Reaction of 4,5-Dichloro-3-nitropyridazin-6-one with Dimethylchloromethyleneammonium Chloride

Deok-Heon Kweon, Su-Dong Cho, Sung-Kyu Kim, Joo-Wha Chung and Yong-Jin Yoon*

Department of Chemistry (& Research Institute of Natural Science), Gyeongsang National University, Chinju 660-701, Korea

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3,4,5-Trichloropyridazin-6-one, 3,4,5,6-tetrachloropyridzine and 4,5-dichloro-3-(*N*,*N*-dimethylamino)-pyridazin-6-one were synthesized from 4,5-dichloro-3-nitropyridazin-6-one and dimethylchloromethyleneammonium chloride selectively.

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3,4,5-Trichloropyridazin-6-one and 3,4,5,6-tetrachloropyridazine are useful materials for the synthesis of pyridazine derivatives. As a part of a continuous program to study the synthesis of multichloropyridazine derivatives, we attempted to prepare 3,4,5-trichloropyridazin-6-one, 3,4,5,6-tetrachloropyridazine and 4,5,6-trichloro-3-nitropyridazine.

Dury [1] reported the synthesis of 1-substituted-3,4,5-trichloropyridazin-6-ones by the chlorination of 1-substituted-4,5-dichloro-3-hydroxypyridazin-6-ones with phosphorus oxychloride. Schonbeck and Kloimstein [2] also reported the synthesis of 3,4,5-trichloropyridazin-6-one by the treatment of 3,4,5,6-tetrachloropyridazine with glacial acetic acid. 3,4,5,6-Tetrachloropyridazine was prepared by the chlorination of 4,5-dichloropyridazin-3,6-dione with a mixture of phosphorus tri- or pentachloride and phosphorus oxychloride [3].

First we attempted to synthesize 4,5,6-trichloro-3-nitropyridazine from 4,5-dichloro-3-nitropyrdazin-6-one (**1**) by Dury's method. However, we found several spots on the tlc plate under Dury's conditions. Thus, we investigated the selective chlorination of 4,5-dichloro-3-nitropyridazin-6-one (**1**).

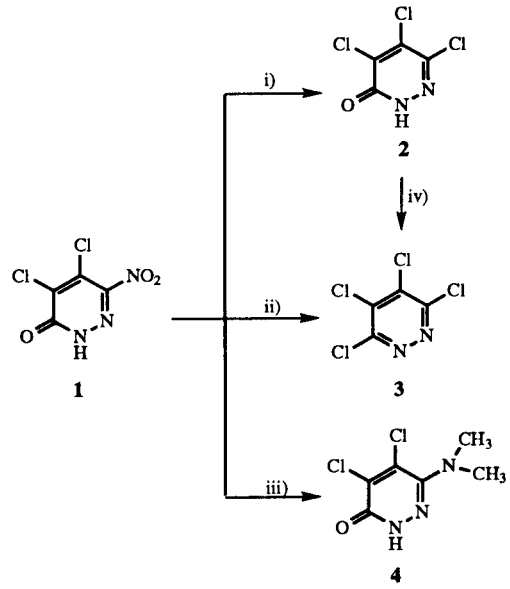
Dimethylchloromethyleneammonium chloride {[$(CH_3)_2$-N^+=CHCl] Cl^-}, readily available by reaction of phosgene, phosphorus oxychloride or thionyl chloride with dimethylformamide, is a highly reactive chlorinating reagent [4]. Thus, we chose dimethylchloromethyleneammonium chloride as the chlorinating reagent of compound **1**.

In this paper we wish to report the results of the title reaction using dimethylchloromethyleneammonium chloride.

A mixture of compound **1** and one equivalent of dimethylchloromethyleneammonium chloride in thionyl chloride was refluxed for 4-5 hours to yield **2** as the major product (78%) and **3** as the minor product (trace) (Method A), but we could not detect any spot for a product when compound **1** was reacted with only thionyl chloride under reflux condition for 2 days. Whereas, treatment of **1** with two equivalents of dimethylchloromethyleneammonium chloride in thionyl chloride at reflux temperature for 7 hours gave **3** as the major product (73%) and **2** as the minor product (trace) (Method B), reaction of **1** with excess dimethylchloromethyleneammonium chloride (6 equivalents) under the same conditions afforded only **3** in 89% yield (Method C). According to our observation, this reaction occurs in two steps; the replacement of the nitro group by chlorine in the first step and then the chlorination of the carbonyl group in the second step. The nitro group is more reactive then the carbonyl group towards dimethylchloromethyleneammonium chloride in our system. Therefore, we tested some conditions to give selectively only compounds **2** or **3** in excellent yields under mild conditions.

