Synthesis of 4,5-Dichloro-1-(4,5-dichloropyridazin-3-yl)pyridazin-6-one

Deok-Heon Kweon, Young-Jin Kang, Hyun-A Chung, Jung-Won Park,
Woo Song Lee and Yong-Jin Yoon*

Department of Chemistry and Research Institute of Natural Sciences,
Gyeongsang National University, Chinju 660-701, Korea

Sung-Kyu Kim

Department of Science Education, Chinju National University of Education, Chinju 660-756, Korea

Motoo Shiro

Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196, Japan

Received June 7, 1999

This paper presents the synthesis of 4,5-dichloro-1-(4,5-dichloropyridazin-3-yl)pyridazin-6-one from 4,5-dichloropyridazin-6-one.

J. Heterocyclic Chem., **36**, 1301 (1999).

Multichloropyridazines are very useful in the pyridazine research field. The preparation of multichloropyridazines from the corresponding pyridazinones using phosphorus oxychloride and/or phosphorus pentachloride has been reported [1]. In connection with our research program for the study on the synthesis of novel pyridazine derivatives, we attempted a multichloropyridazinylpyridazin-6-one from 4,5-dichloropyridazin-6-one. Coad, *et al.* [2] reported the formation of 3-chloro-1-(6-chloropyridazin-3-yl)pyridazin-6-one as a by-product during the chlorination of pyridazine-3,6-dione with phosphorus oxychloride.

Therefore, we investigated the synthesis of multichloropyridazinylpyridazin-6-one from 4,5-dichloropyridazin-6-one using phosphorus oxychloride or phosphorus pentachloride.

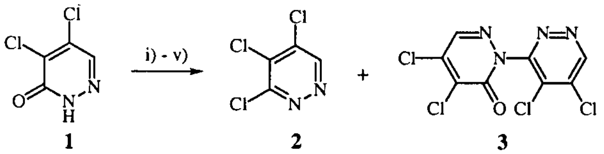
In this paper we wish to report the reaction of **1** with phosphorus oxychloride or phosphorus pentachloride and the establishment of the structure for **3**.

Reaction of **1** with excess phosphorus oxychloride under reflux condition gave only **2** in 67% yield (Method A). However, the chlorination of **1** with phosphorus pentachloride under reflux condition yielded **2** (36%) and **3** (46%) (Method C).

On the other hand, reaction of **1** with phosphorus oxychloride in dry toluene at reflux temperature gave only **2** in 67% yield (Method B). Chlorination of **1** with phosphorus pentachloride in acetonitirle at reflux temperature also yielded only **2** in 51% yield (Method E). Whereas, reaction of **1** with phosphorus pentachloride in dry toluene at reflux temperature afforded only **3** in 81% yield (Method D). According to our results, the chlorination of **1** with phosphorus pentachloride is remarkably influenced by the solvents.

In order to establish the structure of **3**, we attempted the dehalogenation of **3**. Compound **3** was dehalogenated with Pd/C and hydrogen in the presence of aqueous sodium hydroxide (10%) in methanol to give dimethoxypyridazinylpyridazin-6-one (**4** or **6**). The infrared spectrum of this product showed the absorption band of one carbonyl at 1660 cm^{-1}. The ^{1}H nmr spectrum of this product also showed the proton signals of two OCH_3 groups and four aromatic hydrogens (H_{C-3} = δ 7.74 ppm, $J_{3,5}$ = 2.8 Hz; H_{C-5} = δ 6.15 ppm, $J_{5,3}$ = 2.8 Hz; $H_{C-4'}$ = δ 7.25 ppm, $J_{4',6'}$ = 2.7 Hz; $H_{C-6'}$ = δ 8.87 ppm, $J_{6',4'}$ = 2.7 Hz). According to our previous report [3] and the spectral data, the structure of dimethoxypyridazinylpyridazin-6-one may be regarded as **4** or **6**. Even if the positions of the two methoxy groups of this product were confirmed at C-4 and at C-5' for **4** or C-6' for **6**, we could not establish the linkage of two rings.

