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Jinglan Zhou [a] , Jui-Yi Tsai [a] , Kamal Bouhadir [a] & Philip B. Shevlin [a]

[a] Department of Chemistry , Auburn University , Auburn, AL, 36830

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N^2-ACETYL-O^6-(2-(P-NITROPHENYL)ETHYL)GUANINE: A CONVENIENT BUILDING BLOCK FOR THE SYNTHESIS OF 9-SUBSTITUTED GUANINE DERIVATIVES

Jinglan Zhou, Jui-Yi Tsai, Kamal Bouhadir and Philip B. Shevlin*

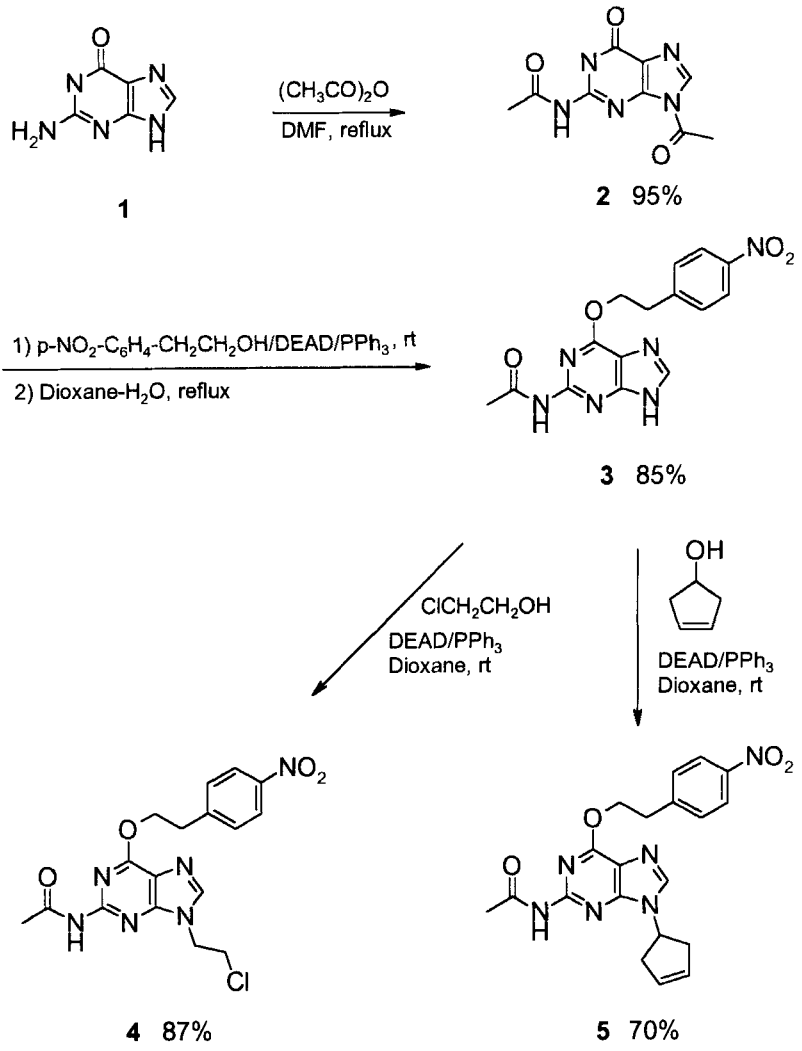
Department of Chemistry, Auburn University, Auburn, AL 36830

Abstract: Readily accessible N^2-acetyl-O^6-(2-(p-nitrophenyl)ethyl)guanine can undergo Mitsunobu reactions with either a primary or secondary alcohol to generate guanine derivatives. X-ray data indicates that only the desired 9-subsituted derivatives of guanine are formed.

During the course of our studies on nucleic acid base attached functional polymers, we encountered difficulty in synthesizing 9-(2-chloroethyl)guanine, dehydrochlorination of which provides 9-vinylguanine, the monomer needed to prepare guanine attached polyethylene.[1] A simple hydroxyethylation-chlorination of guanine is not applicable to the synthesis of 9-(2-chloroethyl)guanine. While the reaction of adenine with ethylene carbonate in refluxing DMF gave the desired 9-(2-hydroxyethyl)adenine in good yield, hydroxyethylation of guanine generated predominately 7-substituted guanine.[2] A literature search reveals that one of the commonly used approaches to 9-substituted guanine derivatives relies

* To whom correspondence should be addressed.

on the construction of the purine base step by step starting with 2-amino-4, 6-dichloropyrimidine.[3] It is obvious that this reaction scheme involves too many steps and therefore it was not pursued. In 1992, Benner and co-workers reported a convenient building block for carbocyclic analogs of guanosine.[4] In their work, N^2-isobutyryl-O^6-(2-(p-nitrophenyl)ethyl)guanine was used in Mitsunobu reactions with carbocyclic alcohols to give exclusively 9-substituted guanosine analogs. Protecting groups were removed by base hydrolysis afterwards. If this regioselective Mitsunobu coupling were to work with primary alcohols as well, reaction of N^2-isobutyryl-O^6-(2-(p-nitrophenyl)ethyl)guanine with 2-chloroethanol ought to give us the 9-chloroethylated guanine derivative. An unexpected difficulty was encountered in the preparation of 9-acetyl-N^2-isobutyrylguanine, precursor to N^2-isobutyryl-O^6-(2-(p-nitrophenyl)ethyl)guanine. Treatment of N^2-isobutyrylguanine with acetic anhydride repeatedly generated a mixture of 9-acetyl-N^2-isobutyrylguanine together with 9,N^2-diacetylguanine **2**. The ratio of these two compounds varied depending on the number of equivalents of acetic anhydride used. A simple solution to this problem was to use **2** instead of 9-acetyl-N^2-isobutyrylguanine in the reaction sequence. Thus, 9,N^2-diacetylguanine **2** was readily prepared from guanine **1** in only one step by treating the base with large excess of acetic anhydride in refluxing DMF. Reaction of **2** with 2-(p-nitrophenyl)-ethanol under Mitsunobu conditions gave 9,N^2-diacetyl-O^6-(2-(p-nitrophenyl)ethyl)guanine which underwent hydrolysis in refluxing dioxane-H_2O to give N^2-acetyl-O^6-(2-(p-nitrophenyl)ethyl)guanine **3**. Mitsunobu coupling of **3** with 2-chloroethanol afforded 9-(2-chloroethyl)-N^2-



