# Synthesis of 3-Chloropyridazine-6-carboxylic Acid Hydrazide and Selective Hydrazinolysis of 3,6-Substituted Pyridazines

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**3-Chloropyridazine-6-carboxylic acid hydrazide (5) was synthesized by employing hydrazine monohydrate and methyl levulinate as starting materials through five steps, including hydrazinolysis. Selective hydrazinolysis of 3,6-substituted pyridazines was investigated.**

**Keywords** 3-chloropyridazine-6-carboxylic acid hydrazide; synthesis; hydrazinolysis; pyridazine derivative; chelating agent

Pyridazine derivatives have antihypertensive,[2)] antipyretic,[3)] analgesic,[3)] anticonvulsant,[4)] and anthelmintic activities,[5)] as well as amebiasis resistance,[6)] antitumor activity (carcinoma inhibition),[7,8)] growth-inhibitory activity against *Escherichia coli*, *Staphylococcus aureus* and *Shigella dyseuteriae*[9)] and activity against tubercle bacilli.[6)] Moreover, pyridazine derivatives have been reported to chelate transition metals such as silver, *etc.*[10)] Although many reports have appeared concerning the utility and preparation of these derivatives, previous preparations have been carried out by modifying commercial pyridazine and 3,6-dihydroxypyridazine, or by oxidation of a series of phthalazines. We have already synthesized 3-hydrazinopyridazine and 3-pyridazinecarboxylic acid hydrazide, and confirmed that they chelate metal ions such as nickel and aluminum. We developed detection methods for these metals by spectrophotometry and spectrofluorometry, using those compounds.[11)]

It is difficult to synthesize 3-chloropyridazine-6-carboxylic acid hydrazide (**5**) by known routes, because the maleic anhydrides having chloro and/or carboxylate substituents are not readily available. The purpose of this paper is to present a new synthetic pathway to **5** and to describe the selective hydrazinolysis of 3,6-substituted pyridazines.

**Hydrazinolysis at the 3,6-Positions** When 3-chloropyridazine-6-ethyl carboxylate (**4**) was reacted with hydrazine to form **5** at higher temperature than room temperature, 3-hydrazinopyridazine-6-ethyl carboxylate (**6**), 3-hydrazinopyridazine-6-carboxylic acid (**7**) and 3-hydrazinopyridazine-6-carboxylic acid hydrazide (**8**), were dominantly formed (Table I). Liebermann reported that when 3-pyridazone-6-ethyl carboxylate was chlorinated with $POCl_3$, 3-chloropyridazine-6-carboxylic acid was obtained, and when a mixture of 3-chloropyridazine-6-carboxylic acid and hydrazine was refluxed for 5 h, only the dihydrazide (**8**) was obtained.[12)] We investigated this difference in reaction products, paying particular attention to reaction temperature and substituent effect. In our investigation, when **4** and hydrazine were heated either directly at 100 °C or in ethanol under reflux, only **8** was obtained in nearly 100% yield. When the mixture was heated at 60 °C, **5**, **6**, **7** and **8** were obtained. Compound **7** and 3-hydroxypyridazine-6-carboxylic acid hydrazide (**9**) were obtained by hydrolysis of **6** and **5** with hydrochloric acid, respectively. Compounds **9** and **8** were also obtained by hydrazinolysis of **3** and **5**, respectively. On the other hand, reaction of the 6-carboxylic acids (**2** and **7**) with hydrazine hardly occurred, in contrast to Liebermann's method. A comparison of the reactions of **3**, **4** and **5** with hydrazine at the 3,6-positions suggested that the differences of reactivity depend on the electron density at the reactive site, such as carbonyl carbon, and the existence of an acidic proton such as a hydroxyl hydrogen. If an acidic proton exists in a substituent moiety, hydrazine, being a base, forms an acid–base pair with that substituent. The polarity and acidity of the reactive substituents both contribute to overall nucleophilicity, and higher nucleophilicity results in lower reactivity. In view of the effects of substituents and reaction temperature, selective hydrazinolysis was thought to be possible. If hydrazinolysis is required at the 6-position, then **3** and **4** should be used under mild conditions, namely below room temperature, as stated above. Conversely, if the 3-substituted pyridazine is required, then 3-chloropyridazine-6-carboxylic acid should be used as a precursor. If both the 3- and 6-positions are required to react with hydrazine, derivative **4** is used at 100 °C.

