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Received March 4, 1998

Some 1-alkyl-4-(4-amino-2,6-dichlorophenoxy)-5-halopyridazin-6-ones were synthesized chemoselectively from 1-alkyl-4,5-dihalopyridazin-6-ones and 4-amino-2,6-dichlorophenol *via* a fluoride ion-assisted reaction.

J. Heterocyclic Chem., **35**, 1401 (1998).

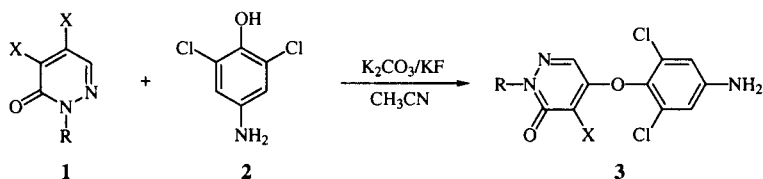
In connection with our research program for the synthesis of aryl heteroaryl ether containing diazines, we needed to synthesize some 1-alkyl-4-(4-amino-2,6-dichlorophenoxy)-5-halopyridazin-6-ones. Phenyl pyridazinyl ether can be synthesized through the corresponding phenoxides. However, we found two products when 1-alkyl-4,5-dihalopyridazin-6-ones were allowed to react with 4-amino-2,6-dichlorophenol in the presence of potassium carbonate in acetonitrile. However, we were particularly interested in the chemoselective synthesis of **3** from **1** and **2** *via* one step under mild

conditions. Therefore, we attempted to investigate the title reaction.

According to Emsley *et al.* [1], the esterification of carboxylic acids with alkyl halides is promoted by potassium fluoride. The syntheses of alkyl aryl ethers [2] and phenyl pyridazinyl ethers [3] from phenols *via* fluoride ion assisted reaction also was reported.

In the previous paper [4], we reported the synthesis of 4-(4-amino-2,6-dichlorophenoxy)-5-halo-1-(2-oxopropyl)pyridazin-6-ones using potassium fluoride/potassium carbonate.

Scheme 1



1,3	a	b	c	d	e	f	g	h
X	Cl	Cl	Cl	Cl	Cl	Cl	Br	Br
R	Me	Et	<i>n</i> -Pr	<i>i</i> -Pr	<i>n</i> -Bu	-CH ₂ COOCH ₃	Et	-CH ₂ COOCH ₃

Table 1
Yields, Melting Points and Infrared Spectral Data of Compounds **3**

Compound No.	Isolated Yield (%)	mp (°C)	ir (potassium bromide, cm ⁻¹)
3a	61	286-287	3500, 3350, 3200, 1650, 1610, 1480, 1400, 1240
3b	69	161-162	3500, 3350, 3000, 1660, 1620, 1490, 1410, 1240, 1100, 840, 820
3c	90	192-193	3500, 3350, 3200, 1660, 1600, 1480, 1330, 1230, 1100, 860
3d	73	145-146	3500, 3350, 3250, 3000, 1650, 1600, 1480, 1380, 1260, 1230, 840, 820
3e	78	170-171	3470, 3330, 2950, 1640, 1480, 1220, 1090
3f	72	244-245	3500, 3390, 3270, 3040, 2990, 1760, 1670, 1610, 1490, 1390, 1330, 1240, 1160, 820
3g	86	188-189	3500, 3350, 3230, 3000, 1650, 1620, 1480, 1400, 1270, 1240, 820
3h	86	232-233	3510, 3400, 3270, 3000, 1760, 1680, 1620, 1500, 1400, 1330, 1250, 830

Table 2
¹H Nmr Spectral Data of Compounds **3**

Compound No.	Solvent [b]	¹ H nmr (ppm) [a]				Others
		1H ₃ (s)	Ar 2H (s)	NH ₂ (bs)		
3a	D	7.57	6.73	5.86	3.86 (s, CH ₃)	
3b	D	7.60	6.73	5.86	1.25 (t, CH ₃), 4.12 (q, CH ₂)	
3c	D	7.60	6.73	5.86	0.85 (t, CH ₃), 1.70 (m, CH ₂), 4.06 (t, CH ₂)	
3d	D	7.62	6.72	5.85	1.26 (d, 2CH ₃ , J = 6.6), 5.12 (m, CH)	
3e	D	7.60	6.73	5.86	0.88 (t, CH ₃), 1.26 (m, CH ₂), 1.67 (m, CH ₂), 4.09 (t, CH ₂)	
3f	D	7.69	6.74	5.87	3.69 (s, OMe), 4.95 (s, CH ₂)	
3g	D	7.48	6.73	5.86	1.25 (t, CH ₃), 4.12 (q, CH ₂)	
3h	D	7.57	6.75	5.87	3.65 (s, OMe), 4.95 (s, CH ₂)	