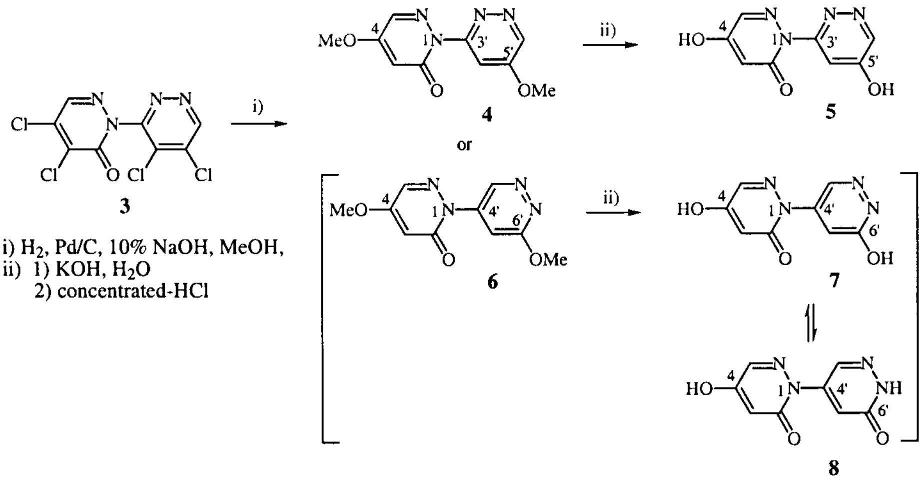
Scheme I



i) Method A; $POCl_3$, reflux, ii) Method B; $POCl_3$, toluene, reflux, iii) Method C; PCl_5, reflux, iv) Method D; PCl_5, toluene, reflux, v) Method E; PCl_5, acetonitrile, reflux

In order to confirm the linkage position of two pyridazine rings, dimethoxypyridazinylpyridazin-6-one **4** or **6** was converted to the corresponding dihydroxy derivative **5** or **7**. If the linkage of the two rings for the dihydroxy derivatives are N1-C4' as in structure **7**, compound **7** is tautomerized to **8**. The infrared spectrum of **8** may exhibit the absorption bands of two carbonyl groups and an NH or the characteristic peaks of free pyridazin-6-one at 3300-2800 cm^{-1}. However we did not detect the characteristic peaks of the free pyridazin-6-one. In addition, the proton resonance spectrum of dihydroxypyridazinylpyridazin-6-one, **5** or **7** also exhibited only the proton signals of two OH groups and four aromatic protons. Therefore, the linkage of two rings for dihydoxypyridazinylpyridazin-6-one may be regarded as N1-C3' linkage as in structure **5**.

Scheme II



i) H_2, Pd/C, 10% NaOH, MeOH,
ii) 1) KOH, H_2O
2) concentrated-HCl

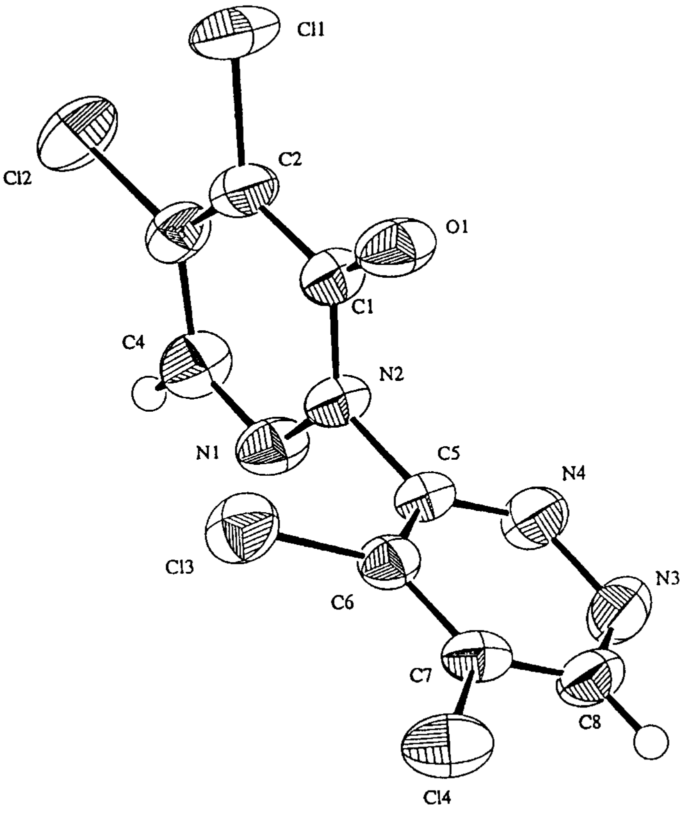


Figure 1. An ORTEP drawing of **3**.