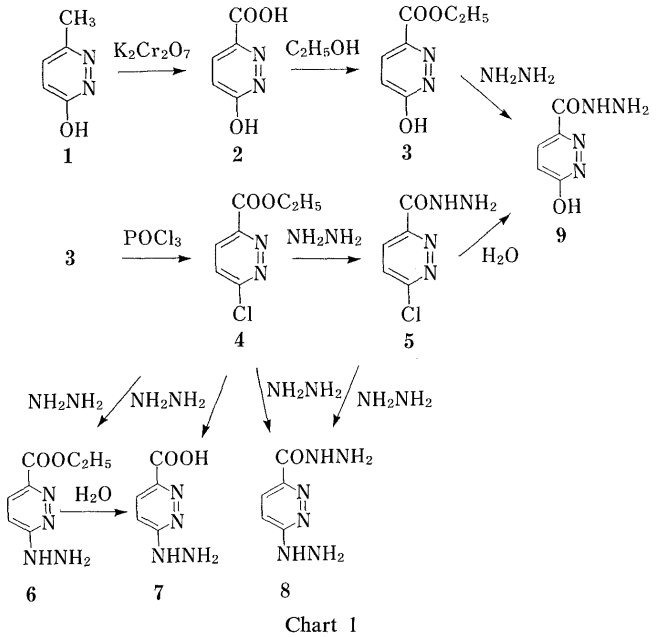


Chart 1

TABLE I. Products by Hydrazinolysis of **4** at Various Temperatures

| Temperature (°C) | Products | | | |
|---|---|---|---|---|
| ≧95 | | | | **8** (1) |
| 55—65 | **5** (0.37) | **6** (0.44) | **7** (0.15) | **8** (0.04) |
| 40—55 | **5** (0.77) | **6** (0.19) | **7** (0.04) | |
| Room temperature | **5** (1) | | | |

For an example, the ratio at each reaction temperature is shown in parentheses. Ratios were determined by column chromatography (see the text).

These results may be applicable to hydrazinolysis and amination of other aromatic compounds as well.

## Experimental

The title compound was synthesized by employing hydrazine and methyl levulinate as starting materials, as shown in Chart 1. Syntheses of **1** and **2** were performed by use of the modified Liebermann's method.[13]

The structure of each product was confirmed mainly by elemental analysis and mass spectrometry (MS). The melting point was measured on a Yanagimoto micro melting point apparatus without correction. The infrared (IR) spectra were recorded on a Hitachi 260-30 spectrometer. The $^1$H- and $^{13}$C-nuclear magnetic resonance (NMR) spectra were recorded with a JEOL JNM GX-400 ($^1$H, 400 MHz; $^{13}$C, 100 MHz) spectrometer. Chemical shifts are given on the $\delta$-scale (ppm downfield from tetramethylsilane as an internal standard). Elemental analyses of C, H and N were performed on a Yanagimoto MT-3 elemental analyzer. Electron-impact (EI) MS was run on a JEOL JMS D-300 mass spectrometer. Column chromatography was carried out on an open silica gel column (packing material, Wakogel C-200, Wako Pure Chemicals; column, 30 × 2 cm i.d.; solvents, dichloromethane: methanol = 100 : 0→ 0 : 100). The purity of the compound was roughly examined by thin layer chromatography (Wakogel B-5FM, Wako Pure Chemicals). Detection was made by short-wavelength ultraviolet light (254 nm).

