The Alkylation of 6-Chloropurine with Alcohols by Mitsunobu Reaction[1)]

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A general procedure has been developed for the preparation of 9-alkylated adenines by the Mitsunobu reaction between 6-chloropurine and several alcohols, followed by the replacement of the chlorine with ammonia. A lesser amount of the 7-alkylpurines was also obtained, irrespective of the alcohol used.

Keywords Mitsunobu reaction; 6-chloropurine; 9-substituted purine; 7-substituted purine; alkylation; adenine

One of the research interests in this laboratory has been the synthesis of novel nucleoside analogs in which the carbohydrate moiety is replaced with a variety of cycloalkanes, cycloalkenes and their substituted derivatives.[2)] Thus far, we have reported the synthesis and biological evaluation of purine- and pyrimidine-type nucleosides having three-,[3)] four-,[4)] and five-membered carbocycles in place of the sugar moiety.[5)] For the synthesis of these compounds, we used the corresponding cycloalkylamines as intermediates and constructed purine and pyrimidine rings by the use of well-established ring formation reactions. Because some of these compounds have interesting biological activities[3,5)] and the construction of a purine moiety from an amino function by the known method is rather tedious, it was desired to elaborate a simpler method for construction of the purine moiety which would also be applicable to the synthesis of these nucleosides as enantiomerically pure compounds (EPC).

We now wish to report a method for synthesis of 9-alkylated purine analogs from corresponding alkanols, which is simple and applicable to EPC synthesis of purine nucleosides. While there are many reports concerning the alkylation of purine derivatives, we were interested in the work done by Szarek *et al.*[6,7)] in which the condensation between 6-chloropurine and protected carbohydrates having a free anomeric hydroxyl group was accomplished by Mitsunobu reaction.[8)] The reasons for our interest are 1) the reaction conditions are mild enough to be applicable to a variety of functionalized alcohols, 2) the alkylation occurs regioselectively at the 9-position of 6-chloropurine, and 3) the chlorine in 6-chloropurine is either converted to an amino function or removed to give adenine or purine.

Three alcohols (**2a**, **2b**, and **5**) were used as the substrates in the present study. The former two were selected to examine the regioselectivity of the reactions for the purine moiety and the third one to examine the regio- and stereoselectivities of the reaction for the allyl alcohol moiety.

The results of reactions of 6-chloropurine (**1**) with ethanol (**2a**), benzyl alcohol (**2b**), and monosilylated *cis*-2-cyclopentene-1,4-diol (**5**) in tetrahydrofuran (THF) in the presence of triphenylphosphine and diethyl azodicarboxylate are summarized in Table I.

The Mitsunobu reactions between 6-chloropurine (**1**) and the primary alcohols (**2a** and **2b**) gave two products (**3a** and **3b** as the major and **4a** and **4b** as the minor products), respectively. While **3** could be readily separated from **4** by flash column chromatography (silica gel), a difficulty arose in the separation of these products from triphenylphosphine oxide or bis(ethoxycarbonyl)hydrazine (the latter is less polar than the former). For example, in the chromatography, **3a** and **4b** were contaminated with the phosphine oxide and **3b** with the hydrazine. The ultraviolet (UV) absorption maxima at *ca.* 265 nm for the former compounds (**3**) and at *ca.* 270 nm for the latter (**4**) are in agreement with those of 9- and 7-alkylated purines.[9)] The proton-nuclear magnetic resonance (^{1}H-NMR) spec-

TABLE I. Reactions of 6-Chloropurine (**1**) with Ethanol (**2a**), Benzyl Alcohol (**2b**), and *cis*-2-Cyclopentene-1,4-diol (**5**)

Substrate	Product	Yield (%)	δ (2- and 8-H)[11)]	
2a	**3a**	81[a)]	8.17	8.77
	4a	14	8.30	8.87
2b	**3b**	71[a)]	8.15	8.80
	4b	25[a)]	8.35	8.87
5	**6**	58	8.03	8.77
	7	11[a)]	8.18	8.90

a) The yields were calculated from the intensity of the ^{1}H-NMR signals.

