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Studies on Pyrimidine Derivatives. XXIX.[1] Synthesis of Pyrimidines fused with Five-membered Heterocycles by Cross-coupling of 5-Iodopyrimidines with Phenylacetylene and Styrene

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2,4-Dimethyl-6-phenyl-furo- and -thieno-[2,3-*d*]-pyrimidine were synthesized by cross-coup ing of 2,6-dim< thyl-5-iodopyrimidines with phenylacetylene in the presence of palladium catalyst, followed by cyclization of the resulting phenylethynylpyrimidines. 2,4-Dimethyl-6-phenyl[2,3-*d*]pyrimidine was also synthesized by the thermal decomposition of 4-azido-2,6-dimethyl-5-styrylpyrimidine, which was obtained from the 4-chloro derivative.

Keywords——palladium catalyst; cross-coupling reaction; phenylacetylene; styrene; 5-iodopyrimidine; furo[2,3-*d*]pyrimidine; thieno[2,3-*d*]pyrimidine; pyrrolo[2,3-*d*]pyrimidine

In the preceding paper of this series,[1] the synthesis of various types of pyridopyrimidines through the cross-coupling of halopyrimidines with α,β-unsaturated esters or phenylacetylene was reported. These results stimulated us to investigate the method more extensively. The present paper deals with the synthesis of fused pyrimidine ring systems such as furo[2,3-*d*]-pyrimidine, thieno[2,3-*d*]pyrimidine, and pyrrolo[2,3-*d*]pyrimidine.

After a solution of 5-iodo-2,6-dimethyl-4(3*H*)-pyrimidinone (**1**) and phenylacetylene in triethylamine containing a catalytic amount of bis(triphenylphosphine)palladium(II) dichloride and cuprous iodide had been heated at 50°C for 24 h, 2,4-dimethyl-5-phenylethynyl-4(3*H*)-pyrimidinone (**2**) was isolated by the usual work-up. On heating in triethylamine under reflux, **2** was readily cyclized to 4,6-dimethyl-2-phenylfuro[2,3-*d*]pyrimidine (**3**). Treatment of **3** with excess phosphorus pentasulfide failed to give the corresponding thieno[2,3-*d*]pyrimidine, while the same treatment of **2** gave 4,6-dimethyl-2-phenylthieno[2,3-*d*]pyrimidine (**4**) in 75% yield. Further, 4-chloro-2,6-dimethyl-5-phenylethynylpyrimidine (**6**) was also transformed into **4** in good yield by reaction with sodium hydrosulfide in boiling ethanol. In this route, the starting compound (**6**) was synthesized by the reaction of **2** with phosphoryl chloride and by the cross-coupling reaction of 4-chloro-5-iodo-2,6-dimethylpyrimidine (**5**) with phenylacetylene in 72 and 66% yields, respectively.

In the above synthesis of **3** and **4**, the final ring-closure reactions are due to the addition of a hydroxyl or mercapto group at the 4-position of the pyrimidine ring to the 5-phenylethynyl group. Accordingly, in order to prepare the corresponding pyrrolo[2,3-*d*]pyrimidine in a similar fashion, **6** was heated with ethanolic ammonia at 120°C in a sealed tube, but the product obtained in 75% yield was 4-amino-2,6-dimethyl-5-phenylethynylpyrimidine (**7**), instead of the desired 4,6-dimethyl-2-phenylpyrrolo[2,3-*d*]pyrimidine (**8**). The cyclization of **7** to **8** was tried under various conditions as shown in Chart 1, but **7** was always recovered unchanged.

Further attempts were made to synthesize **8**. First, **5** was treated with styrene under usual olefin-coupling conditions, because 4-chloro-5-iodopyrimidines are known to under cross-coupling at the 5-position.[2] However, the yield of 4-chloro-2,6-dimethyl-5-styrylpyrimidine (**10**) from 5 was unsatisfactory (32%), so an alternative route was then devised for the improved synthesis of **10**. Thus, **1** reacted with styrene under the usual conditions for the olefin-coupling reaction to give 2,6-dimethyl-5-styryl-4(3*H*)-pyrimidinone (**9**), the dehydroxy-chlorination of which afforded **10**. The overall yield of **10** from **1** *via* **9** was 56%.