**3-Hydroxy-6-methylpyridazine (1)** Light yellow plates. mp 123—124 °C. *Anal.* Calcd for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.50; H, 5.53; N, 25.36. MS *m/z*: 110 ($M^+$).

**3-Hydroxypyridazine-6-carboxylic Acid (2)** Colorless powder. mp 256—257 °C. *Anal.* Calcd for $C_5H_4N_2O_3$: C, 42.87; H, 2.88; N, 20.00. Found: C, 42.80; H, 3.10; N, 19.98. MS *m/z*: 140 ($M^+$).

**3-Hydroxypyridazine-6-ethyl Carboxylate (3)** A solution of **2** (8.6 g, 61 mmol) in 60 ml of hydrogen chloride in ethanol (hydrogen chloride gas generated by reacting sodium chloride with sulfuric acid was passed into ethanol in an ice bath) was refluxed for 14 h. The precipitate was filtered off and dried to give 5.4 g (52.5%) of **3** as green plates. mp 130—131 °C. *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.90; H, 4.85; N, 16.56. MS *m/z*: 168 ($M^+$).

**3-Chloropyridazine-6-ethyl Carboxylate (4)** A solution of **3** (5.4 g, 32 mmol) in phosphorus oxychloride (50.0 ml) was heated at 100 °C for 2 h. The solution was concentrated *in vacuo* to about 10 ml, and the residue was carefully added to 100 g of ice. The precipitate was filtered off and recrystallized from benzene to give 5.0 g (84.4%) of **4** as a colorless powder. mp 154—155 °C. *Anal.* Calcd for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; N, 15.01. Found: C, 45.01; H, 3.80; N, 14.92. MS *m/z*: 186 ($M^+$).

**3-Chloropyridazine-6-carboxylic Acid Hydrazide (5)** A solution of **4** (1.0 g, 5.4 mmol) and hydrazine anhydride (0.3 g, 9.4 mmol) in ethanol (100 ml) was allowed to stand at room temperature for 12 h. The precipitate was filtered off and recrystallized from benzene to give 0.9 g (96.3%) of **5** as colorless needles. mp 254—255 °C. IR (KBr): 3300, 3120, 3050, 1650, 1500, 1140, 1060, 930, 850, 750 cm$^{-1}$. *Anal.* Calcd for $C_5H_5ClN_4O$: C, 34.80; H, 2.92; N, 32.47. Found: C, 34.72; H, 2.95; N, 32.41. MS *m/z*: 172 ($M^+$), 141 ($M^+ - NHNH_2$), 137 ($M^+ - Cl$), 113 ($M^+ - CONHNH_2$), 78 (pyridazine).

**Separation of 5, 3-Hydrazinopyridazine-6-ethyl Carboxylate (6), 3-Hydrazinopyridazine-6-carboxylic Acid (7) and 3-Hydrazinopyridazine-6-carboxylic Acid Hydrazide (8)** A solution of **4** (1.0 g, 5.4 mmol) and hydrazine anhydride (0.5 g, 9.7 mmol) in ethanol (100 ml) was heated at 60 °C for 3 h. The reaction mixture was cooled in a refrigerator (5 °C) and the precipitate was filtered off. The filtrate was evaporated to dryness and the precipitate and residue were recrystallized from benzene to give 0.9 g of a mixture of **5**, **6**, **7** and **8** as light yellow needles. Chromatography was carried out to separate each hydrazide. Each colored fraction was collected and evaporated to dryness. The yields were 0.2 g (**5**, 21.5%), 0.29 g (**6**, 29.5%), 0.08 g (**7**, 9.6%) and 0.03 g (**8**, 3.3%), each as an amorphous powder.

**5**: *Anal.* Found for $C_5H_5ClN_4O$: C, 34.81; H, 2.93; N, 32.45. MS *m/z*: 172 ($M^+$), 141 ($M^+ - NHNH_2$), 137 ($M^+ - Cl$), 113 ($M^+ - CONHNH_2$), 78 (pyridazine).