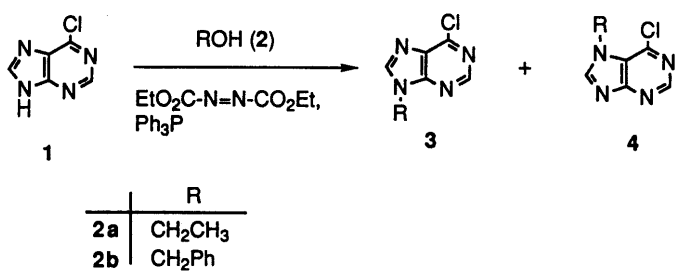

Chart 1

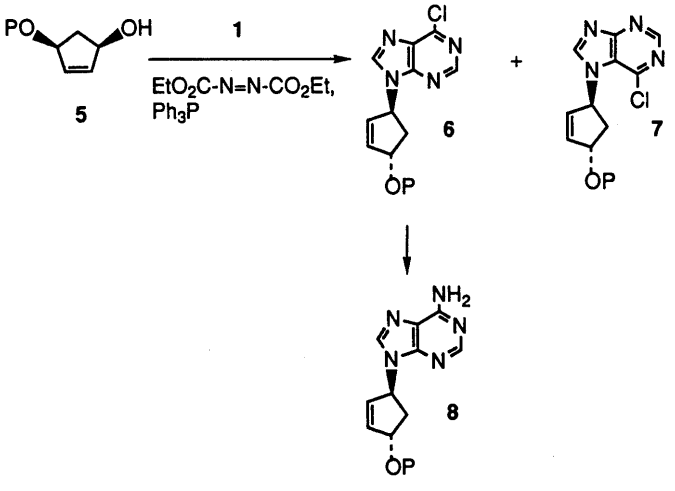

Chart 2

tra of all four products (**3a**, **3b**, **4a**, and **4b**) were identical with those of the corresponding authentic samples.[10]

The reaction of **1** with **5** gave two products (**6** and **7**) (Table I). Since the major product (**6**) has the least polarity among all the products including those derived from the reagents, its isolation is readily achieved by flash chromatography. Since the substitution of hydroxyl groups (including allylic ones) in the Mitsunobu reaction is known to proceed with inversion of configuration, the *trans* relationship between the hydroxyl group and purine moiety in the products (**6** and **7**) was tentatively assigned.[8,12-14]

Taking **6** as a typical example, the corresponding adenine (**8**) was synthesized by heating in methanol containing ammonia in a sealed tube (90 °C). Since catalytic hydrogenolysis of 9-ethyl-6-chloropurine (**3a**) readily affords 9-ethylpurine,[10] the utility of the present reaction for the preparation of 9-substituted adenines and purines from appropriate alcohols including chiral secondary alcohols and alkenols is obvious. In particular, this method would provide a short route to carbocyclic nucleosides having 9-adenine, 9-purine and its 6-chloro derivative, and even 9-hypoxanthine as the heterocycles.

In conclusion, our results may be summarized as follows. 1) Contrary to the selective formation of the 9-substituted purine reported by Szarek *et al.*, the regioselectivity is poor for 6-chloropurine. However, the method is useful for one-step synthesis of 9-substituted purines from less readily available alcohols including chiral ones. 2) The condensation of 6-chloropurine (**1**) with alcohols proceeds predominantly at the 9-position of the former. Though products substituted at the 7-position of **1** may also be formed in minor amounts, separation of 9- and 7-substituted 6-chloropurines is readily achieved by flash chromatography due to the large difference in their polarity. Hence, the former compounds are eluted much faster than the latter. 3) The fact that **5** affords the S_N2 products [neither retention nor S_N2' (allylic rearrangement) occurs] implies that the method is useful for EPC synthesis of carbocyclic nucleosides by the use of chiral alcohols.

Experimental

All melting points were determined on a Yanagimoto micro hot stage and are uncorrected. ^{1}H-NMR spectra were recorded with a JEOL JNM-PMX 60 or JEOL JNM-GX 500 spectrometer with tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (MS) were obtained on a JEOL JMS-DX-303 mass spectrometer. Merck Kieselgel $60F_{254}$ was employed for thin layer chromatography (TLC). The ratio of mixture of solvents used for flash chromatography (silica gel purchased from Yazawa Scientific Co., Ltd.) is shown as volume/volume. When the product was contaminated with either bis(ethoxycarbonyl)hydrazine or triphenylphosphine oxide, the structure of products (**3a**, **3b**, **4b**, and **7**) was determined by analysis of the ^{1}H-NMR spectrum (500 MHz) and the yields were calculated from the intensity of signals.