Furthermore, the structure of **3** was unambiguosly confirmed by an X-ray analysis as shown in Figure 1 (Tables 4-13). Compound **3** contains five carbon-nitrogen bonds and two nitrogen-nitrogen bonds. The longest carbon-nitrogen bond is C5-N2 [1.441(3) Å], whereas the shortest carbon-nitrogen bond is C4-N1 [1.286(3) Å]. The bond lengths of two nitrogen-nitrogen bonds also are similar. The dihedral angle between two rings is 76.73°.

Table 1

Yields, Melting Points and Infrared Spectral Data of **2-5**

Compound No	Method (%)	Yield (lit mp)	Mp (°C) (cm^{-1})	IR (Potassium bromide)
2	A	67	55-56	3060, 1520, 1260, 1030, 820
	B	67	(61) [4]	
	C	36		
	E	51		
3	C	46	195-197	3090, 1680, 1580, 1360, 1220
	D	81		
4		32	170-172	3100, 2980, 1660, 1630, 1605, 1570, 1480, 1420, 1360, 1285, 1265, 1220
5		15	269-270	3450, 3400, 3100, 3060, 1660, 1620, 1560, 1470, 1380, 1320, 1280, 1270, 1240, 1200, 1120, 980, 850, 720, 700

Table 2

Nmr Spectral Data of **2-5**

Compound No	Solvent [a]	^1H NMR (δ, ppm) [b]	^{13}C NMR (δ, ppm)
2	C	9.12 (s, 1H)	136.0, 137.7, 150.6, 155.8
3	D	8.05 (s, $1H_3$), 9.38 (s, $1H_{3'}$)	134.1, 134.2, 138.1, 138.3, 138.9, 153.8, 154.4, 155.2
4	C	3.82 (s, 3H), 3.90 (s, 3H), 6.15 (d, 1H, J = 2.8), 7.25 (d, 1H, J = 2.7), 7.74 (d, 1H, J = 2.8), 8.87 (d, 1H, J = 2.7)	56.2, 56.5, 103.9, 107.5, 135.0, 144.3, 157.5, 159.1, 161.4, 161.9
5	D	3.74 (bs, 2OH), 5.55 (d, Ar. 1H, J = 2.3), 6.69 (d, Ar. 1H, J = 2.4), 7.57 (d, Ar. 1H, J = 2.6), 8.09 (d, Ar, 1H, J = 2.4)	99.7, 107.8, 127.0, 138.5, 145.1, 151.4, 160.9, 164.5

[a] Solvent; C = Deuteriochloroform. D = Dimethyl-d_6 sulfoxide [b] Abbreviations used: s = singlet. d = doublet. bs = broad singlet. Ar = Aromatic. J = Hz unit. The proton signal of the OH group was exchangeable with deuterium oxide.

Table 3
Elemental Analytical Data of **2-5**

Compound No	Molecular Formula	Elemental Analyses(%) (Calcd/Found)		
		C	H	N
2	$C_4HN_2Cl_3$	26.19	0.55	15.27
		26.50	0.59	15.40
3	$C_8H_2N_4Cl_4O$	30.80	0.65	17.96
		30.93	0.83	18.05
4	$C_{10}H_{10}N_4O_3$	51.28	4.30	23.92
		51.34	4.35	23.99
5	$C_8H_6N_4O_3$	46.61	2.93	27.18
		46.72	3.00	27.34

Table 4
Crystal Data for **3**

Emperical Formular	$C_8H_2ON_4Cl_4$
Formular Weight	311.94
Crystal color, Habit	Colorless, prismatic
Crystal Dimmensions	0.30 x 0.10 x 0.08 mm
Crystal System	Triclinic
Lattice Type	Primitive
Indexing Images	2 oscillations at 1.0 minutes
Camera Radius	127.40 mm
Lattice Parameters	a = 7.233 (3) Å, b = 11.568(4) Å, c = 6.933(2) Å, α = 97.23(2)°, β = 103.20(1)°, γ = 88.33(1)° V = 560.2(3) Å^3
Space Group	P$\bar{1}$ (#2)
Z value	2
D_{calcd}	1.849 g/cm^3
F_{000}	308.00
μ(MoKα)	42.82 cm^{-1}