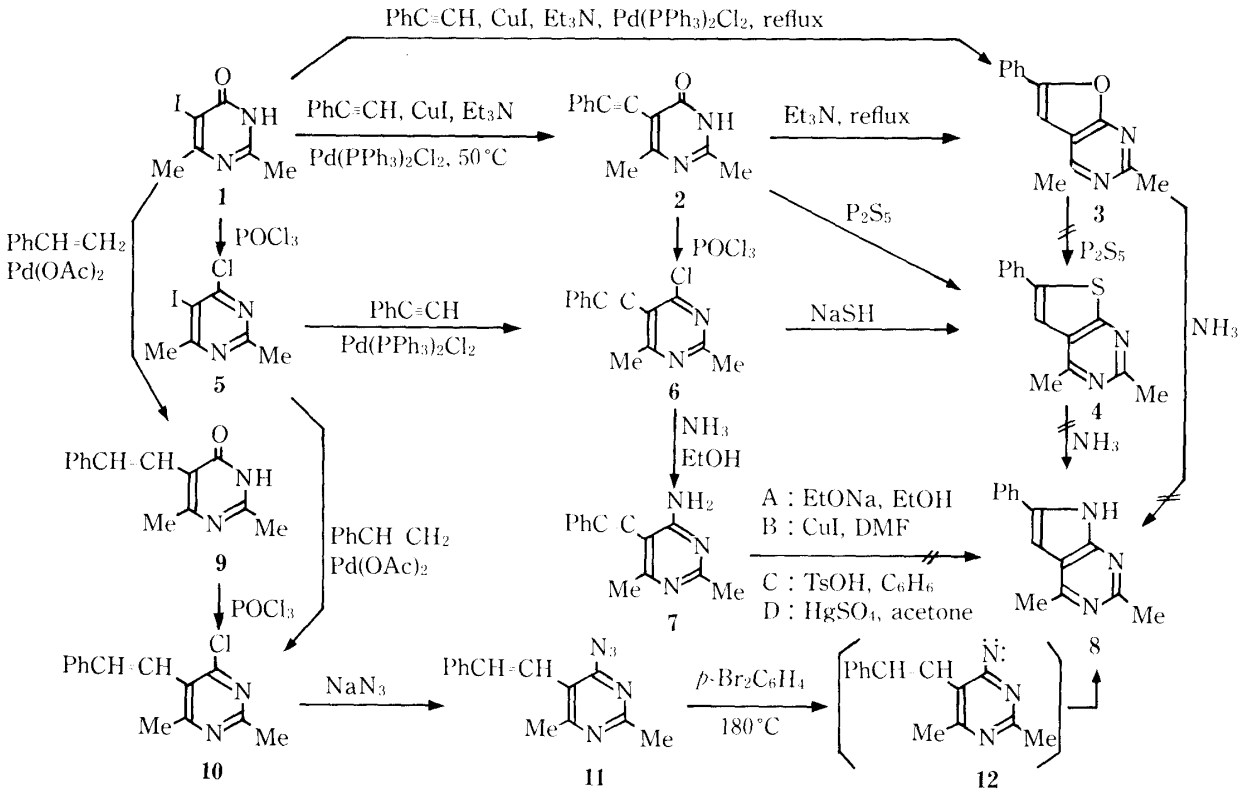

Chart 1

4-Chloro-2,6-dimethyl-5-styrylpyrimidine (**10**) thus obtained reacted with sodium azide in ethanol under reflux to give the corresponding azide (**11**). When **11** was heated at 180°C for 30 min in *p*-dibromobenzene, **8** was isolated in good yield. A pyrimidinenitrene (**12**) is probably an intermediate of the reaction. The proton magnetic resonance (PMR) spectrum of **8** was quite similar to those of **3** and **4**.

