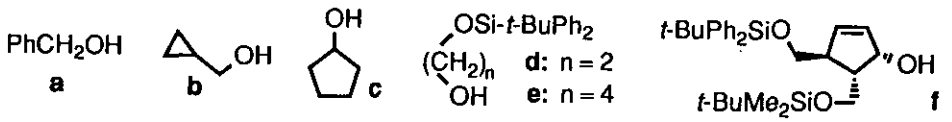
# THE ALKYLATION OF 2-AMINO-6-CHLOROPURINE WITH ALCOHOLS BY MITSUNOBU REACTION FOR A SYNTHESIS OF CARBOCYCLIC GUANOSINE ANALOGS[1]

Akemi Toyota,* Nobuya Katagiri, and Chikara Kaneko

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

**Abstract**--Mitsunobu reaction of 2-amino-6-chloropurine with various alcohols which provides a convenient method for a synthesis of carbocyclic or acyclic guanosine analogs is described

Numerous syntheses of carbocyclic nucleosides have been reported because of their potent anti-viral[2] and anti-tumour activities.[3] Among the various synthetic methods of purine nucleosides, glycosylation of 6-chloropurine with an appropriately tailored carbohydrate moiety by Mitsunobu procedure as a key step seems most convenient and advantageous owing to stereo-specific one-stage formation of the adenine nucleoside.[4,5] By using this procedure, we have succeeded in the synthesis of (-)-BCA [(1*R*,4*S*,5*R*)-9-(4,5-bishydroxymethylcyclopent-2-en-1-yl)-9*H*-adenine] having a potent anti-HIV activity.[6] However, little is known concerning the synthesis of guanosine analogs using similar way except a recent work using $N^2$-isobutyryl-$O^6$-[2-(*p*-nitrophenylethyl]guanine,[7] which was synthesized from guanine *via* 3 steps.[8] The commercially available 2-amino-6-chloropurine (**1**) as the nucleobase would provide a more straightforward method for carbocyclic or acyclic guanosine analogs. Although **1** has been used as a guanosine precursor in the alkylation reaction by either alkyl halides,[9] sulfonates[10] or $\pi$-allyl $Pd^0$ complex[11] in the presence of base, it has not been used in the Mitsunobu reaction due probably to its insolubility against organic solvents such as THF and possibility of the $N^2$ and/or $N^3$ alkylations. Recently, we found that purine which was sparingly soluble in THF dissolved gradually during the reaction to give the $N^9$-substituted products in fair to good yields.[12] Being encouraged by this observation, we then applied this reaction to the alkylation of 2-amino-6-chloropurine (**1**) with a variety of alcohols (**a**-**g**) by Mitsunobu reaction[13] and here we describe

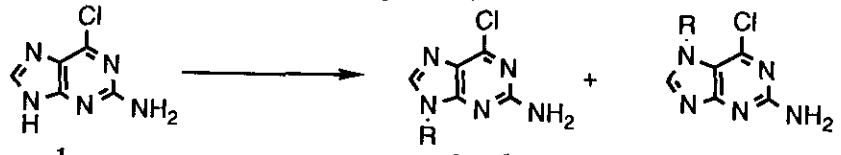



the successful result.

Treatment of **1** and benzyl alcohol (**a**) with $Ph_3P$ and DEAD in THF in the presence of molecular sieves (4Å) at room temperature for 10 h gave the $N^9$- (**2a**) and the $N^7$-products (**3a**) in 66% and 20% yields, respectively. The uv absorption maxima at 310 nm for **2a** and at 318 nm for **3a** are consistant with those of the corresponding 9- and 7-benzylated purines.[9] The alkylation of **1** with other alcohols (**b-e**) under the same conditions gave the corresponding 9-alkyl isomers (**2b-2e**) as major products with small amounts of the 7-alkyl isomers (**3b-3e**). The result is summarized in Table 1. The structures of the products were again assigned on the basis of uv spectra, just like as in the cases of **2a** and **3a**.