Table 5
Intensity Measurements for **3**

Diffractometer	Rigaku RAXIS-RAPID Imaging Plate
Radiation	Mo-Kα (λ = 0.71069 Å) Graphite monochromated
Detector Aperture	270.0 mm x 256.0 mm
Data Images	55 exposures at 0.2 minutes per degree
Oscillation Range (φ = 0.0°, χ = 45.0°)	ω 130.0 – 190.0° with 4.0° step
Oscillation Range (φ = 180.0°, χ = 45.0°)	ω 0.0 – 160.0° with 4.0° step
Camera Radius	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	55.0°
No. of Reflections measured	Total: 1832, Unique: 1499 (R_{int} = 0.017)
Corrections	Lorentz-polarization, Secondary extinction (coefficient: 4.13048e-06)

Table 6
Structure Solution and Refinement for **3**

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Mininized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least Squares Weights	Where $w = 1 / \sigma^2(Fo) = [\sigma^2_c(Fo) + (p^2/4)Fo^2]^{-1}$
p-factor	0.0560
No. Observations (I > 2.00 σ(I))	1498
No. Variables	155
Reflection/Parameter Ratio	9.66
Residuals: R; Rw	0.031; 0.044
Goodness of Fit Indicator	1.21
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final diffraction map	0.18 e$^-$/Å^3
Minimum peak in Final diffraction map	- 0.21 e$^-$/Å^3

Table 7
Atomic Coordinates and B_{iso}/B_{eq} for **3**

Atom	X	Y	z	B_{eq}
C1(1)	0.2473(1)	0.55820(6)	0.7281(1)	4.94(2)
Cl(2)	0.2854(1)	0.61677(6)	1.1988(1)	4.94(2)
Cl(3)	0.50369(9)	0.10505(6)	0.8040(1)	4.24(2)
Cl(4)	0.3718(1)	-0.15784(6)	0.6526(1)	4.82(2)
O(1)	0.1797(3)	0.3050(2)	0.6022(3)	4.40(4)
N(1)	0.1980(3)	0.2797(2)	1.1097(3)	3.48(5)
N(2)	0.1841(3)	0.2569(2)	0.9091(3)	2.94(4)
N(3)	-0.0942(3)	-0.0019(2)	0.7543(4)	4.11(5)
N(4)	-0.0400(3)	0.1090(2)	0.8168(3)	3.66(5)
(C1)	0.1976(4)	0.3351(2)	0.7795(4)	3.25(5)
C(2)	0.2333(3)	0.4545(2)	0.8779(4)	3.32(5)
C(3)	0.2493(3)	0.4784(2)	1.0751(4)	3.39(5)
C(4)	0.2301(4)	0.3860(2)	1.1884(4)	3.73(5)
C(5)	0.1377(3)	0.1371(2)	0.8317(3)	2.76(4)
C(6)	0.2769(3)	0.0608(2)	0.7824(3)	2.89(4)
C(7)	0.2180(4)	-0.0521(2)	0.7177(3)	3.21(5)
C(8)	0.0306(4)	-0.0797(2)	0.7075(4)	3.68(5)
H(4)	0.2419	0.4041	1.3280	4.4
H(8)	-0.0099	-0.1580	0.6645	4.4

$B_{eq} = (8/3)\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{12}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$

Further work including the chemical transformation and the biological activity of pyridazin-3'-ylpyridazin-6-ones is 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 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. X-Ray diffrection data were obtained with a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation. Open-bed chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

Chlorination of 4,5-Dichloropyridazin-6-one (**1**).

Method A.