In the present work, the synthesis of three kinds of pyrimidine fused with a monohetero-five-membered ring was achieved with experimental simplicity. In the pyridine and pyrimidine series, the olefin- and acetylene-coupling reactions at the *β*-position are known to have generality,[3] so the reactions described in this paper may be suitable for the synthesis of various purine-like compounds.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. PMR spectra were taken at 60 MHz with a JEOL LMN-PMX 60 spectrometer. Chemical shifts are expressed in δ value. The following abbreviations are used: s=singlet, d=doublet, and m=multiplet.

2,6-Dimethyl-5-phenylethynyl-4(3*H*)-pyrimidinone (**2**)——A mixture of 2,6-dimethyl-5-iodo-4(3*H*)-pyrimidinone (**1**) (2.5 g, 0.01 mol), phenylacetylene (1.2 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (20 ml) was stirred for 24 h at 50°C. After removal of the solvent, the residue was diluted with H_2O. The resulting mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 and AcOEt as eluents. The AcOEt eluate gave colorless prisms, mp 213—214°C, which were recrystallized from acetone. Yield 1.4 g (63%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2600 (br), 1660. PMR ($CDCl_3$): 2.55 (6H, s), 3.70—4.90 (1H, br), 7.25—7.65 (5H, m). *Anal.* Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.49. Found: C, 75.12; H, 5.50; N, 12.23.

2,4-Dimethyl-6-phenylfuro[2,3-*d*]pyrimidine (3)——i) A mixture of **1** (2.5 g, 0.01 mol), phenylacetylene (1.2 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (20 ml) was refluxed for 24 h. After

removal of the solvent, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave yellow needles, mp 104—105°C. Yield 1.6 g (70%).

ii) A mixture of **2** (1.1 g, 0.005 mol) and Et_3N (10 ml) was refluxed for 12 h. After removal of the solvent, the residue was purified by Al_2O_3 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave yellow needles, mp 104—105°C. Yield 0.9 g (80%). PMR ($CDCl_3$): 2.63 (3H, s), 2.70 (3H, s), 6.86 (1H, s), 7.25—7.96 (5H, m). *Anal.* Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.00; H, 5.42; N, 12.31.

4-Chloro-2,6-dimethyl-5-phenylethynylpyrimidine (6)——i) A mixture of 4-chloro-2,6-dimethyl-5-iodopyrimidine (**5**) (2.7 g, 0.01 mol), phenylacetylene (1.2 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (20 ml) was stirred for 24 h at room temperature. After removal of the solvent, the residue was diluted with H_2O. The resulting mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave colorless needles, mp 75—76°C. Yield 1.6 g (66%).

ii) A mixture of **2** (1.1 g, 0.005 mol) and $POCl_3$ (10 ml) was refluxed for 1.5 h. The mixture was concentrated under reduced pressure, and the residue was poured into ice-water. The resulting mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by Al_2O_3 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave colorless needles, mp 75—76°C. Yield 0.87 g (72%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250. PMR ($CDCl_3$): 2.70 (6H, s), 7.15—7.80 (5H, m). *Anal.* Calcd for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; Cl, 14.61; N, 11.54. Found: C, 69.32; H, 4.60; Cl, 14.50; N, 11.33.

2,4-Dimethyl-6-phenylthieno[2,3-*d*]pyrimidine (4)——i) An EtOH–EtONa solution (20 ml; Na, 0.35 g, 0.015 g atom) of **6** (1.2 g, 0.005 mol) was saturated with H_2S gas, and the mixture was refluxed for 1.5 h. After removal of the solvent, the residue was diluted with H_2O, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from hexane to give colorless needles, mp 81—82°C. Yield 1.0 g (83%).

ii) A mixture of **2** (1.1 g, 0.005 mol), P_2S_5 (1.7 g, 0.0075 mol), and pyridine (10 ml) was refluxed for 2 h. After removal of the pyridine under reduced pressure, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by Al_2O_3 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave colorless needles, mp 81—82 °C. Yield 0.9 g (75%). PMR ($CDCl_3$): 2.57 (6H, s), 7.20—7.93 (6H, m). *Anal.* Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.65; S, 13.35. Found: C, 70.19; H, 4.97; N, 11.61; S, 13.26.