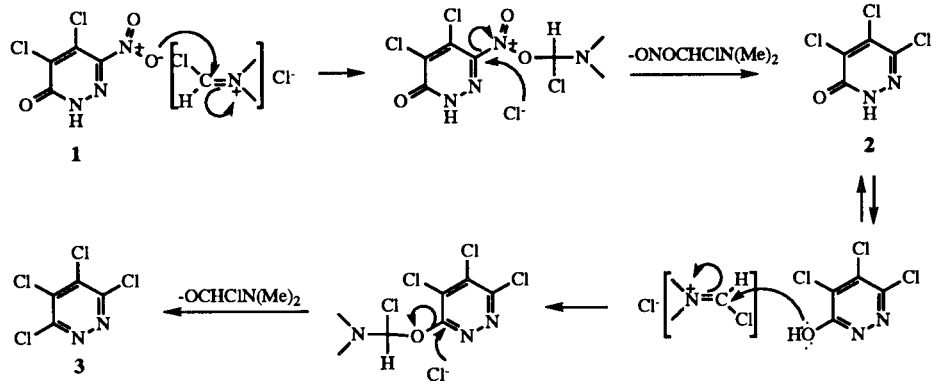
The reaction of 4,5-dichloro-3-nitropyridazin-6-one (**1**) with one or two equivalents of dimethylchloromethyleneammonium chloride in dry benzene at reflux temperature for 2-3 hours gave only 3,4,5-trichloropyridazin-6-one (**2**) in 95-98% yields (Method D and E). A mixture of **1** and one equivalent of dimethylchloromethyleneammonium chloride in dry toluene was refluxed for 2 hours and

Scheme 1



i) Methods A, D, E, F and H ii) Methods B, C, G and I
iii) Methods L and M iv) Methods J and K

Scheme 2



afforded **2** as the main product (76%) yield and **3** as the minor product (trace) (Method F). Whereas, treatment of **1** with two equivalents of dimethylchloromethyleneammonium chloride in dry toluene at reflux temperature for 2 hours gave **3** as the main product in 86% yield and **2** as the minor product (Method G). A mixture of **1** and four equivalents of dimethylchloromethyleneammonium chloride in dry toluene was refluxed for 1 hour to yield only **3** in 96% yield (Method H).

In addition, we attempted to prepare compound **3** from **2**. Compound **2** was allowed to react without dimethylchloromethyleneammonium chloride in phosphorus oxychloride at reflux temperature for 5 hours to yield **3** as the major product (37%) and bipyridazin-6-one as the minor product (17%) (Method I) [5]. This is similar to Coad's result [3b]. Coad and his coworker observed the formation of 1-(3'-chloro-6'-pyridazyl)-3-chloro-6-pyridazone when pyridazin-3,6-dione was reacted with phosphorus oxychloride.

The reaction of **2** with one or two equivalents of dimethylchloromethyleneammonium chloride in dry toluene at reflux temperature for 4-6 hours afforded **3** in 96-97% yield (Method J and K), but we did not detect any product in the case of the benzene solvent. Also, treatment of **2** with only thionyl chloride, or phosphorus oxychloride, did not yield compound **3**. The chlorinating mechanisms of **1** with dimethylchloromethyleneammonium chloride is proposed in Scheme 2.

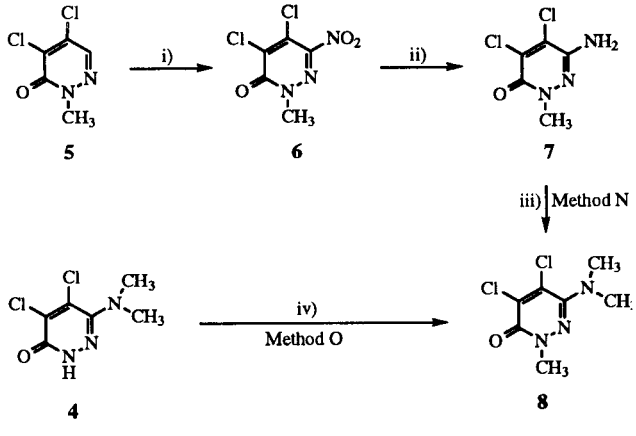
Consequently, the chlorination of nitro and carbonyl groups of compound **1** with dimethylchloromethyleneammonium chloride may be dependent on the reaction temperature.