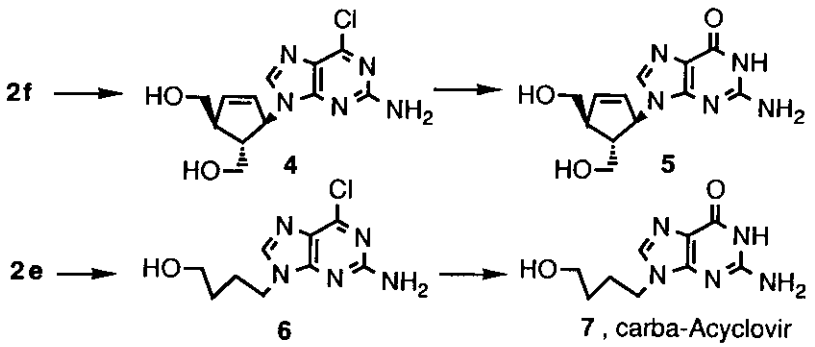
Though reactivity of **1** in these reactions are slightly lower than that of 6-chloropurine,[5,12] the desired $N^9$-alkylated products were obtained in satisfactory yields without exception. The presence of molecular sieves (4Å) enhanced slightly the yields. Just like as the reactions using 6-

Table I. Mitsunobu reaction of 2-amino-6-chloropurine (**1**) with a variety of alcohols.




| Entry | Alcohol | Yield (%) 2 | 3 |
|---|---|---|---|
| 1 | **a** | 66 (69)[a] | 20 (18)[a] |
| 2[b] | **a** | 62 | 17 |
| 3 | **b** | 69 | 17 |
| 4 | **c** | 78 | 7 |
| 5 | **d** | 92 | not detected |
| 6 | **e** | 91 | 8 |
| 7 | **f** | 23 (32)[a] | 12 (8)[a] |

a. The reaction was carried out at 0 °C → room temperature.
b. Without molecular sieves 4Å.




chloropurine,[5,12] use of the alkanols resulted in higher regioselectivity than that of the allyl alcohols. The reaction of **1** with **f** gave the $S_N2$ product **2f** in 23-32% yield due probably to the steric hindrance of side chains on the cyclopentenol.

Compound (**2f**) was desilylated by tetrabutylammonium fluoride to give **4** in 98% yield, which was treated with aq. HCl to give guanine analog of BCA (**5**)[14] in 77% yield. Carba-acyclovir (**7**)[15] having anti-HSV activity[16] was prepared from **2e** in the same manner. Thus, a variety of guanine analogs could be synthesized more efficiently and conveniently by using this protocol. Though guanine could not be used,[13] the similar alkylations of adenine with alcohols (**a**, **c**) under the Mitsunobu conditions gave, in all cases, 9-alkyladenine as the major products and 3-alkyl isomers as the minor ones. This novel synthesis of a series of carbocyclic adenosine analogs will be the subject of our forthcoming paper.

## EXPERIMENTAL

**General Procedure for the Alkylation of 1 with a Variety of Alcohols by Mitsunobu Reaction:** Diethyl azodicarboxylate (0.05 ml, 0.15 mmol) was added in portions to a mixture of the 2-amino-6-chloropurine (0.15 mmol), the alcohol (0.3 mmol), and triphenylphosphine (79 mg, 0.3 mmol) in THF (2.7 ml), which was previously stirred for 15 min in the presence of molecular sieves 4Å (200 mg). The mixture was stirred at room temperature for 10 h. After removal of the solvent *in vacuo*, the product was separated by flash chromatography (silica gel). Elution was carried out in the order of hexane-ethyl acetate, ethyl acetate, ethyl acetate-methanol, and chloroform-methanol as the solvents. As a result, the products were eluted in the following order: the 9-alkylated derivatives and 7-alkylated derivatives. The yields of the products are given in Table I. Melting points and spectroscopic data (uv and $^1$H-nmr) are given in Table II. The structures of **2c**, **2d**, and **2e** were supported by high-resolution mass spectra. **2c**: High-resolution ms *m/z* Calcd for $C_{10}H_{12}N_5Cl$ ($M^+$): 237.0781. Found: 237.0797. **2d**: High-resolution ms *m/z* Calcd for $C_{23}H_{25}N_5OClSi$ ($M^+$-H): 450.1517. Found: 450.1524. **2e**: High-resolution ms *m/z* Calcd for $C_{25}H_{30}N_5OClSi$ ($M^+$-H): 479.1908. Found: 479.1878.

