Notes

Efficient Synthesis of 4,5,6-Trisubstituted-2-aminopyrimidines

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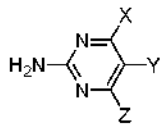
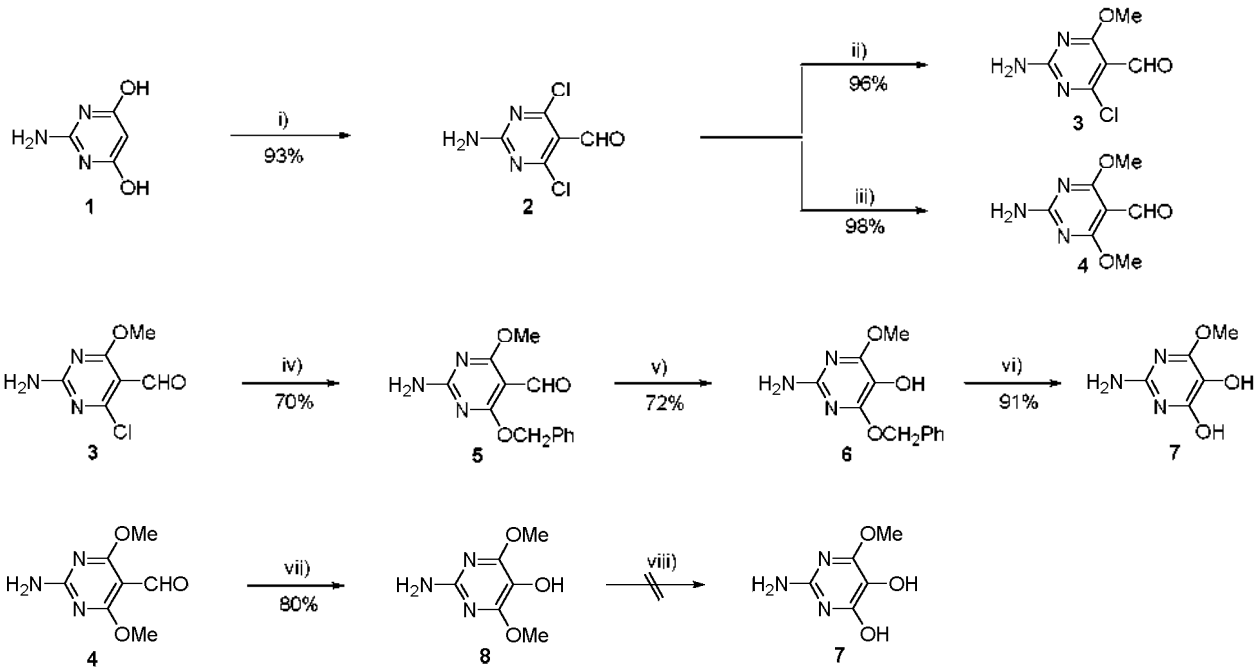
Multisubstituted-2-aminopyrimidines exhibit important pharmacological[1-5] and herbicidal[6-9] properties.[1-9] Thus, new methods for the functionalization of substituted 2-aminopyrimidines have attracted considerable attention in search for a rapid entry these heterocycles and high-throughput screening of their diverse biological properties. In connection with our research program for the evaluation of the biological properties of 4,5,6-trisubstituted-2-aminopyrimidines, we required some 2-amino-4,5,6-trisubstituted-pyrimidines containing the formyl or the hydroxy group at C-5 position and the halogen, the methoxy or the hydroxyl group at C-4 and C-6 positions.



X = Cl, OMe Y = CHO, OH
Z = Cl, OH, OMe

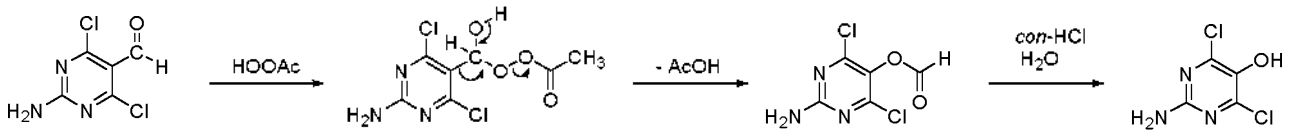
Figure 1. 2-Amino-4,5,6-trisubstituted-pyrimidines.

