Methoxylation of 4,5-Dichloro-2-methyl-6-nitropyridazin-3-one

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This paper presents the methoxylation of 4,5-dichloro-2-methyl-6-nitropyridazin-3-one with potassium carbonate/methanol.

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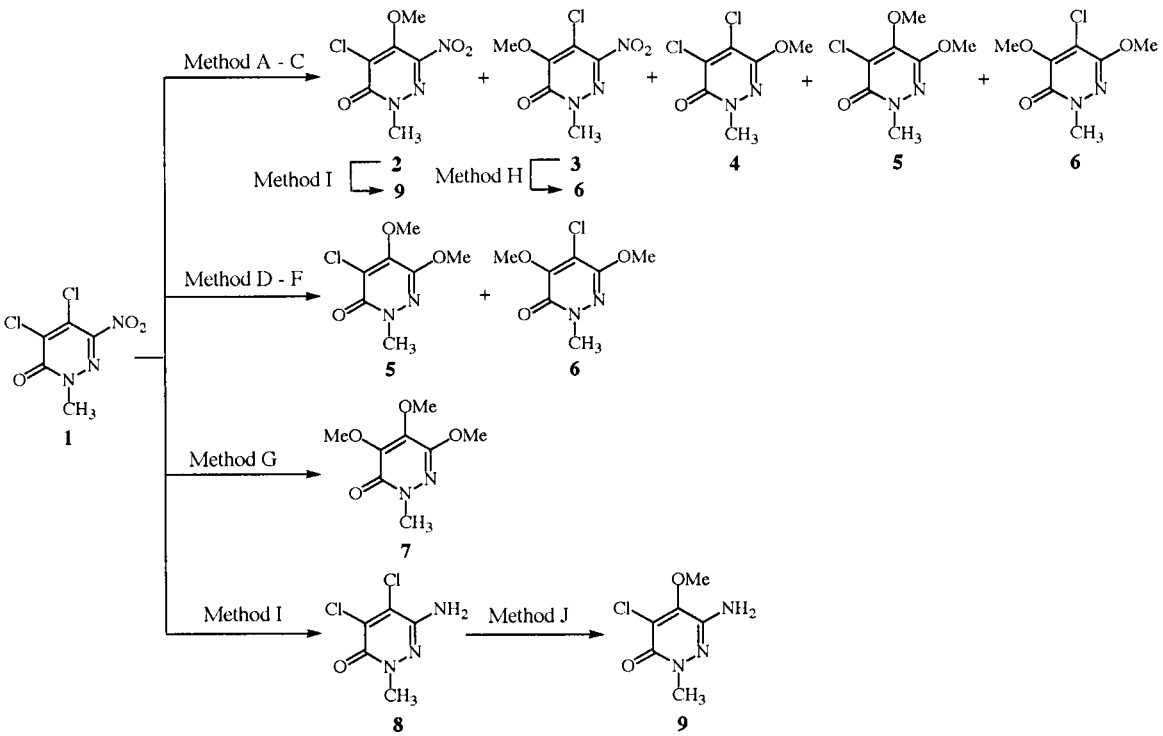
Trisubstituted-pyridazin-3-ones such as 6-nitro (or amino)-4,5-dihalopyridazin-3-ones are useful materials for the synthesis of fused-heterocycles containing pyridazinone [1,2] and various trisubstituted-pyridazin-3-ones [3-7]. Nucleophilic substitution of halogens in heterocycles using alkoxide anions is important because it is one of the conventional methods for the chemical manipulation of heterocycles. Methoxylation of 3,4,5-trichloropyridazine has been reported [8]. The methoxylation of 4,5,6-trisubstituted-pyridazin-3-ones, however, has not been thoroughly examined. In a previous paper [9], we reported that the potassium carbonate/methanol system is convenient for the methoxylation of 4,5-dihalopyridazin-3-ones.

In order to examine the regiochemistry toward nucleophiles and further synthetic application, we investigated in detail the methoxylation of 4,5-dichloro-2-methyl-6-nitropyridazin-3-one (**1**) with potassium carbonate/methanol.

