,5-dihalopyridazin-6-ones **2** by a one-pot reaction.

Scheme I



1,2	a	b
X	Cl	Br

i) R-X', K_2CO_3, DMF, 60-70°; ii) R -X', K_2CO_3, MeOH, reflux (Method A); iii) MeOH, MeONa (Method B); iv) KOH/H_2O, conc-HCl, reflux
R-X' = MeI, EtBr, *n*-PrBr, *i*-PrBr, CH_2=$CHCH_2Br$, *n*-BuBr, $ClCH_2COCH_3$

3,4,5	a	b	c	d	e	f	g	h	i	j	k	l	m	n
X	Cl	Cl	Cl	Cl	Cl	Cl	Cl	Br	Br	Br	Br	Br	Br	Br
R	Me	Et	Pr	*i*-Pr	Allyl	Bu	2-Oxo-propyl	Me	Et	Pr	*i*-Pr	Allyl	Bu	2-Oxo-propyl

In this paper, we wish to report the concurrent alkylation-methoxylation of 4,5-dihalopyridazin-6-ones **2** and the synthesis of 1-alkyl-5-halo-4-hydroxypyridazin-6-ones **5**.

First, we observed several spots on the tlc plate when the mixture of **2**, alkyl halides and potassium cyanide (or potassium hydroxide) in methanol was refluxed. For that reason, we used potassium carbonate instead of potassium cyanide or potassium hydroxide though potassium carbonate is a weaker base.

Reactions of compound **2** with alkyl halides and potassium carbonate (2 equivalents) in methanol yielded only compound **4** in 86-90% yield (Method A). However, we detected other products such as 4,5-dimethoxypyridazin-6-one or **3** when potassium carbonate used over or below 2 equivalents, respectively.

In addition, we attempted to synthesize compound **4** from compound **3** according to Lyga's method [5]. Compound **3** was synthesized according to the usual way. Reaction of 4,5-dihalopyridazin-6-ones **2** with alkyl halides such as iodomethane, bromoethane, 1-bromopropane, 2-bromopropane, 1-chloro-2-oxopropane, allyl bromide and 1-bromobutane in the presence of potassium carbonate in dimethylformamide gave the corresponding 1-alkyl-4,5-dihalopyridazin-6-ones **3** in excellent yield. The structures of compound **3** were established by infrared and ^{1}H nmr spectra.

Treatment of compound **3** with sodium methoxide in methanol afforded only 4-methoxypyridazin-6-ones **4** in 91-92% yield (Method B). These compounds were identical with **4** that was prepared by the Method A.

The infrared spectra of **4** showed the absorption peaks of carbonyl and C-O bonds. The proton magnetic resonance spectra of **4** also showed the signals of methoxy and aromatic protons involving other aliphatic or allyl protons.

Table 1

Melting Points and Spectral Data of 1-Alkyl-4,5-dihalopyridazin-6-ones **3**

Compound No.	mp (°C)	IR (KBr, cm^{-1})	^{1}H NMR (ppm) [f]
3a	87-88 [a]	3100, 3000, 2980, 1650, 1600	3.70 (s, 3H), 7.70 (s, Ar, 1H)
3b	49-50 [b]	3100, 3000, 2900, 1670, 1590	1.39 (t, 3H), 4.20 (q, 2H), 7.80 (s, Ar, 1H)
3c	liquid	3100, 2950, 1680, 1580	1.00 (t, 3H), 1.85 (m, 2H), 4.10 (t, 2H), 7.60 (s, Ar, 1H)
3d	68-69 [c]	3100, 2950, 2850, 1690, 1580	1.30 (d, 3H, J = 6), 1.40 (d, 3H, J = 6), 5.25 (m, 1H), 7.80 (s, Ar, 1H)
3e	44-46	3100, 3060, 2910, 1670, 1600	4.75 (m, 2H), 5.20 (m, 2H), 5.55 (m, H), 7.80 (s, Ar, 1H)
3f	liquid [d]	3100, 3050, 2900, 1690, 1590	0.93 (t, 3H), 1.78 (m, 2H), 4.17 (t, 2H), 7.8 (s, Ar, 1H)
3g	136-137 [e]	3000, 2944, 1730, 1674	2.18 (s, 3H), 4.90 (s, 2H), 7.88 (s, Ar, 1H)
3h	118-119	3010, 3002, 2980, 1660, 1580	3.68 (s, 3H), 8.12 (s, Ar, 1H)
3i	47-48	3080, 2990, 1670, 1560, 1440, 1330	1.28 (t, 3H), 4.11 (q, 2H), 8.15 (s, Ar, 1H)
3j	58-59	3060, 2940, 1650, 1570, 1405, 1250	0.96 (t, 3H), 1.82 (m, 2H), 4.14 (t, 2H), 7.80 (s, Ar, 1H)
3k	85-86	3100, 2950, 1692, 1584	1.28 (d, 3H, J = 6), 1.30 (d, 3H, J = 6), 5.07 (m, 1H), 8.20 (s, Ar, 1H)
3l	66-67	3100, 3060, 2910, 1670, 1600	4.75 (m, 2H), 5.20 (m, 2H), 5.55 (m, 1H), 8.17 (s, Ar, 1H)
3m	liquid	3100, 2995, 2980, 1670, 1580, 1440,	0.95 (t, 3H), 1.39 (m, 2H) 1.78 (m, 2H), 4.17 (t, 2H) 7.80 (s, Ar, 1H)
3n	167-168	3100, 3060, 2990, 1750, 1660, 1580,	2.22 (s, 3H), 4.12 (s, 2H), 8.05 (s, Ar, 1H)