The recent papers described relatively tedious methods for the synthesis of 2-amino-substituted-pyrimidines.[10] However, there have not been the methods available to produce 4,5,6-trisubstituted derivatives bearing the hydroxyl groups at C-5 position by the direct functionalization of 2-aminopyrimidines. Therefore, we attempted to develop of new route for the 5-hydroxy-4,6-disubstitued derivatives. Herein, we reported effi-



i) $POCl_3$, DMF, ii) K_2CO_3 (1 equiv.), MeOH, iii) K_2CO_3 (2 equiv.), MeOH.iv) $PhCH_2OH$, NaH, DMSO, v) (a)AcOOH, AcOH, (b) *conc*-HCl, H_2O, MeOH, vi) Pd/C, H_2, MeOH, vii) (a)AcOOH, AcOH, (b) *conc*-HCl, H_2O, MeOH, viii) BBr_3, CH_2Cl_2.

Scheme 1. Synthesis of 2-amino-4,5,6-trisubstituted-pyrimidines



Scheme 2. Plausible mechanism of the conversion of formyl group to hydroxyl group

cient synthetic routes of some 4,5,6-trisubstituted-2-aminopyrimidines.

Firstly, we attempted the conversion of the formyl group to hydroxyl group after the introduction of the formyl group at C-5 position. According to the literatures,[11-14] *N,N*-Dimethylformamide/phosphorus oxychloride is a good chlorination or formylation agent. Therefore, we attempted concurrently the chlorination and the formylation of 2-amino-4,6-dihydroxypyrimidine (**1**) using DMF/$POCl_3$. Reaction of compound **1** with *N,N*-dimethylformamide/phosphorus oxychloride gave 5-formylpyrimidine **2** in excellent yield.[11]

We also tried the selective methoxylation of **2** using MeOH/K_2CO_3 system, which is a good methoxylation agent for the nitrogen heterocycles.[12,15] Compound **2** was treated with one equivalent of potassium carbonate in methanol to give selectively monomethoxy derivative **3** in 96% yield. Methoxylation of **2** with excess potassium carbonate in methanol also afforded dimethoxyaminopyrimidine **4** in 98% yields. Reaction of **3** with benzyl alcohol in the presence of sodium hydride in DMSO gave compound **5** in 70% yields. On the other hand, we attempted the conversion of formyl group of compounds **4** and **5** to hydroxyl group. Compounds **4** and **5** were oxidized with peroxyacetic acid and then hydrolyzed with *conc*-hydrochloric acid to give 5-hydroxyaminopyrimidien **6** (72%) and **8** (80%) in one-pot. Mills, *et al.*[16] also reported the conversion of 2,3,4-tri-*O*-benzyloxybenzaldehyde to the corresponding hydroxyl derivative using 3-chloroperoxybenzoic acid. The plausible mechanism of this conversion shows in Scheme 2. Debenzylation of **6** with Pd/C/H_2 in methanol afforded 2-amino-4,5-dihydroxy-6-methoxypyrimidine (**7**) in 91% yield. Compound **7**, however, did not prepare by the demethylation of **8** with BBr_3 in methylene chloride.

The structures of the synthetic compounds were established by IR, NMR and elemental analysis (and HRMS for **7**). The infrared spectra of **2** - **8** show the absorption bands of amino group for **2** - **8** and aldehyde for **2** - **5**. In the NMR spectra of **2** - **8**, the proton signals of amino group were detected in the range of δ 5.60 - 8.10 ppm. The proton and carbon signals of aldehyde were detected in the ^1H and ^{13}C spectra of **2** - **5**. The hydroxyl group of **6** - **8** were also detected in the IR, ^1H NMR and ^{13}C NMR spectra. In addition, we determined the molecular weight of **7** by the HRMS.

In summary, we have described the concurrent chloroformylation, selective methoxylation and the easy conversion of the formyl group to hydroxyl group for 2-amino-4,6-dihydroxypyrimidine (**1**). 2-Amino-4,5-dihydroxy-6-methoxypyrimidine (**7**) was firstly synthesis from 2-amino-4,6-dihydroxypyrimidine (**1**) *via* 5 steps. 2-Amino-4,6-dichloro- 5-formylpyrimidine (**2**) was concurrently prepared by the reaction of **1** with Vilsmeire reagent. By controlling of amount of K_2CO_3 in methanol solvent, 4-monomethoxy- and 4,6-dimethoxy-2-amino-5-formylpyrimidines were selectively prepared from 2-amino-4,6-dichloro-5-formylpyrimidine (**2**) in excellent yield. MeOH/K_2CO_3 system is a useful methoxylation agent in the methoxylation of halopyrimidine. The conversion of formyl group of compounds **4** and **5** to hydroxyl group was achieved successfully using peroxyacetic acid in one-pot. Further reaction including the synthesis of various derivatives and the biological activity is currently under investigation.