4-Amino-2,6-dimethyl-5-phenylethynylpyrimidine (7)——An EtOH solution (5 ml) of **6** (1.2 g, 0.005 mol) was saturated with NH_3 gas, and the mixture was heated at 120°C in a sealed tube for 12 h. After removal of the solvent, the residue was diluted with H_2O. The resulting mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from C_6H_6 to give yellow needles, mp 163—164°C. Yield 0.84 g (75%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3400, 2240. PMR ($CDCl_3$): 2.50 (3H, s), 2.55 (3H, s), 5.65 (2H, s), 7.20—7.70 (5H, m). *Anal.* Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.14; H, 5.84; N, 18.81.

2,6-Dimethyl-5-styryl-4(3*H*)-pyrimidinone (9)——A mixture of **1** (2.5 g, 0.01 mol), styrene (1.2 g, 0.012 mol), $Pd(OAc)_2$ (60 mg), and Et_3N (5 ml) was heated at 120°C in a sealed tube for 24 h. After removal of the solvent, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. Recrystallization from acetone gave colorless needles, mp 242—243°C. Yield 1.5 g (66%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2800 (br), 1660. PMR ($CDCl_3$): 2.50 (6H, s), 7.03 (1H, d, J=17.0 Hz), 7.19—7.65 (5H, m), 7.93 (1H, d, J=17.0 Hz), 13.50 (1H, s). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.40; H, 6.26; N, 12.25.

4-Chloro-2,6-dimethyl-5-styrylpyrimidine (10)——i) A mixture of **9** (1.1 g, 0.005 mol) and $POCl_3$ (10 ml) was refluxed for 1.5 h. The mixture was concentrated under reduced pressure, and the residue was poured into ice-water. The resulting mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was purified by Al_2O_3 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave colorless needles, mp 84—86°C. Yield 1.0 g (85%).

ii) A mixture of **5** (2.7 g, 0.01 mol), styrene (1.2 g, 0.012 mol), $Pd(OAc)_2$ (60 mg), and Et_3N (5 ml) was heated at 120°C in a sealed tube for 24 h. After removal of the solvent, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. Recrystallization from hexane gave colorless needles, mp 84—86°C. Yield 0.8 g (32%). PMR ($CDCl_3$): 2.60 (3H, s), 2.65 (3H, s), 6.90 (1H, s), 6.93 (1H, s), 7.25—7.70 (5H, m). *Anal.* Calcd for $C_{14}H_{13}ClN_2$: C, 68.72; H, 5.35; Cl, 14.48; N, 11.45. Found: C, 68.80; H, 5.42; Cl, 14.35; N, 11.33.

4-Azido-2,6-dimethyl-5-styrylpyrimidine (11)——A mixture of **10** (1.2 g, 0.005 mol), NaN_3 (0.4 g, 0.006 mol), and EtOH (10 ml) was refluxed for 1 h. After removal of the solvent, the residue was diluted with H_2O, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from MeOH to give colorless needles, mp 181—182°C (dec.). Yield 1.1 g (90%). PMR ($CDCl_3$): 2.80 (3H, s), 3.10 (3H, s), 7.22 (1H, d, J=17.0 Hz), 7.15—7.95 (5H, m), 8.53 (1H, d, J=17.0 Hz). *Anal.* Calcd for $C_{14}H_{15}N_5$: C, 66.91; H, 5.21; N, 27.87. Found: C, 67.12; H, 5.19; N, 27.83.

2,4-Dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine (8)——A mixture of **11** (0.6 g, 0.0025 mol) and *p*-dibromobenzene (5 g) was heated at 180°C for 0.5 h. The mixture was diluted with C_6H_6 and extracted with 3 N HCl. The aqueous solution was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from ether to give colorless needles, mp 215—216°C. Yield 0.4 g (70%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420. PMR ($CDCl_3$): 2.60 (3H, s), 2.75 (3H, s), 6.75 (1H, s), 7.21—7.90 (5H, m), 11.20 (1H, s). *Anal.* Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.42; H, 5.75; N, 18.65.

References and Notes

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