Table II. Physical and spectroscopic data for 2a-f, 3a-f

| Compd No | mp (°C) | uv (MeOH) $\lambda_{max}$ nm | Solvent | $^1$H-nmr δ |
|---|---|---|---|---|
| 2a[a] | 214-215 (212 °C)[9] | 310 | $CDCl_3$-$CD_3OD$ (10:1) | 5.27 (2H, s), 7.33 (5H, s), 7.81 (1H, s). |
| 3a | ___[b] | 318 | $CDCl_3$-$CD_3OD$ (1:1) | 5.61 (2H, s), 7.19 (2H, m), 7.35 (3H, m), 8.25 (1H, s). |
| 2b | ___[c] | 311 | $CDCl_3$ | 0.33-0.80 (4H, m),1.27 (1H, m), 3.95 (2H, d, *J* = 7 Hz), 5,18 (2H, br s, $NH_2$), 7.92 (1H, s). |
| 3b | ___[b] | 322 | $CDCl_3$-$CD_3OD$ (5:1) | 0.46 (2H, m), 0.74 (2H, m), 1.40 (1H, m), 4.22 (2H, d, *J* =7.3 Hz), 8.16 (1H, s). |
| 2c[d] | 141-143 | 310 | $CDCl_3$ | 1.90 (8H, m), 4.80 (1H, m), 5.34 (2H, br s, $NH_2$), 7.85 (1H, s). |
| 3c | ___[b] | 322 | $CDCl_3$-$CD_3OD$ (5:1) | 1.89 (4H, m), 2.01 (2H, m), 2.32 (2H, m), 5.18 (1H, m), 8.14 (1H, s). |
| 2d[e] | 179-180 | 311 | $CDCl_3$ | 1.02 (9H, s), 3.97 (2H, m), 4.17 (2H, m), 5.10 (2H, br s, $NH_2$), 7.20-7.60 (10H, m), 7.86 (1H, s). |
| 2e | 141-143 | 310 | $CDCl_3$ | 1.03 (9H, s), 1.50-2.17 (4H, m), 3.68 (2H, t, *J* = 6 Hz), 4.05 (2H, t, *J* = 6 Hz), 5.15 (2H, br s, $NH_2$), 7.30-7.66 (10H, m), 7.68 (1H, s). |
| 3e | ___[f] | 321 | $CDCl_3$ | 1.04 (9H, s), 1.55 (2H, m), 1.97 (2H, m), 3.70 (2H, t, *J* = 6 Hz), 4.30 (2H, t, *J* = 7 Hz), 5.15 (2H, br s, $NH_2$), 7.40 (6H, m), 7.62 (4H, m), 7.89 (1H, s). |
| 2f | oil | 310 | $CDCl_3$ | 0.01 (6H, s), 0.83 (9H, s), 1.03 (9H, s), 2.30 (1H, m), 2.90 (1H, m), 3.75 (4H, d x 2, *J* = 6 Hz), 5.01 (2H, br s, $NH_2$), 5.50 (1H, m), 5.73 (1H, m), 6.03 (1H, m), 7.30-7.70 (10H, m), 7.73 (1H, s). |
| 3f | oil | 320 | $CDCl_3$ | -0.23 (6H, s), 0.70 (9H, s), 1.00 (9H, s), 2.20 (1H, m), 3.05 (1H, m), 3.80 (4H, m), 5.80 (1H, m), 6.00 (2H, m), 7.87 (1H, s). |

a. *Anal.* Calcd for $C_{12}H_{10}N_5Cl$: C, 55.50; H, 3.88; N, 26.97. Found: C, 55.31; H, 3.85; N, 26.79.
b. Contaminated with **1**.
c. Contaminated with triphenylphosphine oxide.
d. *Anal.* Calcd for $C_{10}H_{12}N_5Cl{\cdot}0.1H_2O$: C, 50.15; H, 5.14; N, 29.24. Found: C, 50.11; H, 5.20; N, 29.41.
e. *Anal.* Calcd for $C_{23}H_{26}N_5OClSi{\cdot}0.1H_2O$: C, 60.87; H, 5.82; N, 15.43. Found: C, 61.21; H, 6.04; N, 15.03.
f. Contaminated with bis(ethoxycarbonyl)hydrazine.