A mixture of **1** (15 g, 90.92 mmoles) and phosphorus oxychloride (60 ml) was refluxed for 3 hours. After cooling to room

Table 8

Anisotropic Displacement Parameters for **3**

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	0.0883(6)	0.0362(3)	0.0695(5)	- 0.0046(3)	0.0226(4)	0.0202(3)
Cl(2)	0.0798(5)	0.0324(3)	0.0750(5)	-0.0092(3)	0.0257(4)	-0.0122(3)
Cl(3)	0.0427(3)	0.0542(4)	0.0698(5)	-0.0027(3)	0.0224(3)	0.0111(3)
Cl(4)	0.0848(5)	0.0374(3)	0.0679(5)	0.0178(3)	0.0343(4)	0.0050(3)
O(1)	0.088(1)	0.0414(9)	0.040(1)	-0.0078(9)	0.018(1)	0.0070(8)
N(1)	0.059(1)	0.036(1)	0.040(1)	-0.0029(9)	0.018(1)	0.0041(9)
N(2)	0.050(1)	0.0264(9)	0.037(1)	-0.0015(8)	0.0146(9)	0.0044(8)
N(3)	0.048(1)	0.043(1)	0.065(1)	-0.0098(9)	0.012(1)	0.005(1)
N(4)	0.045(1)	0.037(1)	0.058(1)	-0.0014(9)	0.015(1)	0.0059(10)
C(1)	0.047(1)	0.034(1)	0.043(1)	-0.0023(9)	0.012(1)	0.005(1)
C(2)	0.046(1)	0.031(1)	0.052(1)	-0.0005(9)	0.014(1)	0.009(1)
C(3)	0.045(1)	0.031(1)	0.053(2)	-0.0023(9)	0.016(1)	-0.003(1)
C(4)	0.060(2)	0.042(1)	0.041(1)	-0.003(1)	0.018(1)	-0.003(1)
C(5)	0.043(1)	0.0257(10)	0.039(1)	-0.0015(8)	0.013(1)	0.0056(9)
C(6)	0.043(1)	0.036(1)	0.034(1)	-0.0021(9)	0.012(1)	0.0086(9)
C(7)	0.057(1)	0.030(1)	0.038(1)	0.0062(10)	0.016(1)	0.0067(9)
C(8)	0.061(2)	0.031(1)	0.047(1)	-0.008(1)	0.011(1)	0.003(1)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl)$$

Table 9

Bond Lengths for **3**

Atom	Atom	Distance (Å)	Atom	Atom	Distance (Å)
Cl(1)	C(2)	1.702(3)	Cl(2)	C(3)	1.716(2)
Cl(3)	C(6)	1.701(2)	Cl(4)	C(7)	1.717(2)
O(1)	C(1)	1.213(3)	N(1)	N(2)	1.363(3)
N(1)	C(4)	1.286(3)	N(2)	C(1)	1.373(3)
N(2)	C(5)	1.441(3)	N(3)	N(4)	1.341(3)
N(3)	C(8)	1.320(4)	N(4)	C(5)	1.313(3)
C(1)	C(2)	1.464(3)	C(2)	C(3)	1.339(4)
C(3)	C(4)	1.431(4)	C(5)	C(6)	1.393(3)
C(6)	C(7)	1.373(3)	C(7)	C(8)	1.386(4)
C(4)	H(4)	0.95	C(8)	H(8)	0.95

Table 10

Bond Angles for **3**

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
N(2)	N(1)	C(4)	116.9(2)	N(1)	N(2)	C(1)	127.4(2)
N(1)	N(2)	C(5)	113.2(2)	C(1)	N(2)	C(5)	119.3(2)
N(4)	N(3)	C(8)	119.7(2)	N(3)	N(4)	C(5)	118.7(2)
O(1)	C(1)	N(2)	121.7(2)	O(1)	C(1)	C(2)	125.2(3)
N(2)	C(1)	C(2)	113.1(2)	C(1)	C(2)	C(1)	116.5(2)
Cl(1)	C(2)	C(3)	123.2(2)	C(1)	C(2)	C(3)	120.3(2)
Cl(2)	C(3)	C(2)	122.8(2)	Cl(2)	C(3)	C(4)	117.9(2)
C(2)	C(3)	C(4)	119.3(2)	N(1)	C(4)	C(3)	123.0(2)
N(2)	C(5)	N(4)	114.6(2)	N(2)	C(5)	C(6)	120.4(2)
N(4)	C(5)	C(6)	125.1(2)	Cl(3)	C(6)	C(5)	122.0(2)
Cl(3)	C(6)	C(7)	122.8(2)	C(5)	C(6)	C(7)	115.2(2)
Cl(4)	C(7)	C(6)	121.3(2)	Cl(4)	C(7)	C(8)	120.2(2)
C(6)	C(7)	C(8)	118.4(2)	N(3)	C(8)	C(7)	122.9(2)
N(1)	C(4)	H(4)	118.6	C(3)	C(4)	H(4)	118.4
N(3)	C(8)	H(8)	118.6	C(7)	C(8)	H(8)	118.5