[a] Lit mp 134-144° [1], 89-90° [7]. [b] Lit [1,7] mp 49-51°. [c] Lit [1,7] mp 69-70°. [d] Lit [1] mp Liquid. [e] Lit [8] mp 136-137°. [f] Solvent = DMSO-d_6. Coupling constant (J) in Hertz. Abbreviations used: s = singlet, bs = broad singlet, t = triplet, m = multplet, q = quartet, Ar = aromatic.

Compound **4** was hydrolyzed with aqueous potassium hydroxide to form 4-hydroxypyridazin-6-ones **5** in 87-90% yield.

The infrared spectra of compound **5** showed the absorption bands of OH and carbonyl groups. The ^{1}H nmr spectra of **5** showed the signals of the aromatic proton (δ 7.63-8.15 ppm) and hydroxy proton (δ 11.26-11.84 ppm) involving other aliphatic or allyl protons. The molecular formulas of compound **5** were established by the elemental analysis.

Our concurrent alkylaton-methoxylaton is very convenient and regioselective method for the synthesis 1-alkyl-5-halo-4-methoxypyridazin-6-ones **4** from 4,5-dihalopyridazin-6-ones **2** directly.

Table 2

Melting Points and Spectral Data of 1-Alkyl-5-halo-4-methoxypyridazin-6-ones **4**

Compound No.	mp (°C)	IR (KBr, cm^{-1})	^{1}H NMR (ppm) [b]
4a	154-155	3105, 3080, 2995, 1660, 1610, 1400, 1360, 1305, 1200, 1120	3.72 (s, 3H), 4.08 (s, 3H), 8.15 (s, Ar, 1H)
4b	99-100	3100, 3050, 3000, 2970, 1650, 1600 1405, 1350, 1130	1.40 (t, 3H), 4.10 (s, 3H), 4.20 (q, 2H), 7.80 (s, Ar, 1H)
4c	50-51	3010, 2995, 2800, 1660, 1620, 1480, 1320, 1190, 1120	0.86 (t, 3H), 1.71 (m, 2H), 4.05 (t, 2H), 4.08 (s, 3H), 8.25 (s, Ar, 1H)
4d	109-110	3100, 3050, 3000, 2992, 1660, 1605, 1440, 1380, 1280, 1220, 1180, 1105	1.28 (d, 6H, J = 6), 4.08 (s, 3H), 5.14 (m, 1H) 8.31 (s, Ar, 1H)
4e	68-69	3100, 2995, 1660 1620, 1480, 1420, 1360, 1295, 1190 1120	4.08 (s, 3H), 4.70 (d, 2H, J = 5), 5.17 (m, 2H), 5.80 (m, 1H), 8.27 (s, Ar, 1H)
4f	54-55 [a]	3050, 2950, 1650, 1605, 1470, 1405, 1320, 1205, 1175, 1105	0.88 (t, 3H), 1.27 (m, 2H), 1.65 (m, 2H), 4.07 (s, 3H), 4.09 (t, 2H), 8.24 (s, Ar, 1H)
4g	131-132	3004, 2960, 1726, 1663, 1610, 1470, 1360, 1170	2.18 (s, 3H), 4.10 (s, 3H), 5.00 (s, 2H), 8.24 (s, Ar, 1H)
4h	159-160	3040, 2990, 1640, 1600, 1390, 1320, 1285, 1200, 1190, 1090	3.70 (s, 3H), 4.08 (s, 3H), 8.12 (s, Ar, 1H)
4i	127-128	3012, 2970, 1640, 1600, 1394, 1320, 1288, 1100	1.28 (t, 3H), 4.02 (s, 3H), 4.10 (q, 2H), 8.04 (s, Ar, 1H)
4j	75-76	3010, 3050, 2990, 1640, 1600, 1460, 1405, 1310, 1280, 1200, 1180, 1090	0.93 (t, 3H), 1.71 (m, 2H), 4.07 (m, 5H), 8.15 (s, Ar, 1H)
4k	123-124	3012, 2998, 2972, 1656, 1390, 1322, 1288, 1100	1.29 (d, 3H, J = 6), 1.39 (d, 3H, J = 6), 4.07 (s, 3H), 5.39 (m, 1H), 7.80 (s, Ar, 1H)
4l	68-69	3120, 3080, 3010, 2960, 1650, 1610, 1420, 1330, 1300, 1220, 1190, 1100	4.06 (s, 3H), 4.60-6.33 (m, Allyl-5H), 7.70 (s, Ar, 1H)
4m	52-53	3100, 3080, 2990, 1670, 1600, 1470, 1420, 1320, 1290, 1100	0.95 (t, 3H), 1.38 (m, 2H), 1.78 (m, 2H), 4.05 (s, 3H), 4.20 (t, 2H), 7.70 (s, Ar, 1H)
4n	138-139	3110, 3090, 2995, 1740, 1645, 1600, 1390, 1340, 1320, 1280, 1210, 1170, 1080	2.23 (s, 3H), 4.12 (s, 3H), 5.01 (s, 2H), 8.05 (s, Ar, 1H)