Experimental Section

General. Melting points were determined with a capillary apparatus and uncorrected. NMR spectra were recorded on a 300 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a Shimadzu FT-IR & 8400S spectrophotometer. Mass spectra were obtained on a GC Mate 2, JEOL. Elemental analyses were performed with a Perkin Elmer 240C. The open-bed chromatography was carried out on silica gel (70 ~ 230 mesh, Merck) using gravity flow. The column was packed with slurries made from the elution solvent.

2-Amino-4,6-dichloro-5-formylpyrimidine (2): After adding dropwise *N,N*-dimethylformamide (2.45 mL, 31.49 mmol) to a solution of phosphorus oxychloride (7.49 ml, 81.89 mmol) at 5 - 10 °C, compound **1** (2 g, 15.74 mmol) was added slowly. The mixture was stirred for 30 minutes at room temperature and then for 24 hours at 70 °C. After cooling to room temperature, the mixture was poured slowly into ice water. The resulting solution was placed for 24 hours at room temperature. The resulting yellow crystals were filtered, washed with water and then ethyl acetate, and dried in air to give the product **2** in 93% (2.8 g) yield; mp > 250 °C. IR (KBr) 3422, 3320, 3214, 3146, 2881, 1671, 1641, 1538, 1507, 1471, 1358, 1294, 1125, 858, 781 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 2H, D_2O exchangeable), 10.1 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 113.35, 162.13, 163.63, 185.18, 206.96. Elemental analysis calcd for $C_5H_3Cl_2N_3O$: C, 31.28; H, 1.57; N, 21.89. Found: C, 31.30; H, 1.62; N, 21.91.

2-Amino-4-chloro-5-formyl-6-methoxypyrimidine (3): A mixture of **2** (0.15 g, 0.78 mmol), potassium carbonate (0.11 g, 0.78 mmol) and methanol (20 mL) was refluxed for 20 minutes. After evaporating the solvent under reduced pressure, the residue was triturated in water (30 mL). The resulting precipitates were filtered, washed with water and dried in air to give the yellow crystal **3** in 96% (0.14 g) yields; mp 108 - 110 °C. IR (KBr) 3457, 3341, 3241, 2883, 1653, 1622, 1591, 1537, 1462, 1369, 1319, 1227, 1105, 1044, 988, 934 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.90 (s, 3H), 8.10 (bs, 2H, D_2O exchangeable), 9.90 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.00, 104.57, 162.93, 162.99, 171.05, 184.14. Elemental analysis calcd for $C_6H_6ClN_3O_2$: C, 38.42; H, 3.22; N, 22.40.

Found: C, 38.47; H, 3.25; N, 22.47.

2-Amino-5-formyl-4,6-dimethoxypyrimidine (4): A mixture of **2** (0.15 g, 0.78 mmol), potassium carbonate (0.21 g, 1.56 mmol) and methanol (20 mL) was refluxed for 1.5 hours. After evaporating the solvent under reduced pressure, the residue was triturated in water (30 mL). The resulting precipitates were filtered, washed with water and dried in air to give the yellow crystal **4** in 98% (0.138 g) yields; mp 220 - 221 °C. IR (KBr) 3339, 3112, 3024, 2954, 2881, 1658, 1570, 1533, 1505, 1462, 1375, 1258, 1196, 1130, 1092, 1040, 824, 796 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.90 (s, 6H), 7.60 (bs, 2H, D_2O exchangeable), 9.90 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 54.34, 94.68, 163.82, 171.60, 182.75, 199.42. Elemental analysis calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.96; H, 4.98; N, 22.97.

2-Amino-4-benzyloxy-5-formyl-6-methoxypyrimidine (5): After stirring a solution of dry DMSO (30 mL) and sodium hydride (1.9 g, 47.97 mmol) under nitrogen atmosphere, benzyl alcohol (3.6 mL, 35.18 mmol) was added. The mixture was stirred for 1 hour at room temperature. After adding **3** (6 g, 31.98 mmol) to the mixture, the reaction mixture was stirred for 1.5 hours at 80 °C. After cooling to room temperature, methylene chloride (150 mL) and water (80 mL) were added to the reaction mixture. The organic layer was separated and dried on anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of silica gel column (16 × 4.5 cm). The column was eluted with THF/*n*-hexane (2:3, v/v). Fractions containing compound **5** were combined, and the solvent was evaporated under reduced pressure to afford **5** in 70% (5.79 g) yields; mp 134 - 135 °C. IR (KBr) 3569, 3499, 3453, 3360, 3195, 3100, 2994, 2881, 1668, 1641, 1573, 1537, 1498, 1459, 1416, 1371, 1343, 1258, 1200, 1150, 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.9 (s, 3H), 5.40 (s, 2H), 5.60 (bs, 2H, D_2O exchangeable), 7.30-7.40 (m, 5H), 10.20 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.50, 68.41, 96.08, 127.62, 128.05, 128.51, 136.12, 163.19, 171.65, 171.95, 184.87. Elemental analysis calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.26; H, 5.10; N, 16.27.