In this paper, we report the results of the title reaction. Methoxylation of **1** with 0.5 molar equivalent of potassium carbonate in refluxing methanol gave monomethoxy-substituted derivatives **2** (28%) and **3** (62%) (Method A). Compound **1**, however, was reacted with one molar equivalent of potassium carbonate in refluxing methanol to afford **4** (4%), **5** (22%) and **6** (39%) (Method B). Compound **1** was reacted with one molar equivalent of potassium carbonate in methanol at 35° to yield **3** (52%) and **6** (4%) along with the recovered starting material **1** (22%) (Method C). Treatment of **1** with 1.3 molar equivalents of potassium carbonate in refluxing methanol afforded **5** (18%) and **6** (52%) (Method D). Compound **1** was also reacted with 2 molar equivalents of potassium carbonate in methanol at 35° for 4 hours or at reflux temperature for 0.5 hour to give **5** and **6** as the main product (Method E or F).

Scheme 1



Reaction of **1** with excess potassium carbonate (3.4 equivalents) in refluxing methanol for 24 hours gave only 4,5,6-trimethoxy-2-methylpyridazin-3-one (**7**) in excellent yield (Method G). By monitoring the reaction using thin layer chromatography, it was found that compound **7** was formed *via* the following three pathways under our reaction conditions; *viz.*, Pathway 1) **1** → **2** → **5** → **7**, Pathway 2) **1** → **3** → **6** → **7**, Pathway 3) **1** → **4** → **5** or **6** → **7**. Even if the methoxylation of **1** under our reaction condition were not regioselective, the main pathway for the methoxylation **1** to **7** under our condition may be regarded as the pathway 2); *viz.* **1** → **3** → **6** → **7**. And the products distribution and the yields are dependent on the molar ratio of the substrate, potassium carbonate as well as the reaction conditions.

Table 1
Methoxylation of **1**

		Reaction Conditions			Product Distribution (Isolated yield %)					
Entry	Method	Molar Ratio [a]	Temp. (°C)	Time (hrs)	**2**	**3**	**4**	**5**	**6**	**7**
1	A	1:0.5	Reflux	1	28	62	-	-	-	-
2	B	1:1	Reflux	1.5	-	-	4	22	39	-
3	C [b]	1:1	35	2	-	52	-	-	4	-
4	D	1:1.3	Reflux	1	-	-	-	18	52	-
5	E	1:2	35	4	-	-	-	30	62	-
6	F	1:2	Reflux	0.5	-	-	-	32	66	-
7	G	1:3.4	Reflux	24	-	-	-	-	-	92

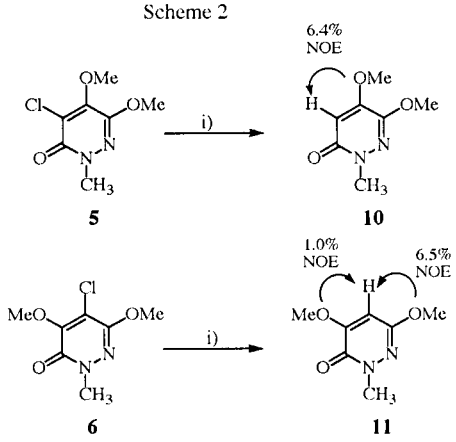
[a] Molar ratio of Substrate **1**/potassium carbonate. [b] The starting material **1** was recovered in 22%.

On the other hand, we attempted the methoxylation of 6-amino-4,5-dichloro-2-methylpyridazin-3-one (**8**) [7] in order to confirm the position of methoxy group of **2**. Compound **8** was reacted with 1.3 molar equivalents of potassium carbonate in refluxing methanol to afford regioselectively only 6-amino-4-chloro-5-methoxy-2-methylpyridazin-3-one (**9**) as the only product in excellent yield (Method J). Reduction of **2** with iron/ammonium chloride in water/chloroform also gave **9**, that was identical with the product of the Method J, in excellent yield (Method I).

In order to establish the structures of the products, we attempted some further reactions of **3**, **5** and **6**. Compound **3** was reacted with potassium carbonate (0.75 equivalents) in refluxing methanol to yield **6** in 95% yield (Method H). Compounds **5** and **6** were dehalogenated with Pd/C and hydrogen in methanol to give **10** (96%) and **11** (87%), respectively.