[a] Abbreviations used: Ar = Aromatic, bs = broad singlet, s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, J = Hz unit. The proton signals of all NH were exchangeable with deuterium oxide. [b] D = dimethyl-d₆ sulfoxide.

In this paper, we would like to report the chemoselective synthesis of some *N*-alkylpyridazinyl 4-amino-2,6-dichlorophenyl ethers.

Reaction of **1** with **2** in the presence of potassium carbonate/potassium fluoride yielded chemoselectively **3** in good yield. However, we detected two products in the case of 4-aminophenol.

The structures of **3** were established by ir, ¹H nmr and elemental analyses. The infrared spectra of **3** show the absorption peaks of the amino group, whereas the absorption peaks of hydroxy group were not detected. The nuclear magnetic resonance spectra of **3** show the proton signals of NH₂ (δ 5.85-5.87), one aromatic proton on the pyridazine ring (δ 7.48-7.69) and two aromatic protons on the benzene ring (δ 6.72-6.75) involving the alkyl protons at N-1 position. The position of substitution on the pyridazine was proved by further reactions [5].

Table 3
 Elemental Analytical Data of **3**

Compound No.	Molecular Formula	Analysis (%)		
		C	H	N
3a	C ₁₁ H ₈ O ₂ N ₃ Cl ₃	41.22	2.52	13.11
		41.34	2.56	13.44
3b	C ₁₂ H ₁₀ O ₂ N ₃ Cl ₃	43.08	3.01	12.56
		43.21	3.36	12.84
3c	C ₁₃ H ₁₂ O ₂ N ₃ Cl ₃	44.79	3.47	12.05
		44.80	3.66	12.33
3d	C ₁₃ H ₁₂ O ₂ N ₃ Cl ₃	44.79	3.47	12.05
		44.83	3.57	12.35
3e	C ₁₄ H ₁₄ O ₂ N ₃ Cl ₃	46.37	3.89	11.59
		46.56	3.97	11.78
3f	C ₁₃ H ₁₀ O ₄ N ₃ Cl ₃	41.24	2.66	11.10
		41.35	2.98	11.22
3g	C ₁₂ H ₁₀ N ₃ O ₂ Cl ₂ Br	38.03	2.69	11.09
		38.33	2.89	11.32
3h	C ₁₃ H ₁₀ N ₃ O ₄ Cl ₂ Br	36.91	2.38	9.93
		37.02	2.74	10.10

The chemoselectivity of 4-amino-2,6-dichlorophenol (**2**) under our reaction conditions may be due to the high acidity of the hydroxy group and the hydrogen bond between the fluoride ion and the hydrogen atom of phenol [1].

Extension of this methodology to other haloheterocycles is now in progress.

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 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-Alkyl-4,5-dihalopyridazin-6-ones **1** were prepared by Cho's method [6].

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-methylpyridazin-6-one (**3a**).

A mixture of **1a** (3 g, 16.85 mmoles), **2** (2.98 g, 16.85 mmoles), potassium fluoride (2.5 g, 43 mmoles), potassium carbonate (3.2 g, 23 mmoles) and acetonitrile (50 ml) was refluxed for 2 hours. The solvent was evaporated under reduced pressure. The residue was poured into water (150 ml) with stirring and then filtered. The resulting solid was washed with dichloromethane (50 ml) and treated with charcoal in acetone. The solvent was evaporated under reduced pressure and dried in air to give **3a** in 61% (3.27 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-ethylpyridazin-6-one (**3b**).