2-Amino-4-benzyloxy-5-hydroxy-6-methoxypyrimidine (6): A mixture of **5** (3.07 g, 11.84 mmol), peroxyacetic acid (2.5 mL, 32%, 11.84 mmol) and acetic acid (47 mL) was stirred for 0.5 hours at room temperature. After evaporating the solvent under reduced pressure, methanol (24 mL), water (12 mL) and *conc*-HCl (2.4 mL) were added to the residue. The resulting mixture was stirred for 15 minutes at room temperature, and water (118 mL) was then added. The solution was neutralized to pH 7 using aqueous NaOH (40%). The product was extracted with ethyl acetate (300 mL). The organic layer was dried on anhydrous magnesium sulfate. After evaporating the solvent, the residue was applied to the top of silica gel column (15 × 4.5 cm). The column was eluted with THF/*n*-hexane (2:3, v/v). Fractions containing the product were combined and the solvent was evaporated under reduced pressure to give **6** in 72% (2.1 g) yields; mp 118 - 120 °C. IR (KBr) 3509, 3385, 3256, 3194, 3053, 3024, 2984, 2944, 1620, 1576, 1449, 1362, 1144 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 5.90 (bs, 2H, D_2O exchangeable), 7.31-7.45 (m, 5H), 7.40 (s, 1H, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.54, 67.10, 114.84, 128.15, 128.34, 128.74, 137.76, 155.19, 159.77, 160.76. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_3$ 247.0957, Found: *m/z* 247.0951. Elemental analysis calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.32; H, 5.34; N, 17.02.

2-Amino-4,5-dihydroxy-6-methoxypyrimidine (7): A solution of **6** (0.7 g, 2.83 mmol), Pd/C (10%, 0.5 g) and methanol (80 mL) was stirred for 1 hour under hydrogen atmosphere (using toy balloon) at room temperature. After filtering by Celite 545, the solvent was evaporated under reduced pressure to give **7** in 91% (0.4 g) yields; mp > 250 °C. IR (KBr) 3323, 3230, 3190, 2992, 2948, 1649, 1622, 1595, 1459, 1389, 1361, 1319, 1258, 1217, 1120, 1072 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.70 (s, 3H), 6.20 (bs, 2H, D_2O exchangeable), 7.20 (bs, 1H, D_2O exchangeable), 10.80 (bs, 1H, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.58, 116.09, 148.84, 156.86, 159.52. HRMS(EI): Exact mass calcd for $C_5H_7N_3O_3$ 157.0487. Found: *m/z* 157.0480. Elemental analysis calcd for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.27; H, 4.54; N, 26.79.

2-Amino-5-hydroxy-4,6-dimethoxypyrimidine (8): A mixture of **4** (1.37 g, 7.5 mmol), peroxyacetic acid (1.6 mL, 32%, 7.5 mmol) and acetic acid (30 mL) was stirred for 1 hour at 50 °C. After evaporating the solvent under reduced pressure, methanol (5 mL), water (7.5 mL) and *conc*-HCl (1.5 mL) were added to the residue. The resulting mixture was stirred for 15 minutes, and water (75 mL) was then added. The solution was neutralized to pH 7 using aqueous NaOH (40%). The product was extracted with ethyl acetate (150 mL). The organic layer was dried on anhydrous magnesium sulfate. After evaporating the solvent, the residue was applied to the top of silica gel column (17 × 3 cm). The column was eluted with THF/*n*-hexane (1:1, v/v). Fractions containing the product were combined and the solvent was evaporated under reduced pressure to give **8** in 80% (1.04 g) yields; mp > 250 °C. IR (KBr) 3486, 3466, 3375, 3239, 3008, 2986, 2957, 2895, 1630, 1576, 1478, 1456, 1383, 1330, 1228, 1190 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 6H), 5.90 (bs, 2H, D_2O exchangeable), 7.60 (s, 1H, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.59, 114.85, 155.26, 160.35. Elemental analysis calcd for $C_6H_9N_3O_3$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.08; H, 5.34; N, 24.59.

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