The substituted position of the methoxy group for **4** was established easily by the elemental analysis. It is also easy to distinguish between 5,6-dimethoxy derivative **10** and 4,6-dimethoxy derivative **11** by the NOE (between C5-OMe protons and C4-H proton for **10**; between C6-OMe (or C4-OMe) protons and C5-H proton for **11**)

Scheme 2



i) Pd/C, H_2, MeOH, room temperature.

and also comparing the chemical shift values of C4-H for **10** and C5-H for **11** with Katz's value [3]. The ^{1}H NMR spectrum of **10** showed proton signals for three methyl groups each a singlet (δ 3.67, 3.80, 3.86 ppm) and one proton singlet at δ 6.12 corresponding to that at C4. The ^{1}H NMR spectrum of **11** showed proton signals corresponding to three methyl groups as singlet (δ 3.61, 3.85, 3.89 ppm) and one proton at C5 as singlet (δ 6.16 ppm). In particular, irradiation of the methoxy proton at C5 of **10** resulted in a 6.4% nuclear Overhauser enhancement of the proton at C4. Irradiation of the methoxy proton at C6 and at C4 of **11** also resulted in a 6.5% and 1.0% nuclear Overhauser enhancement of the proton at C5, respectively. The position of methoxy group for **9** was proved by the further reaction [10]. Compound **9** was also prepared by the reduction of **2**. Therefore, the structures of **2**, **3**, **5**, **6** and **9** are proposed as the structures as in Scheme I.

Further work including the biological activity and the synthetic application 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 MHz or a Bruker FTNMR-DRX 500 MHz 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 chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. 4,5-Dichloro-2-methyl-6-nitropyridazin-3-one (**1**) was prepared by Kweon's method [7].

Reaction of **1** with Potassium Carbonate/Methanol.

General Procedure (Method A – F).

A mixture of **1**, potassium carbonate and methanol was stirred at reflux temperature (Method A, B, D, F) or at 35° (Method C, E) until compound **1** disappeared. After cooling to room temper-

ature, 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 10 - 12 cm). The column was eluted with a suitable solvent such as *n*-hexane/ethyl acetate (10:1, v/v for Method A, C, E), chloroform/diethyl ether (20:1, v/v for Method B), chloroform (Method D) and *n*-hexane/ethyl acetate (2:1, v/v for Method F). Fractions containing the product were combined and evaporated under reduced pressure to give the product. Each fraction was detected by tlc; *viz.* Rf values (chloroform/diethyl ether = 20:1, v/v) = 0.85 for **1**, 0.8 for **2**, 0.70 for **3**, 0.66 for **4**, 0.53 for **5** and 0.47 for **6**. The amounts of **1** (mmoles), K_2CO_3 (mmoles) and methanol (ml) were the following; *viz* Method A = 1.15:2.29:10; Method B = 4.53:4.53:15; Method C = 4.53:4.53:30; Method D = 4.46:5.80:10; Method E = 4.46:8.92:30; Method F = 3.59:7.14:30.

4-Chloro-5-methoxy-2-methyl-6-nitropyridazin-3-one (**2**).

Mp 65-66°; ir (potassium bromide): 3000, 1680, 1610, 1540, 1370, 1320, 1300, 1110, 1060, 1020, 890 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.71 (s, 3H), 4.32 ppm (s, 3H); ^{13}C nmr (deuteriochloroform): δ 40.4, 61.3, 115.5, 147.1, 153.0, 156.1 ppm.

Anal. Calcd. for $C_6H_6N_3O_4Cl$: C, 32.82; H, 2.75; N, 19.14. Found: C, 32.87; H, 2.80; N, 19.24.

5-Chloro-4-methoxy-2-methyl-6-nitropyridazin-3-one (**3**).

Mp 54-55°; ir (potassium bromide): 3000, 1680, 1610, 1560, 1520, 1380, 1290, 1160, 900 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.84 (s, 3H), 4.18 ppm (s, 3H); ^{13}C nmr (deuteriochloroform): δ 41.2, 62.3, 125.5, 144.5, 150.2, 158.5 ppm.