[a] Lit [9] mp liquid. [b] Solvent = DMSO-d_6. Coupling constant (J) in Hertz. Abbreviations used: s = singlet, bs = broad singlet, t = triplet, m = multplet, q = quartet, Ar = aromatic.

Table 3

Melting Points and Spectral Data of 1-Alkyl-5-halo-4-hydroxy pyridazin-6-ones 5

Compound No.	mp (°C)	IR (KBr, cm^{-1}) [a]	^{1}H NMR (ppm) [b]
5a	260-261	3320 (br), 1660, 1598, 1470, 1320, 1140, 1022	3.60 (s, 3H), 7.71 (s, Ar, 1H), 11.60 (bs, OH)
5b	233-235	3090 (br), 1645, 1605, 1400, 1380, 1195, 1083	1.33 (t, 3H), 4.15 (q, 2H), 7.75 (s, Ar, 1H), 11.38 (bs, OH)
5c	201-203	3140 (br), 1650, 1602, 1592, 1405, 1380, 1280, 1205, 1096	0.93 (t, 3H), 1.80 (m, 2H), 4.09 (q, 2H), 7.74 (s, Ar, 1H), 11.26 (bs, OH)
5d	248-250	3100 (br), 1660, 1605, 1580, 1400, 1380, 1280, 1203, 1085	1.30 (s, 3H), 1.32 (s, 3H), 5.21 (m, 1H), 7.77 (s, Ar, 1H), 11.30 (bs, OH)
5e	176-177	3100 (br), 1640, 1590, 1400, 1380, 1280, 1200, 1100	4.71-6.03 (m, Allyl 5H), 7.77 (s, Ar, 1H), 11.50 (bs, OH)
5f	169-170	3320 (br), 1634, 1375, 1276, 1184, 1071	0.86 (t, 3H), 1.25 (q, 2H), 1.63 (m, 2H), 4.01 (t, 2H), 7.76 (s, Ar, 1H), 11.40 (bs, OH)
5g	215-216	3100 (br), 1740, 1650, 1580, 1395, 1290, 1180, 1085	2.21 (s, 3H), 4.92 (s, 2H), 7.90 (s, Ar, 1H), 11.82 (bs, OH)
5h	285-286	3210 (br), 1640, 1590, 1390, 1280, 1195, 1070	3.69 (s, 3H), 7.67 (s, Ar, 1H), 11.88 (bs, OH)
5i	224-225	3300 (br), 1658, 1566, 1490, 1322, 1240, 1146, 1042	1.23 (t, 3H), 4.08 (q, 2H), 7.63 (s, Ar, 1H), 11.60 (bs, OH)
5j	199-200	3300 (br), 1650, 1600, 1460, 1358, 1200, 1092	0.98 (t, 3H), 1.73 (m, 2H), 4.08 (t, 2H), 8.15 (s, Ar, 1H), 11.50 (bs, OH)
5k	250-251	3350 (br), 1644, 1600, 1342, 1278, 1196, 1080	1.20 (s, 3H), 1.31 (s, 3H), 5.11 (m, 1H), 7.77 (s, Ar, 1H), 11.70 (bs, OH)
5l	176-177	3300 (br), 1640, 1600, 1396, 1272, 1180, 1070	4.66-6.23 (m, Allyl 5H), 7.77 (s, Ar, 1H), 11.80 (bs, OH)
5m	177-178	3320 (br), 1640, 1600, 1580, 1400, 1380, 1350, 1280, 1200, 1085	0.93 (t, 3H), 1.33 (m, 2H), 1.73 (m, 2H), 4.12 (q, 2H), 7.68 (s, Ar, 1H), 11.53 (bs, OH)
5n	190-191	3310 (br), 1750, 1680, 1580, 1400, 1360, 1300, 1230, 1200, 1100	2.21 (s, 3H), 4.92 (s, 2H), 7.87 (s, Ar, 1H), 11.84 (bs, OH)

[a] br = broad. [b] Solvent = DMSO-d_6. Abbreviations used: s = singlet, bs = broad singlet, t = triplet, m = multplet, q = quartet, Ar = aromatic. The proton signals of all OH were exchangeable with deuterium oxide.