temperature, the mixture was poured into ice water (1000 ml) with stirring. The product was extracted with chloroform (100 ml x 3). Chloroform solution was washed with water (250 ml x 2), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3.0 x 10 cm). The column was eluted with chloroform. Fractions containing **2** (Rf = 0.48, chloroform) were combined and evaporated under reduced pressure to yield **2** in 67% (10.83 g) yield.

Method B.

A mixture of **1** (1 g, 6.06 mmoles), phosphorus oxychloride (1.13 ml, 12.12 mmoles) and dry toulene (20 ml) was refluxed for 25 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. Chloroform (50 ml) and ice water (50 ml) were added to the residue with stirring. The chloroform layer was separated and evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 3 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give **2** in 67% (0.75 g) yield.

Method C.

A mixture of **1** (8 g, 48.48 mmoles) and phosphorus pentachloride (12 g, 57.63 mmoles) was refluxed for 3 hours. After cooling to room temperature, the mixture was poured into ice water (500 ml) with stirring. The product was extracted with chloroform (100 ml x 3). Chloroform solution was washed with water (200 ml x 2), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 5 cm). First the column was eluted with *n*-hexane. Fractions containing **2** (Rf = 0.48, chloroform) were combined and evaporated under reduced pressure to give **2** in 36% (3.2 g) yield. The column was then eluted with chloroform. Fractions containing **3** (Rf = 0.30, chloroform) were combined and evaporated under reduced pressure to give **3** in 46% (3.5 g) yield.

Method D.

A mixture of **1** (1 g, 6.06 mmoles), phosphorus pentachloride (1.3 g, 6.06 mmoles) and dry toluene (15 ml) was refluxed for 8 hours. After evaporating the solvent under reduced pressure,

Table 11

Torsion Angles for **3**

Atom	Atom	Atom	Atom	Angle(°)	Atom	Atom	Atom	Atom	Angle(°)
Cl(1)	C(2)	C(1)	O(1)	0.8(4)	Cl(1)	C(2)	C(1)	N(2)	-178.7(2)
Cl(1)	C(2)	C(3)	Cl(2)	0.1(3)	Cl(1)	C(2)	C(3)	C(4)	178.2(2)
Cl(2)	C(3)	C(2)	C(1)	-178.4(2)	Cl(2)	C(3)	C(4)	N(1)	178.2(2)
Cl(3)	C(6)	C(5)	N(2)	-1.8(3)	Cl(3)	C(6)	C(5)	N(4)	179.3(2)
Cl(3)	C(6)	C(7)	Cl(4)	-0.2(3)	Cl(3)	C(6)	C(7)	C(8)	179.3(2)
Cl(4)	C(7)	C(6)	C(5)	-179.5(2)	Cl(4)	C(7)	C(8)	N(3)	-179.5(2)
O(1)	C(1)	N(2)	N(1)	-178.7(2)	O(1)	C(1)	N(2)	C(5)	-3.3(4)
O(1)	C(1)	C(2)	C(3)	179.5(2)	N(1)	N(2)	C(1)	C(2)	0.8(4)
N(1)	N(2)	C(5)	N(4)	74.7(3)	N(1)	N(2)	C(5)	C(6)	-104.2(3)
N(1)	C(4)	C(3)	C(2)	0.0(4)	N(2)	N(1)	C(4)	C(3)	0.6(4)
N(2)	C(1)	C(2)	C(3)	0.0(3)	N(2)	C(5)	N(4)	N(3)	-177.2(2)
N(2)	C(5)	C(6)	C(7)	177.5(2)	N(3)	N(4)	C(5)	C(6)	1.7(4)
N(3)	C(8)	C(7)	C(6)	1.0(4)	N(4)	N(3)	C(8)	C(7)	-0.7(4)
N(4)	C(5)	N(2)	C(1)	-101.4(3)	N(4)	C(5)	C(6)	C(7)	-1.4(4)
C(1)	N(2)	N(1)	C(4)	-1.1(4)	C(1)	N(2)	C(5)	C(6)	79.7(3)
C(1)	C(2)	C(3)	C(4)	-0.4(4)	C(2)	C(1)	N(2)	C(5)	176.2(2)
C(4)	N(1)	N(2)	C(5)	-176.8(2)	C(5)	N(4)	N(3)	C(8)	-0.7(4)
C(5)	C(6)	C(7)	C(8)	0.0(3)					