Anal. Calcd. for $C_6H_6N_3O_4Cl$: C, 32.82; H, 2.75; N, 19.14. Found: C, 32.90; H, 2.86; N, 19.21.

4,5-Dichloro-6-methoxy-2-methylpyridazin-3-one (**4**).

Mp 132-133° (*n*-hexane/ethyl acetate = 3:1, v/v: lit mp 135° [11]); ir (potassium bromide): 2980, 1680, 1605, 1540, 1480, 1415, 1405, 1340, 1290, 1200, 1090, 1060, 1000, 905, 870, 760, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H), 3.92 ppm (s, 3H); ^{13}C nmr (deuteriochloroform): δ 40.2, 55.4, 130.6, 136.6, 148.6, 155.4 ppm.

Anal. Calcd. for $C_6H_6N_2O_2Cl_2$: C, 34.48; H, 2.89; N, 13.40. Found: C, 34.56; H, 2.92; N, 13.53.

4-Chloro-5,6-dimethoxy-2-methylpyridazin-3-one (**5**).

Mp 82-83° (*n*-hexane/chloroform = 2:1, v/v); ir (potassium bromide): 3000, 1660, 1600, 1460, 1410, 1300, 1200, 1140, 940 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65 (s, 3H), 3.88 (s, 3H), 4.27 ppm (s, 3H); ^{13}C nmr (deuteriochloroform): δ 40.1, 55.0, 60.5, 117.1, 150.0, 152.5, 155.9 ppm.

Anal. Calcd. for $C_7H_9N_2O_3Cl$: C, 41.09; H, 4.43; N, 13.69. Found: C, 41.18; H, 4.66; N, 13.87.

5-Chloro-4,6-dimethoxy-2-methylpyridazin-3-one (**6**).

Mp 94-95° (*n*-hexane/ethyl acetate = 4:1, v/v); ir (potassium bromide): 3000, 1670, 1620, 1550, 1480, 1420, 1350, 1205, 1160, 1060, 1040, 980 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.68 (s, 3H), 3.90 (s, 3H), 4.04 ppm (s, 3H); ^{13}C nmr (deuteriochloroform): δ 39.7, 54.6, 61.0, 123.7, 148.3, 149.3, 157.8 ppm.

Anal. Calcd. for $C_7H_9N_2O_3Cl$: C, 41.09; H, 4.43; N, 13.69. Found: C, 41.23; H, 4.65; N, 13.87.

Method G.

A mixture of **1** (0.814 g, 3.63 mmoles), potassium carbonate (1.705 g, 12.3 mmoles) and methanol (30 ml) was refluxed for 24 hours. After cooling to room temperature, the mixture was filtered and washed with chloroform (10 ml). The combined filtrate was evaporated under reduced pressure. The resulting residue was dissolved in water and the solution was then neutralized with diluted hydrochloric acid solution (15%). The solution was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give **7** as pink powder, mp 79-81°; ir (potassium bromide): 2950, 1660, 1630, 1570, 1495, 1419, 1360, 1320, 1280, 1210, 1170, 1120, 1030 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.62 (s, 3H), 3.86 (s, 3H), 4.03 (s, 3H), 4.08 (s, 3H) ppm (s, 3H); ^{13}C nmr (deuteriochloroform): δ 38.4, 54.0, 59.8, 60.5, 140.3, 142.6, 148.9, 158.3 ppm.

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.11; H, 6.24; N, 14.13.

Methoxylation of **3.**

Method H.

A mixture of **3** (0.104 g, 0.47 mmoles), potassium carbonate (0.049 g, 0.354 mmoles) and methanol (20 ml) was refluxed for 4.5 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was triturated in ethyl acetate. The mixture was filtered, and the filtrate was evaporated under reduced pressure to give **6** that was identical with **6** obtained by Methods B - F.

Reduction of **1** and **2** [7].

Method I.