**6**: $^1$H-NMR ($CD_3OD$): $\delta$; 1.40 (3H, t, $CH_3$), 4.43 (2H, q, $CH_2$), 4.89 (br s, $NHNH_2$), 7.19 (1H, d, C(5)-H), 7.96 (1H, d, C(4)-H). *Anal.* Calcd for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.53; N, 30.75. Found: C, 46.10; H, 5.50; N, 30.76. MS *m/z*: 182 ($M^+$), 154 ($M^+ - C_2H_5$), 138 ($M^+ - OC_2H_5$), 110 ($M^+ - COOC_2H_5$), 78 (pyridazine).

**7**: IR (KBr): 1700, 1300 cm$^{-1}$. $^1$H-NMR ($CD_3OD$): $\delta$; 5.23 (br s, $NHNH_2$), 7.19 (1H, d, C(5)-H), 8.19 (1H, d, C(4)-H). $^{13}$C-NMR ($CD_3OD$): $\delta$: 121.8 (d, C-5), 132.6 (d, C-4), 155.9 (s, C-6), 163.4 (s, COOH). *Anal.* Calcd for $C_5H_6N_4O_2 \cdot 3H_2O$: C, 28.85; H, 5.81; N, 26.91. Found: C, 28.65; H, 5.92; N, 26.72. MS *m/z*: 154 ($M^+$), 124 ($M^+ - NHNH_2$), 109 ($M^+ - COOH$), 78 (pyridazine).

**8**: *Anal.* Calcd for $C_5H_8N_6O$: C, 35.71; H, 4.80; N, 49.98. Found: C, 35.70; H, 4.92; N, 50.00. MS *m/z*: 168 ($M^+$), 137 ($M^+ - NHNH_2$), 109 ($M^+ - CONHNH_2$), 78 (pyridazine).

**Hydrolysis of 5 and 6** Hydrochloric acid solution (10%, 50 ml) containing **5** or **6** (1.0 g) was refluxed for 2.5 h. The solvent was evaporated off and the residue gave 0.5 g (55.8%) of 3-hydroxypyridazine-6-carboxylic acid hydrazide (**9**) and 0.4 g (44.7%) of **7** as light yellow plates, respectively.

**7**: *Anal.* Found for $C_5H_6N_4O_2 \cdot 3H_2O$: C, 28.86; H, 5.82; N, 26.90. MS *m/z*: 154 ($M^+$), 124 ($M^+ - NHNH_2$), 109 ($M^+ - COOH$), 78 (pyridazine).

**9**: mp 234—235 °C. *Anal.* Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.95; H, 3.90; N, 36.30. MS *m/z*: 154 ($M^+$), 137 ($M^+ - OH$), 123 ($M^+ - NHNH_2$), 95 ($M^+ - CONHNH_2$), 78 (pyridazine).

**Hydrazinolysis of 3** A solution of **3** (1.0 g, 6.0 mmol) and hydrazine anhydride (0.5 g, 9.7 mmol) in ethanol (60 ml) was heated under reflux for 3 h. The precipitate was filtered off and dried to give 0.8 g (87.3%) of **9** as light yellow needles. *Anal.* Found for $C_5H_6N_4O_2$: C, 38.74; H, 3.96; N, 36.13. MS *m/z*: 154 ($M^+$), 137 ($M^+ - OH$), 123 ($M^+ - NHNH_2$), 95 ($M^+ - CONHNH_2$), 78 (pyridazine).

**Hydrazinolysis of 5** A solution of **5** (1.0 g, 5.8 mmol) and hydrazine anhydride (2.0 g, 38.9 mmol) was heated under reflux for 8 h. The precipitate was filtered off and recrystallized from ethanol to give 0.5 g (51.2%) of **8**. *Anal.* Found for $C_5H_8N_6O$: C, 35.71; H, 4.79; N, 49.99. MS *m/z*: 168 ($M^+$), 137 ($M^+ - NHNH_2$), 109 ($M^+ - CONHNH_2$), 78 (pyridazine).

## References and Notes


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