Table 12

Non-bonded Contacts out to 3.60 Å for **3**

Atom	Atom	Distance	ADC [12]	Atom	Atom	Distance	ADC [12]
Cl(1)	Cl(4)	3.563(1)	56501	Cl(2)	C(1)	3.556(3)	56702
Cl(2)	N(4)	3.591(2)	56702	Cl(3)	N(3)	3.201(3)	65501
Cl(3)	N(4)	3.282(3)	65501	Cl(3)	C(7)	3.579(3)	65702
Cl(4)	N(1)	3.517(3)	65702	O(1)	C(4)	3.227(3)	55401
O(1)	C(8)	3.324(3)	55602	O(1)	N(1)	3.422(3)	55401
N(1)	C(8)	3.408(3)	55702	N(3)	N(4)	3.295(3)	55702
N(3)	C(7)	3.323(3)	55602	N(3)	N(3)	3.363(5)	55702
N(3)	C(5)	3.515(4)	55702	N(3)	C(8)	3.579(4)	55602
N(4)	C(8)	3.343(4)	55702	C(3)	C(3)	3.556(5)	56702
C(7)	C(8)	3.578(3)	55602	C(8)	C(8)	3.456(5)	55602

Table 13

Least Squares Planes for **3**

Plane number 1		Plane number 2	
Atoms defining plane	Distance	Atoms defining plane	Distance
N(1)	-0.005(2)	N(3)	0.001(3)
N(2)	0.004(2)	N(4)	-0.007(2)
C(1)	-0.002(3)	C(5)	0.008(2)
C(2)	-0.002(2)	C(6)	-0.004(2)
C(3)	0.003(2)	C(7)	-0.004(2)
C(4)	0.002(3)	C(8)	0.007(3)

Summary

Plane	Mean deviation	χ^2
1	0.0030	13.0
2	0.0050	30.7

Dihedral angles between planes (°)

Plane	1
2	76.73

the residue was triturated in water (50 ml). The precipitate was filtered and dissolved in chloroform (60 ml). The chloroform solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give **3** in 81% (0.77 g) yield.

Method E.

A mixture of **1** (1 g, 6.06 mmoles), phosphorus pentachloride (1.3 g, 6.06 mmoles) and acetonitrile (15 ml) was refluxed for 25 hours. After evaporating the solvent under reduced pressure, ice water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered and washed with ice water (100 ml x 4). The residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give only **2** in 51% (0.57 g) yield.

Dehalogenation of **3**.

A mixture of Pd/C (0.6 g), **3** (0.71 g, 2.276 mmoles), aqueous sodium hydroxide (10%, 5 ml) and methanol (30 ml) was stirred for 70 hours under hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the residue was washed with methanol (40 ml). The solution was evaporated under reduced pressure and dried in air to give **4** in 32% (0.17 g) yield.

Demethylation of 4-Methoxy-1-(5'-methoxypyridazin-3'-yl)pyridazin-6-one (**4**).

A mixture of **4** (0.46 g, 1.95 mmoles), potassium hydroxide (0.33 g, 5.81 mmoles) and water (10 ml) was refluxed for 7 hours. After cooling to room temperature, the solution was neutralized with dilute hydrochloric acid (1 ml of concentrated hydrochloric acid was diluted to 10 ml) and evaporated under reduced pressure. The residue was dissolved in methanol (40 ml) and coevaporated with silica gel (2 g) under reduced pressure. It was applied to the top of an open-bed silica gel column (2.0 x 5 cm). First the column was eluted with ethyl acetate to remove byproducts and then eluted with chloroform/methanol (10:1, v/v).

Fractions containing **5** were combined and evaporated under reduced pressure to give **5** in 47% (0.19 g) yield.

X-Ray Structural Analysis of Compound **3**.