**Preparation of (±)-2-Amino-9-(4'β, 5'α-bishydroxymethylcyclopent-2'-en-1'β-yl)-6-chloropurine (4)**: To a solution of **2f** (31 mg, 0.048 mmol) in THF (0.5 ml) was added tetrabutylammonium fluolide (1 M in THF, 0.1 ml) at 0 °C and the mixture was stirred for 2 h. The resulting mixture was partitioned between water (0.2 ml) and ethyl acetate (3 x 3 ml). The combined organic extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (10% methanol/ethyl acetate) to give **4** (13.5 mg, 98%), mp 183-185 °C (MeOH). 300 MHz $^1$H-nmr ($CD_3OD$) δ: 2.34 (1H, tdd, *J* = 6, 6, and 6 Hz, $C_5$'-H), 2.79 (1H, m, $C_4$'-H), 3.66 and 3.73 (each 1H, AB type's dd, *J* = 11 and 5 Hz, $C_4$'-$CH_2OH$), 3.78 (2H, d, *J* = 6 Hz, $C_5$'-$CH_2OH$), 5.45 (1H, m, $C_1$'-H), 5.84 and 6.13 (each 1H, m, olefinic-H x 2), 8.11 (1H, s). High-resolution ms *m/z* Calcd for $C_{12}H_{14}N_5O_2Cl$ ($M^+$): 295.0836. Found: 295.0835. *Anal.* Calcd for $C_{12}H_{14}N_5O_2Cl{\cdot}0.3H_2O$: C, 47.86; H, 4.89; N, 23.25. Found: C, 48.17; H, 4.77; N, 22.86.

**Preparation of (±)-9-(4'β, 5'α-Bishydroxymethylcyclopent-2'-en-1'β-yl)guanine (5)**: A suspension of **4** (4 mg, 0.014 mmol) in 1 N hydrochloric acid (0.15 ml) was refluxed for 1 h. The reaction mixture was neutralized with powder sodium bicarbonate and evaporated *in vacuo*. The residue was purified by preparative tlc with 25% MeOH/$CHCl_3$ as the eluent solvent to give **5** (3

77%). Uv and nmr spectral data agreed with those reported for **5** synthesized by an alternative route.[14]

**Preparation of 2-Amino-9-(4-hydroxybut-1-yl)-6-chloropurine (6)**: Desilylation of **2e** (62 mg, 0.13 mmol) with the same procedure for that of **2f** using TBAF (0.13 mmol) provided **6** (26 mg, 83%) colorless prisms, mp 194-196 °C. 300 MHz $^1$H-nmr ($CD_3OD$) δ: 1.53 (2H, m, $C_{3'}$-$H_2$), 1.94 (2H, m, $C_{2'}$-$H_2$), 3.58 (2H, t, $J$ = 6.5 Hz, $CH_2OH$), 4.17 (2H, t, $J$ = 7Hz, $C_{1'}$-$H_2$), 8.09 (1H, s). High-resolution ms *m/z* Calcd for $C_9H_{12}N_5OCl$ ($M^+$): 241.0730. Found: 241.0702. *Anal.* Calcd for $C_9H_{12}N_5OCl \cdot 0.067H_2O$: C, 44.50; H, 5.04; N, 28.84. Found: C, 44.73; H, 5.12; N, 28.60.