Mitsunobu Reaction of 6-Chloropurine (1) with Primary Alcohols (2a and 2b) The Reaction of **1** with Ethanol (**2a**): Triphenylphosphine (199 mg, 0.76 mmol) was added at room temperature over a period of 5 min to a mixture of **1** (59 mg, 0.38 mmol), ethanol (35 mg, 0.76 mmol), and diethyl azodicarboxylate (132 mg, 0.76 mmol) in THF (2.3 ml), and the mixture was kept standing at room temperature for 16 h. After removal of the solvent *in vacuo*, the product was separated by flash chromatography. Elution with ethyl acetate–hexane (1:3) gave **3a** (56 mg, 81%) as a mixture with triphenylphosphine oxide, and elution with ethyl acetate gave **4a** (10 mg, 14%) as a colorless solid. **3a** (contaminated with Ph_3PO): UV λ_{max}^{MeOH} nm: 265. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (3H, t, J=8 Hz, CH_3), 4.38 (2H, q, J=8 Hz, CH_2), 8.17 and 8.77 (each 1H, s, purine-H × 2). **4a**: mp 121—122 °C (hexane) (lit.[10a] mp 122—123 °C).

The Reaction of **1** with Benzyl Alcohol (**2b**): The product from the reaction of **1** (59 mg, 0.38 mmol) with **2b** (82 mg, 0.76 mmol) under the same conditions as above was subjected to flash chromatography. Elution with hexane–ethyl acetate (2:1) gave **3b** (66 mg, 71%) as a solid contaminated with bis(ethoxycarbonyl)hydrazine, and then **4b** (24 mg, 25%) as a solid contaminated with triphenylphosphine oxide. **3b** (contaminated with the hydrazine): UV λ_{max}^{MeOH} nm: 265. ^{1}H-NMR ($CDCl_3$) δ: 5.47 (2H, s, CH_2), 7.35 (5H, br s, C_6H_5), 8.15 and 8.80 (each 1H, s, purine-H × 2). **4b** (contaminated with the phosphine oxide): ^{1}H-NMR ($CDCl_3$) δ: 5.70 (2H, s, CH_2), 7.3—7.5 (5H, masked by the signals of the phosphine oxide), 8.35 and 8.87 (each 1H, s, purine-H × 2).

The Reaction of 1 with Mono-*tert*-butyldimethylsilyl Ether of *cis*-2-Cyclopentene-1,4-diol (5) a) Preparation of the Monosilylated Diol (**5**): *tert*-Butyldimethylsilyl chloride (543 mg, 3.6 mmol) was added to a solution of *cis*-2-cyclopentene-1,4-diol (300 mg, 3.00 mmol) and imidazole (510 mg, 7.50 mmol) in dimethylformamide (3 ml) at room temperature, and the mixture was stirred for 19 h. After addition of water (25 ml), the mixture was extracted with ether (3 × 25 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography [hexane–ethyl acetate (3:1)] to give **5** (364 mg, 51%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.01 [6H, s, $Si(CH_3)_2$], 0.92 [9H, s, $C(CH_3)_3$], 1.3—1.7 and 2.45—2.9 (each 1H, m, CH_2), 4.45—4.8 (2H, m, CH-O × 2), 5.90 (2H, br s, olefinic H).

