

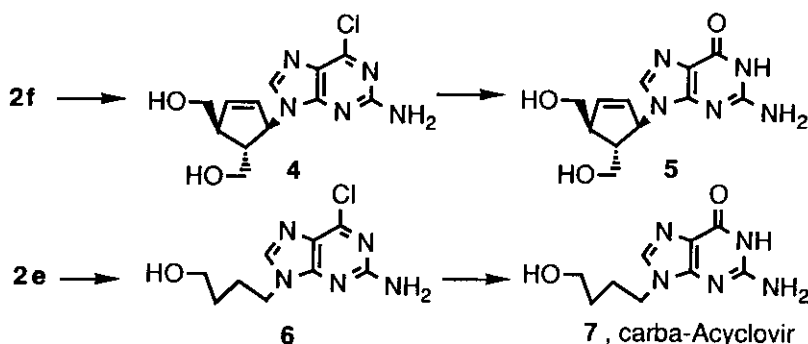
THE ALKYLATION OF 2-AMINO-6-CHLOROPURINE WITH ALCOHOLS BY MITSUNOBU REACTION FOR A SYNTHESIS OF CARBOCYCLIC GUANOSINE ANALOGS¹

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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-viral² 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 stereospecific 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 sulfonates¹⁰ or π -allyl Pd⁰ complex¹¹ 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 reaction¹³ and here we describe



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 activity¹⁶ 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 ¹H-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 C₁₀H₁₂N₅Cl (M⁺): 237.0781. Found: 237.0797. 2d: High-resolution ms *m/z* Calcd for C₂₃H₂₅N₅OCiSi (M⁺-H): 450.1517. Found: 450.1524. 2e: High-resolution ms *m/z* Calcd for C₂₅H₃₀N₅OCiSi (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	$^1\text{H-nmr}$ δ
2a ^a	214-215 (212 °C) ⁹	310	CDCl ₃ -CD ₃ OD (10:1)	5.27 (2H, s), 7.33 (5H, s), 7.81 (1H, s).
3a	— ^b	318	CDCl ₃ -CD ₃ OD (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 ₃ OD (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 ₃ OD (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 C₁₂H₁₀N₅Cl: 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 C₁₀H₁₂N₅Cl·0.1H₂O: C, 50.15; H, 5.14; N, 29.24. Found: C, 50.11; H, 5.20; N, 29.41.

e. Anal. Calcd for C₂₃H₂₆N₅OClSi·0.1H₂O: 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 fluoride (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 $^1\text{H-nmr}$ (CD₃OD) 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'}-CH₂OH), 3.78 (2H, d, $J = 6$ Hz, C_{5'}-CH₂OH), 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 C₁₂H₁₄N₅O₂Cl (M⁺): 295.0836. Found: 295.0835. Anal. Calcd for C₁₂H₁₄N₅O₂Cl·0.3H₂O: 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/CHCl₃ 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 ¹H-nmr (CD₃OD) δ: 1.53 (2H, m, C_{3'}-H₂), 1.94 (2H, m, C_{2'}-H₂), 3.58 (2H, t, *J* = 6.5 Hz, CH₂OH), 4.17 (2H, t, *J* = 7 Hz, C_{1'}-H₂), 8.09 (1H, s). High-resolution ms *m/z* Calcd for C₉H₁₂N₅OCl (M⁺): 241.0730. Found: 241.0702. *Anal.* Calcd for C₉H₁₂N₅OCl·0.067H₂O: 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 resulting precipitation was collected by filtration, washed with water and dried in vacuo to give **7** (12.4 mg, 100%), mp 260-263 °C. Uv λ_{max} (MeOH) nm: 255. 300 MHz ¹H-nmr (CD₃OD) δ: 1.52 (2H, m, C_{3'}-H₂), 1.89 (2H, m, C_{2'}-H₂), 3.57 (2H, t, *J* = 6.5 Hz, CH₂OH), 4.07 (2H, t, *J* = 7 Hz, C_{1'}-H₂), 7.72 (1H, s). High-resolution ms *m/z* Calcd for C₉H₁₃N₅O₂ (M⁺): 223.1069. Found: 223.1066. *Anal.* Calcd for C₉H₁₃N₅O₂·1.1H₂O: C, 44.47; H, 6.30; N, 28.82. Found: C, 44.55; H, 6.69; N, 28.84.

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