Data collection: A colorless prismatic crystal of $C_8H_2ON_4Cl_4$ having approximate dimensions of 0.30 x 0.10 x 0.08 mm was mounted on a glass fiber.

Indexing was performed from 2 oscillations which were exposed for 1.0 minute. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Cell constants and an orientation matrix for data collection corresponded to a primitive triclinic cell with dimensions: a = 7.233 (3), b = 11.568 (4), c = 6.933 (2) Å, α = 97.23 (2), β = 103.20 (1), γ = 88.33 (1)°, V = 560.2 (3) $Å^3$. For Z = 2 and molecular weight = 311.94, the calculated density is 1.85 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: $P\bar{1}$ (#2). The data were collected at a temperature of 25 ±1° to a maximum 2θ value of 55.0°. A total of 55 images corresponding to 220.0° oscillation angles, were collected with 2 different goniometer settings. Exposure time was 0.20 minute per degree. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. Data were processed by the PROCESS-AUTO program package.

Data Reduction: Of the 1832 reflections which were collected, 1499 were unique (R_{int} = 0.017); equivalent reflections were merged. The linear absorption coefficient, μ, for Mo-Kα radiation is 42.8 cm^{-1}. No absorption correction was applied. The data were corrected for Lorentz polarization effects. A correction for secondary extinction was applied (coefficient = 4.13048e-06).

Structure Solution and Refinement: The structure was solved by direct methods [5] and expanded using Fourier techniques [6]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement [7] was based on 1498 observed reflections (I > 2.00 σ (I)) and 155 variable parameters and convereged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.031$; $R_w = \sqrt{\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2} = 0.044$. The standard deviation of an observation of unit weight [8] was 1.21. The weighting scheme was based on counting statistics and included a factor (p = 0.056) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus |*Fo*|, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and -0.21 $e^{-1}/Å^3$, respectively. Neutral atom scattering factors were taken from Cromer and Wabers [9]. The values for the mass attenuation coefficients are those of Creagh and Hubbel [10]. All calculations were performed using the teXsan [11] crystallographic software package of Molecular Structure Corporation.

Acknowledgments.

The authors wish to acknowledge the financial support of the Korean Research Foundation made in the program year of 1998 (1998-015-D00175).

REFERENCES AND NOTES

[1] A. R. Katritzky and A. J. Boulton, Advances in Heterocyclic Chemistry, Vol **9**, Academic Press, New York, 1968, p 249.

[2] P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury and C. Wilkins, *J. Org. Chem.*, **28**, 218 (1968)

[3] D. H. Kweon, Y. J. Kang, H.-A Chung and Y. J. Yoon, *J. Heterocyclic Chem.*, **35**, 819 (1998)

[4] R. H. Mizzoni, P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1973 (1951)

[5] SIR97: A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, A New Tool for Crystal Structure Determination and Refimement, *J. Appl. Cryst.*, (1998) in press.

[6] DIRDIF94: P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel and J. M. M. Smits, (1994), The DIRDIF-94 Program System, Technical Refort of the Crystallography Laboratory, University of Nijmergen, The Netherlands.

[7] Least-Squares: Function minimized: $\Sigma w(|Fo| - |Fc|)^2$, where $w = 1/\sigma^2|Fo| = [\sigma^2{}_c(Fo) + (p^2/4)Fo^2]^{-1}$, $\sigma_c(Fo)$ = e.s.d. based on counting statistics. p = p-factor.

[8] Standard deviation of an observation of unit weight: $\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$, where *No* = number of observations, *Nv* = number of variables.

[9] D. T. Cromer and J. T. Waber, International Tables for X-ray Crystallography, Vol **IV**, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

[10] D. C. Creagh and J. H. Hubbell, International Tables for Crystallography, Vol **C**, A. J. C. Wilson, ed, Kluwer Academic Publishers, Boston, Table 4.2.4.3, 1992 pp 200-206.

[11] teXsan: Crystal Structure analysis Package, Molecular Structure Corporation (1985 & 1992).

[12] The ADC (atomic designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA = 5, TB = 5, TC = 5) can be represented. The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below. For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN = 1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis. An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that residue in the same asymmetric unit. Symmetry Operators: (1) X, Y, Z; (2) -X, -Y, -Z.