b) The Mitsunobu Reaction: Triphenylphosphine (734 mg, 2.82 mmol) was added at room temperature over a period of 10 min to a stirred mixture of **1** (216 mg, 1.4 mmol), *cis*-4-*tert*-butyldimethylsilyloxy-2-cyclopenten-1-ol (300 mg, 1.40 mmol) and diethyl azodicarboxylate (487 mg, 2.80 mmol) in THF (8.4 ml). The mixture was stirred at room temperature for 1 h, then the solvent was evaporated *in vacuo*. The residue was subjected to flash chromatography. Elution with hexane–ethyl acetate (3:1) afforded **6** (284 mg, 58%) as a colorless solid, and further elution with the same solvent mixture (1:1) gave **7** (56 mg, 11%) as a mixture with bis(ethoxycarbonyl)hydrazine, followed by a third product (22 mg, 4%) as a solid. Though an analytical sample of the last compound could not be prepared due to its instability, the spectral data (see below) clearly showed that it was either 1- or 3-substituted 6-chloropurine. **6**: mp 126—127 °C (hexane). UV λ_{max}^{MeOH} nm (ε): 266 (7800). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.119 and 0.121 [each 3H, s, $Si(CH_3)_2$], 0.92 [9H, s, $C(CH_3)_3$], 2.34 (1H, ddd, J=13.5, 7.5, 4 Hz, $C_{5'}$-H), 2.48 (1H, ddd, J=13.5, 9, 4 Hz, $C_{5'}$-H), 5.25 (1H, m, CH-O), 5.95 (1H, m, CH-N), 6.05 (1H, ddd, J=5, 2, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.35 (1H, ddd, J=5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 8.03 and 8.77 (each 1H, s, purine-H × 2). *Anal.* Calcd for $C_{16}H_{23}ClN_4OSi \cdot 1/4H_2O$: C, 54.07; H, 6.66; N, 15.77. Found: C, 53.96; H, 6.36; N, 15.62. **7** (contaminated with the hydrazine): UV λ_{max}^{MeOH} nm: 269. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.103 and 0.11 [each 3H, s, $Si(CH_3)_2$], 0.91 [9H, s, $C(CH_3)_3$], 2.27 (1H, ddd, J=15, 7.5, 3.5 Hz, $C_{5'}$-H), 2.50 (1H, ddd, J=15, 7.5, 5 Hz, $C_{5'}$-H), 5.14 (1H, m, CH-O), 6.14 (1H, ddd, J=5, 2, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.23 (1H, m, CH-N), 6.38 (1H, ddd, J=5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 8.18 and 8.90 (each 1H, s, purine-H × 2).

1- or 3-(*trans*-4'-*tert*-Butyldimethylsilyloxycyclopent-2'-enyl)-6-chloro-1*H*- or -3*H*-purine: UV λ_{max}^{MeOH} nm: 280. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.118 and 0.125 [each 3H, s, $Si(CH_3)_2$], 0.92 [9H, s, $C(CH_3)_3$], 2.39 (1H, ddd, J=15, 7.5, 4 Hz, $C_{5'}$-H), 2.66 (1H, ddd, J=15, 8, 4 Hz, $C_{5'}$-H), 5.23 (1H, m, CH-O), 6.10 (1H, ddd, J=5, 2, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.41 (1H, m, CH-N), 6.46 (1H, ddd, J=5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 8.32 and 8.55 (each 1H, s, purine-H × 2). MS m/z (M^+): 350.

9-(*trans*-4'-*tert*-Butyldimethylsilyloxycyclopent-2'-enyl)-9*H*-adenine (8) Compound **6** (74 mg, 0.21 mmol) in methanol (10 ml) saturated with ammonia at −10 °C was heated in a sealed tube at 90 °C for 12 h. The residue obtained after evaporation of the solvent *in vacuo* was purified by flash chromatography (ethyl acetate) to give **8** (61 mg, 88%), mp 166—168 °C (ethyl acetate–hexane). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.103 and 0.106 [each 3H, s, $Si(CH_3)_2$], 0.91 [9H, s, $C(CH_3)_3$], 2.31 (1H, ddd, J=14, 7, 4 Hz, $C_{5'}$-H), 2.43 (1H, ddd, J=14, 8, 4 Hz, $C_{5'}$-H), 5.21 (1H, m, CH-O), 5.68 (2H, br s, NH_2), 5.86 (1H, m, CH-N), 6.05 (1H, ddd, J=5, 3, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.25 (1H, ddd, J=5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 7.71 and 8.37 (each 1H, s, purine-H × 2). High-resolution MS m/z Calcd for $C_{16}H_{26}N_5OSi$ (M^++H): 332.1907. Found: 332.1899. *Anal.* Calcd for $C_{16}H_{25}N_5OSi$: C, 57.97; H, 7.60; N, 21.13. Found: C, 57.93; H, 7.61; N, 21.02.

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