A mixture of **1** (13.4 mmoles) or **2** (0.605 mmoles), iron powder (3 g for **1**, 0.2 g for **2**), ammonium chloride (6 g for **1**, 0.19 g for **2**), water (100 ml for **1**, 10 ml for **2**) and chloroform (100 ml for **1**, 20 ml for **2**) was stirred for 21 hours for **1** or 12 hours for **2** at room temperature. The mixture was applied to the top of an open-bed silica gel column (2.5 x 9 cm). Fractions containing the product were combined and evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexane (1:3, v/v) to give the corresponding 6-amino derivatives **8** or **9**.

6-Amino-4,5-dichloro-2-methylpyridazin-3-one (**8**).

Mp 194-195° (lit. mp 193-195° [7]); ir (potassium bromide): 3500, 3350, 2980, 1650, 1620, 1590, 1460, 1360, 1215, 1040, 900 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.59 (s, 3H), 4.42 ppm (bs, NH2, D_2O exchangeable); ^{13}C nmr (deuteriochloroform): δ 40.5, 129.3, 136.2, 144.1, 155.2 ppm.

Anal. Calcd. for $C_5H_5N_3OCl_2$: C, 30.95; H, 2.60; N, 21.66. Found: C, 31.10; H, 2.80; N, 21.74.

6-Amino-4-chloro-5-methoxy-2-methylpyridazin-3-one (**9**).

Mp 84-85°; ir (potassium bromide): 3530, 2950, 2860, 1630, 1590, 1500, 1450, 1380, 1190 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.62 (s, 3H), 4.13, (s, 3H), 4.43 ppm (bs, NH_2, D_2O exchangeable); ^{13}C nmr (deuteriochloroform): δ 40.0, 61.0, 122.0, 144.2, 149.1, 157.8 ppm.

Anal. Calcd. for $C_6H_8N_3O_2Cl$: C, 38.01; H, 4.25; N, 22.16. Found: C, 38.23; H, 4.37; N, 22.29.

6-Amino-4-chloro-5-methoxy-2-methylpyridazin-3-one (**9**).

Method J.

A mixture of **8** (0.5 g, 2.58 mmoles), potassium carbonate (0.46 g, 3.35 mmoles) and methanol (10 ml) was refluxed for 2 hours. After cooling to room temperature, the mixture was filtered and washed with methanol (50 ml). The combined filtrate was evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:1, v/v) to give **9**. This product was identical with **9** that was prepared from **2** by the Method I.

5,6-Dimethoxy-2-methylpyridazin-3-one (**10**).

A mixture of **5** (0.24 g, 1.18 mmoles), Pd/C (0.2 g) and methanol (20 ml) was stirred for 7 hours under hydrogen atmosphere (using a toy balloon) at room temperature. The mixture was filtered using Celite 545 resin and washed with chloroform (30 ml). The combined filtrate was evaporated under reduced pressure. After dissolving the residue in water, the solution was neutralized with aqueous potassium carbonate solution (10%). The product was extracted with chloroform (30 ml). The organic solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give **10**. Recrystallization of a small sample from ethyl acetate/*n*-hexane (1:3, v/v) yielded an analytical sample, mp 108-109°; ir (potassium bromide): 3005, 2960, 1685, 1620, 1570, 1460, 1340, 1220, 1180, 1120, 1060, 1020, 960, 930, 840, 820 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.67 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 6.12 ppm (s, 1H); ^{13}C nmr (deuteriochloroform): δ 39.4, 54.1, 56.4, 98.7, 153.4, 155.5, 156.8 ppm.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.59; H, 6.14; N, 16.70.

4,6-Dimethoxy-2-methylpyridazin-3-one (**11**).

A mixture of **6** (0.25 g, 1.25 mmoles), Pd/C (0.2 g) and methanol (20 ml) was stirred for 40 hours at room temperature under hydrogen atmosphere (using a toy balloon). The mixture was filtered using Celite 545 resin and washed with methanol (30 ml). The combined filtrate was evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate/*n*-hexane (1:3, v/v) to give **11**, mp 133-134°; ir (potassium bromide): 3080, 2980, 2905, 1680, 1620, 1580, 1500, 1430, 1290, 1260, 1000 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.16 ppm (s, 1H); ^{13}C nmr (deuteriochloroform): δ 38.4, 54.5, 56.2, 104.9, 146.8, 153.5, 161.4 ppm.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.45; H, 6.12; N, 16.67.

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