Further work including the synthesis of pyridazinooxazines and other reactions are under way in our laboratory.

Table 4

Elemental Analysis of 1-Alkyl-5-halo-4-hydroxypyridazin-6-ones 5

Compound No.	Molecular Formula	Calcd./Found (%)		
		C	H	N
5a	$C_5H_5N_2O_2Cl$	37.40	3.14	17.45
		37.60	3.28	17.15
5b	$C_6H_7N_2O_2Cl$	41.28	4.04	16.05
		41.32	4.15	16.00
5c	$C_7H_9N_2O_2Cl$	44.58	4.81	14.85
		44.62	4.92	14.60
5d	$C_7H_9N_2O_2Cl$	44.58	4.81	14.85
		44.53	4.79	14.84
5e	$C_7H_7N_2O_2Cl$	45.06	3.78	15.01
		45.34	3.89	14.95
5f	$C_8H_{11}N_2O_2Cl$	47.42	5.47	13.82
		47.54	5.67	13.76
5g	$C_7H_7N_2O_3Cl$	41.50	3.48	13.83
		41.80	3.68	13.70
5h	$C_5H_5N_2O_2Br$	29.29	2.46	13.66
		29.31	2.58	13.59
5i	$C_6H_7N_2O_2Br$	32.90	3.22	12.79
		32.89	3.24	12.82
5j	$C_7H_9N_2O_2Br$	36.07	3.89	12.02
		36.23	3.93	12.13
5k	$C_7H_9N_2O_2Br$	36.07	3.89	12.02
		36.21	3.95	12.24
5l	$C_7H_7N_2O_2Br$	36.39	3.05	12.12
		36.54	3.25	12.01
5m	$C_8H_{11}N_2O_2Br$	38.89	4.49	11.34
		39.01	4.87	11.23
5n	$C_7H_7N_2O_3Br$	34.03	2.86	11.34
		34.32	2.92	11.11

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 LECO Micro Carbon Hydrogen Determinator (CHN-800). 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.

Synthesis of 1-Alkyl-4,5-dihalopyridazin-6-ones 3.

A mixture of 4,5-dihalopyridazin-6-one [6] (**2**, 18.2 mmoles), alkyl halide (18.4 mmoles) and anhydrous potassium carbonate (2.54 g, 18.4 mmoles) in dimethylformamide (30 ml) was stirred for 2 hours at 50-60°. After cooling to room temperature, the reaction mixture was poured into the solution of chloroform (100 ml) and water (500 ml) with stirring. The organic phase was then separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform. Fractions containing the product were combined. The solvent was evaporated under reduced pressure to give the 1-alkyl-4,5-dihalopyridazin-6-ones **3** in 87-94% yield.

Synthesis of 1-Alkyl-5-halo-4-methoxypyridazin-6-ones **4**.

Method A.

A mixture of 4,5-dihalopyridazin-6-one (**2**, 18.2 mmoles), alkyl halide (18.4 mmoles), anhydrous potassium carbonate (36.8 mmoles) in methanol (80 ml) was refluxed for 8 hours. After cooling to room temperature, the reaction mixture was filtered. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform. Fractions containing the product were combined. The solvent was evaporated under reduced pressure to give 1-alkyl-5-halo-4-methoxypyridazin-6-ones **4** in 86-90% yield.

Method B.

A mixture of 1-alkyl-4,5-dihalopyridazin-6-one (**3**, 12 mmoles), sodium methoxide (14.4 mmoles) in dry methanol (80 ml) was stirred for 12 hours at room temperature. After cooling to room temperature, the reaction mixture was filtered. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform. Fractions containing the product were combined. The solvent was evaporated under reduced pressure to give compound **4** in 91-92% yield.

Synthesis of 1-Alkyl-5-halo-4-hydroxypyridazin-6-ones **5**.

A mixture of 1-alkyl-5-halo-4-methoxypyridazin-6-one (**4**, 10 mmoles), potassium hydroxide (11 mmoles) in water (70 ml) was refluxed for 3 hours. After cooling to room temperature, concentrated hydrochloric acid (10 ml) was added to the mixture with stirring. The product was filtered, washed with water (100 ml) and dried in air to give compound **5** in 87-90% yield.

Acknowledgments.

This study is supported by the Korean Ministry and Education through Research Fund (BSRI-96-3441).

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