A mixture of **1b** (2.5 g, 12.95 mmoles), **2** (2.31 g, 13 mmoles), potassium fluoride (2 g, 34.43 mmoles), potassium carbonate

(2 g, 14.47 mmoles) and acetonitrile (60 ml) was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was poured into water (50 ml) with stirring and then filtered. The resulting solid was washed with water (200 ml) and treated with charcoal in acetone. The solvent was evaporated under reduced pressure and recrystallized from diethyl ether/*n*-hexane (1:1, v/v) to give **3b** in 69% (2.98 g) yield.

4-(4-amino-2,6-dichlorophenoxy)-5-chloro-1-propylpyridazin-6-one (**3c**).

A mixture of **1c** (2.5 g, 12.1 mmoles), **2** (2.15 g, 12.1 mmoles), potassium fluoride (2 g, 34.43 mmoles), potassium carbonate (2 g, 14.47 mmoles) and acetonitrile (60 ml) was refluxed for 8 hours. After cooling, the mixture was filtered and washed with acetonitrile (50 ml). The combined filtrate was evaporated under reduced pressure. The residue was washed with water (200 ml) and 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 and evaporated under reduced pressure to give **3c** in 90% (4.2 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-isopropylpyridazin-6-one (**3d**).

A mixture of **1d** (1.8 g, 8.7 mmoles), **2** (1.55 g, 8.7 mmoles), potassium fluoride (2 g, 34.43 mmoles), potassium carbonate (2 g, 14.47 mmoles) and acetonitrile (50 ml) was refluxed for 4 hours. The solvent was evaporated under reduced pressure. The residue was poured into water (50 ml) with stirring and then filtered. The resulting solid was washed with water (200 ml) and treated with charcoal in acetone. The solvent was evaporated under reduced pressure to give **3d** in 73% (2.2 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-butylpyridazin-6-one (**3e**).

A mixture of **1e** (1.52 g, 6.88 mmoles), **2** (1.2 g, 6.88 mmoles), potassium fluoride (2 g, 34.43 mmoles), potassium carbonate (2 g, 14.47 mmoles) and acetonitrile (50 ml) was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was poured into water (50 ml) with stirring and was then filtered. The resulting solid was washed with water (200 ml) and treated with charcoal in chloroform. The solvent was evaporated under reduced pressure and recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to give **3e** in 78% (1.9 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-chloro-1-(methoxycarbonylmethyl)pyridazin-6-one (**3f**).

A mixture of **1f** (5 g, 21.1 mmoles), **2** (3.94 g, 22.13 mmoles), potassium fluoride (4 g, 68.86 mmoles), potassium carbonate (4 g, 28.94 mmoles) and acetonitrile (50 ml) was refluxed for 6 hours. The solvent was evaporated under reduced pressure. The residue was poured into water (100 ml) with stirring, filtered and

washed with water (100 ml x 2). The crystal was treated with charcoal in acetone. The solvent was evaporated under reduced pressure to give **3f** in 72% (6.0 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-bromo-1-ethylpyridazin-6-one (**3g**).

A mixture of **1g** (4.75 g, 16.85 mmoles), **2** (3 g, 16.85 mmoles), potassium fluoride (3 g, 51.64 mmoles), potassium carbonate (3 g, 21.71 mmoles) and acetonitrile (50 ml) was refluxed for 8 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in acetone (50 ml) and filtered. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 5 cm). The column was eluted with *n*-hexane/dichloromethane (1:9, v/v). Fractions containing the product were combined. The solvent was evaporated under reduced pressure. The residue was triturated in *n*-hexane (50 ml), and the solvent was then evaporated under reduced pressure. The crystal was recrystallized from diethyl ether/*n*-hexane (1:1, v/v) to give **3g** in 86% (5.49 g) yield.

4-(4-Amino-2,6-dichlorophenoxy)-5-bromo-1-(methoxycarbonylmethyl)pyridazin-6-one (**3h**).

A mixture of **1h** (5.49 g, 16.85 mmoles), **2** (3 g, 16.85 mmoles), potassium fluoride (3 g, 51.64 mmoles), potassium carbonate (3 g, 21.71 mmoles) and acetonitrile (100 ml) was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3.5 x 5 cm). The column was eluted with acetonitrile. Fractions containing the product were combined. The solvent was evaporated under reduced pressure and washed with diethyl ether (50 ml) to afford **3h** in 86% (3.26 g) yield.

Acknowledgment.

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

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