Compounds **2** and **3** were spectroscopically the same as an authentic sample, respectively.

Whereas, treatment of **1** with one or two equivalents of dimethylchloromethyleneammonium chloride in dry dimethylformamide at reflux temperature leads to an interesting reaction resulting in good yields of compound **4** instead of compound **2** or **3** (Method L and M).

On the other hand, the position of the *N,N*-dimethyl group for **4** is shown in Scheme 3. Nitration of **5** with potassium nitrate and concentrated sulfuric acid gave

Scheme 3



i) KNO_3, conc-H_2SO_4, reflux ii) Fe/NH_4Cl/$CHCl_3$/H_2O

iii) $(CH_3)_2SO_4$, K_2CO_3, $CHCl_3$ iv) CH_3I, K_2CO_3, Acetone

Table 1

Reaction Conditions and Results [a]

Method	Starting Material	Solvent	DCMAC (Equivalents)	Time (hours)	Product (%) [b] 2	3	4
A	1	S	1	4-5	79	Tr	
B	1	S	2	7-8	Tr	73	
C	1	S	6	4-5		89	
D	1	B	1	3	95		
E	1	B	2	2	98		
F	1	T	1	2	76	Tr	
G	1	T	2	2	Tr	86	
H	1	T	4	1		96	
I	1	P	0	5		37 [c]	
J	2	T	1	6		96	
K	2	T	2	4		97	
L	1	D	1	4			88
M	1	D	2	2			85

[a] All reactions were carried out under reflux conditions. Abbreviation used: DCMAC = Dimethylchloromethyleneammonium chloride. S = Thionyl chloride, B = Benzene, T = Toluene, P = Phosphorus oxychloride, D = Dimethyl formamide [b] Isolated yield; Tr = trace, The by-product (trace) was detected on the tlc plate, but it could not be isolated. [c] Bipyridazin-6-one as a by-product was isolated in 17% yield [5].

Table 2

Melting Points and Infrared Spectral Data of Compounds **2-4** and **6-8**

Compound No.	mp (°C)	IR (cm^{-1}) (KBr)
2	226-227 [a]	3120, 3090, 3050, 2950, 2880, 1718, 1658, 1570, 1280, 1182, 1120, 1060, 960, 860, 800, 720
3	85-86 [b]	1500, 1480, 1280, 1190, 1080, 880, 800, 620
4	193-194	3220, 3150, 3050, 2980, 2920, 1680, 1580, 1460, 1430, 1280, 1160
6	98-99	2950, 2900, 1690, 1592, 1500, 1360, 1340, 1300, 1260, 1060, 1000, 900, 742
7	193-195	3500, 3350, 3250, 2955, 1640, 1600, 1585, 1520, 1450, 1400, 1340, 1220, 1020, 880
8	96-97	2950, 2900, 1650, 1570, 1440, 1410, 1300, 1210, 1080, 1010, 980

[a] Lit [2] mp 224-226°. [b] Lit [2,3] mp 85-86°.

Table 3

NMR Spectral Data of Compounds **2-4** and **6-8**

Compound No.	Solvent [a]	^{1}H NMR [b] (ppm)	^{13}C NMR (ppm)
2	D	13.82 (bs, NH)	135.7, 135.9, 136.3, 155.9
3	C		138.1, 155.3
4	C	3.16 (s, 6H)	42.4, 115.9, 138.4, 146.3, 158.2
6	D	3.75 (s, 3H)	41.1, 129.1, 136.3, 143.8, 155.6
7	D	3.52 (s, 3H) 6.10 (bs, NH) 7.37 (bs, NH)	39.3, 128.9, 133.9, 144.8, 153.3
8	D	3.07 (s, 6H) 3.55 (s, 3H)	39.5, 42.4, 115.7, 136.8, 145.7, 156.8

[a] C = Deuteriochloroform, D = DMSO-d_6. [b] Abbreviations used: s = Singlet, bs = Broad singlet. The proton signals of all NH were exchangeable with deuterium oxide.