**Preparation of 9-(4-Hydroxybut-1-yl)guanine (7)**: A suspension of **6** (13.4 mg, 0.055 mmol) in 1 N hydrochloric acid was refluxed for 1 h. The reaction solution was neutralized with powder sodium bicarbonate. The resuting precipitation was collected by filtration, washed with water and dried in vacuo to give **7** (12.4 mg, 100%), mp 260-263 °C. Uv $\lambda_{max}$ (MeOH) nm: 255. 300 MHz $^1$H-nmr ($CD_3OD$) δ: 1.52 (2H, m, $C_{3'}$-$H_2$), 1.89 (2H, m, $C_{2'}$-$H_2$), 3.57 (2H, t, $J$ = 6.5 Hz, $CH_2OH$), 4.07 (2H, t, $J$ = 7 Hz, $C_{1'}$-$H_2$), 7.72 (1H, s). High-resolution ms *m/z* Calcd for $C_9H_{13}N_5O_2$ ($M^+$): 223.1069. Found: 223.1066. *Anal.* Calcd for $C_9H_{13}N_5O_2 \cdot 1.1H_2O$: C, 44.47; H, 6.30; N, 28.82. Found: C, 44.55; H, 6.69; N, 28.84.

## ACKNOWLEDGMENT

This work is sopported in part by a Grant-in-Aid for Scientific Research to A. T. (Grant No. 04771864) from the Ministry of Education, Science and Culture, Japan.

## REFERENCES AND NOTES

1. This paper forms Part 32 of "Synthesis of nucleosides and related compounds". Part 31: N. Katagiri, T. Shiraishi, A. Toyota, H. Sato, C. Kaneko, and T. Aikawa, *Chem. Pharm. Bull.*, in press.
2. V. E. Marquetz and M.-I. Lim, *Medicinal Res. Rev.*, 1986, **6**, 1.
3. M. MacCoss and M. J. Robins, 'Chemistry of Antitumour Agents', ed. by D. E. V. Wilman, Blackie and Son, U. K., 1990, p. 261.
4. V. A. Marquez, C. K. H. Tseng, S. P. Treanor, and J. S. Driscoll, *Nucleosides Nucleotides*, 1987, **6**, 239; H. J. Bestmann and D. Roth, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 99.
5. A. Toyota, N. Katagiri, and C. Kaneko, *Chem. Pharm. Bull.*, 1992, **40**, 1039.
6. N. Katagiri, A. Toyota, T. Shiraishi, H. Sato, and C. Kaneko, *Tetrahedron Lett.*, 1992, **33**, 3507.
7. T. F. Jenny, N. Provisani, and S. A. Benner, *Tetrahedron Lett.*, 1991, **32**, 7029.
8. T. F. Jenny, K. C. Schneider, and S. A. Benner, *Nucleosides Nucleotides*, 1992, **11**, 1257.
9. J. A. Montgomery, K. Hewson, and C. Temple, Jr., *J. Med. Pharm. Chem.*, 1962, **5**, 15; M. R. Harnden and R. L. Jarvest, *Tetrahedron Lett.*, 1985, **26**, 4265.
10. W. T. Ashton, L. C. Meurer, C. L. Cantone, A. K. Field, J. Hannah, J. D. Karkas, R. Liow, G-F. Patel, H. C. Perry, A. F. Wagner, E. Walton, and R. L. Tolman, *J. Med. Chem.*, 1988, **31**, 2304; M. T.

Jones, S. A. Noble, C. A. Robertson, R. Storer, R. M. Highcock, and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1427.

11. C. T. Evans, S. M. Roberts, K. A. Shoberu, and A. G. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 589.
12. A. Toyota, N. Katagiri, and C. Kaneko, *Synthetic Commun.*, in press.
13. Use of guanine itself as the base in Mitsunobu reaction resulted in a recovery of the starting material.
14. N. Katagiri, M. Nomura, H. Sato, C. Kaneko, K. Yusa, and T. Tsuruo, *J. Med. Chem.*, 1992, **35**, 1882.
15. A. Yamazaki, *Chem. Pharm. Bull.*, 1969, **17**, 1268.
16. A. Larsson, S. Alenius, N. G. Johansson, and B. Öberg, *Antiviral Res.*, 1983, **3**, 77.

Received, 9th February, 1993