Table 4

Elemental Analytical Data of Compounds **2-4** and **6-8**

Compound No.	Molecular Formula	Calcd./Found (%) C	H	N
2	$C_4HN_2OCl_3$	24.09	0.51	14.05
		23.90	0.58	13.93
3	$C_4N_2Cl_4$	22.05		12.86
		22.10		12.94
4	$C_6H_7N_3OCl_2$	34.64	3.39	20.20
		34.65	3.27	20.34
6	$C_5H_3N_3O_3Cl_2$	26.81	1.35	18.76
		26.54	1.34	18.81
7	$C_5H_5N_3OCl_2 \cdot 1/2H_2O$ [a]	29.58	2.98	20.70
		29.34	2.77	20.95
8	$C_7H_9N_3OCl_2$	37.86	4.08	18.92
		37.51	3.80	18.94

[a] The presence of water was verified by proton magnetic resonance spectroscopy.

compound **6** in a 64% yield. Reduction of **6** with iron/ammonium chloride/chloroform/water system afforded the 3-amino compound **7** in 93% yield. Compound **7** was reacted with dimethyl sulfate in the presence of potassium carbonate in chloroform to afford **8** in 68% yield (Method N). The reaction of **4** with methyl iodide in the presence of potassium carbonate in acetone also yielded compound **8** in 88% yield (Method O).

The structures of compound **4**, **6**, **7** and **8** was established by ir, nmr and elemental analysis.

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 (parts 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 in silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the eluent solvent.

Reaction of 4,5-Dichloro-3-nitropyridazin-6-one (**1**) with Dimethylchloromethyleneammonium Chloride.

Methods A-C.

A solution of *N,N*-dimethylformamide (1, 2 or 6 equivalents) in thionyl chloride (10 ml) was stirred for 20 minutes at room temperature. Compound **1** (1 g, 4.76 mmoles) [6] was added to the mixture. The mixture was then refluxed until compound **1** disappeared. After cooling to room temperature, excess thionyl chloride was removed under reduced pressure. Cold water (50 ml) was added to the resulting residue with stirring. The precipitate was filtered, washed with water (50 ml x 10) and dried in air to give the crude product. The crude product was applied to the top of an open-bed silica gel column (2.5 x 5 cm). The column was eluted with chloroform. Fractions containing the product were combined and then evaporated under reduced pressure to give compounds **2** or **3**.

Methods D-H.

A solution of *N,N*-dimethylformamide (1, 2 or 4 equivalents) and thionyl chloride (or phosphorus oxychloride, 1, 2 or 4 equivalents) in dry benzene or toluene (10 ml) was stirred for 20 minutes at room temperature. Compound **1** (1 g, 4.76 mmoles) was added to the mixture. The mixture was then refluxed until compound **1** disappeared. After cooling to room temperature, excess thionyl chloride was removed under reduced pressure. Cold water (50 ml) was added to the resulting residue with stirring. The precipitate was filtered, washed with water (50 ml x 10) and dried in air to give the crude product. The crude product was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform. Fractions containing the product were combined and then evaporated under reduced pressure to give compound **2** or **3**.

Method I.

A mixture of compound **1** (3 g, 14.3 mmoles) and phosphorus oxychloride (15 ml) was refluxed for 5 hours. After cooling to room temperature, the mixture was poured into ice water (400 ml) with stirring. The yellowish precipitate was filtered, washed with water (50 ml x 5) and dried in air. The resulting precipitate was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform/*n*-hexane (1:1, v/v). Fractions containing the product were combined and then evaporated under reduced pressure to give compound **3** in 37% (0.8 g) yield and bipyridazin-6-one in 17% (0.37 g) yield [5], respectively. Compound **3** was identical with the product that was prepared by Methods B and C.

Methods J and K.

A solution of *N,N*-dimethylformamide (1 or 2 equivalents) and thionyl chloride (or phosphorus oxychloride, 1 or 2 equivalents) in dry benzene or toluene (10 ml) was stirred for 20 minutes at room temperature. Compound **2** (1 g, 5.01 mmoles) was added to the solution. The mixture was then refluxed until compound **2** disappeared. After cooling to room temperature, the solvent was removed under reduced pressure. Cold water (50 ml) was added to the resulting residue with stirring. The precipitate was filtered, washed with water (50 ml x 10) and dried in air to give the crude product. The crude product 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 and then evaporated under reduced pressure to give compound **3**. This product was identical with **3** that was prepared by Methods B, C and G.

Method L and M.

A mixture of thionyl chloride (1 or 2 equivalents) and dry *N,N*-dimethylformamide (10 ml) was stirred for 20 minutes at room temperature. Compound **1** (4.76 mmoles) was added to the mixture. The mixture was then refluxed until compound **1** disappeared. After cooling to room temperature, the mixture was poured into ice water (150 ml) with stirring. The product was extracted with chloroform (25 ml x 2). 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 5 cm). The column was eluted with chloroform. Fractions containing the product were combined and then evaporated under reduced pressure. Cold water (100 ml) was added to the residue with stirring. The resulting crystals were filtered and dried in air to give compound **4**.

4,5-Dichloro-1-methyl-3-nitropyridazin-6-one (**6**).

A mixture of **5** [7] (9 g, 50.2 mmoles), potassium nitrate (20 g, 197.8 mmoles) and concentrated sulfuric acid (150 ml) was refluxed for 4.5 hours. After cooling to room temperature, the mixture was poured into ice water (500 ml) with stirring. The resulting crystals were filtered, washed with water (200 ml x 5) and dried in air to give **6** in 64% (7.2 g) yield.

3-Amino-4,5-dichloro-1-methylpyridazin-6-one (**7**).

A mixture of **6** (3 g, 13.4 mmoles), iron powder (3 g) [8], ammonium chloride (6 g, 112 mmoles), water (100 ml) and chloroform (100 ml) was stirred for 20 hours at room temperature. The reaction mixture was applied to the top of an open-bed silica gel column (2.5 x 8 cm). Fractions were combined, and the solvent was evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give compound **7** in 93% yield.

4,5-Dichloro-3-(*N,N*-dimethylamino)-1-methylpyridazin-6-one (**8**).

Method N.

A mixture of **7** (1 g, 5.15 mmoles), potassium carbonate (1 g, 7.2 mmoles), dimethylsulfate (2 g, 15.8 mmoles) and chloroform (15 ml) was refluxed for 23 hours. After cooling to room temperature, water (20 ml) was added to the resulting residue with stirring. The organic layer was separated. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 cm x 5 cm). The column was eluted with chloroform. Fractions containing the product were combined. The solvent was evaporated under reduced pressure to give the crude product. The crude product was recrystallized from chloroform/*n*-hexane (5:1, v/v) to afford **8** in 68% (0.78 g) yield.

Method O.

A mixture of **4** (0.5 g, 2.4 mmoles), methyl iodide (0.5 g, 3.5 mmoles), potassium carbonate (2 g, 14.47 mmoles) and acetone (15 ml) was stirred for 8 hours. The solvent was evaporated under reduced pressure. Water (20 ml) was added to the residue with stirring. The resulting crystals were filtered, washed with water (100 ml x 5) and dried in air to give **8** in 88% (0.47 g) yield. This product was identical with compound **8** that was prepared by the Method N.

Acknowledgment.

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REFERENCES AND NOTES

[1] K. Dury, *Angew. Chem., Int. Ed. Engl.*, **4**, 292 (1965).

[2] R. Schonbeck and E. Kloimstein, *Monatsh. Chem.*, **99**, 15 (1968).

[3a] C. J. Pennino, U.S. Patent 2,846,433 (Cl. 260-250), 05 Aug. 1958; [b] P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury and C. Wilkins, *J. Org. Chem.*, **28**, 218 (1963).

[4a] Z. Arnold, *Collect. Czech. Chem. Commun.*, **24**, 4048 (1959); [b] H. H. Bosshard, R. Mory, M. Chid and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959); [c] J. Zemlicka, J. Smrt and F. Sorm, *Tetrahedron Letters*, 397 (1962).

[5] Y. J. Yoon, unpublished results. The elucidation of the structure for bipyridazin-6-one will be presented elsewhere.

[6a] S. D. Cho, J. W. Chung, W. Y. Choi, S. K. Kim and Y. J. Yoon, *J. Heterocyclic Chem.*, **31**, 199 (1994); [b] T. Teri, H. Azuma and R. Hatorri, Japanese Patent, 1299 (1967); *Chem. Abstr.*, **66**, 6161 (1967).

[7] K. Dury, *Angew. Chem.*, **77**, 282 (1965).

[8] Iron powder was washed with concentrated hydrochloric acid and then methanol. The activated iron powder was dried in air.