acetyl-O^6-(2-nitrophenyl)guanine **4** in 87% yield. Only the desired 9-substituted purine was formed as demonstrated by its X-ray crystal structure.

N^2-acetyl-O^6-(2-(p-nitrophenyl)ethyl)guanine **3** was also successfully reacted with a secondary alcohol, 4-hydroxycyclopentene,[5] under Mitsunobu

conditions to give N^2-acetyl-9-(3-cyclopentenyl)-O^6-(2-(p-nitrophenyl)ethyl)guanine, **5**, a potentially useful functionalized carbocyclic guanosine analog.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer using $CDCl_3$ as solvent (unless otherwise indicated) and TMS as internal standard. Mass spectra were obtained on Finnigan 3300 or VG 7070E mass spectrometers.

9, N^2-Diacetylguanine, 2

To a suspension of guanine **1** (15.1 g, 0.100 mol) in 150 mL of DMF was added acetic anhydride (30.6 g, 0.300 mol) at room temperature. The mixture was heated at 160°C for 2 h to yield a clear solution. After evaporation of the solvent, the residue was washed with sat. sodium bicarbonate and a small amount of cool ethanol to give 22.3 g (95%) of **2**. ^1H NMR (DMSO-d_6, 250 MHz) δ 2.19 (s, 3H), 2.80 (s, 3H), 8.30 (s, 1H), 11.68 (br s, 2H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 23.9, 24.7, 121.7, 137.7, 147.3, 154.9, 168.3, 173.6, 174.0; MS (EI) m/z (rel int) 193 (M, 44), 151 (100), 134 (12), 110 (28), 109 (35), 108 (20); HRMS calcd for $C_9H_9N_5O_3$ 235.0706, found 235.0708.

N^2-Acetyl-O^6-(2-(p-nitrophenyl)ethyl)guanine, 3

To a suspension of **2** (2.21 g, 0.010 mol), 2-(p-nitrophenyl)ethanol (2.51 g, 0.015 mol) and triphenyl-phosphine (3.93 g, 0.015 mol) in 50 mL of dry dioxane was added DEAD (2.5 mL, 0.015 mol) in 10 mL of dioxane dropwise at 0°C

under nitrogen. The mixture was stirred at room temperature overnight to yield a clear solution to which 25 mL of water was added and the mixture refluxed for 1 h. After cooling, the precipitate was collected to give 2.88 g (85%) of **3**. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 1.13 (d, J = 6.8, 6H), 2.84-2.97 (m, 1H), 4.75 (t, J = 6.8, 2H), 7.58 (d, J = 8.6, 2H), 8.03 (s, 1H), 8.10 (d, J = 8.6 H, 2H), 10.15, (br s, 1H); MS (EI) m/z (rel int) 342 (M, 0.7), 193 (39), 151 (100), 134 (15), 119 (12); HRMS calcd for $C_{15}H_{14}N_6O_4$ 342.1078, found 342.1079.

9-(2-Chloroethyl)-N^2-acetyl-O^6-(2-(p-nitrophenyl)-ethyl)guanine, 4

To a suspension of **3** (3.42 g, 0.010 mol), 2-chloroethanol (0.80 mL, 0.012 mol) and triphenylphosphine (3.14 g, 0.012 mol) in 50 mL of dry dioxane was added DEAD (2.0 mL, 0.012 mol) in 10 mL of dioxane dropwise at 0°C under nitrogen. The mixture was stirred at room temperature overnight to yield a clear solution. The solvent was removed and residue was purified by flash chromatography (50% EtOAc-hexane) to give 3.51 g (87%) of **4.** ^{1}H NMR (250 MHz) δ 2.55 (s, 3H), 3.32 (t, J = 6.7, 2H), 3.92 (t, J = 5.6, 2H), 4.50 (t, J = 5.6, 2H), 4.79 (t, J = 6.7, 2H), 7.49 (d, J = 8.7, 2H), 7.91 (s, 1H), 7.93 (br s, 1H), 8.16 (d, J = 8.7, 2H); ^{13}C NMR (62.9 MHz) δ 25.2, 35.1, 42.0, 45.8, 67.0, 117.7, 123.8, 129.9, 142.1, 145.5, 146.9, 152.1, 152.9, 160.7, 170.6; MS (EI) m/z (rel int) 404 (M, 0.3), 255 (9), 213 (16), 187 (11), 185 (36), 151 (21), 149 (34), 139 (10), 136 (100), 119 (36), 106 (26); HRMS calcd for $C_{17}H_{17}ClN_6O_4$ 404.1002, found 404.1002.

N^2-Acetyl-9-(3-cyclopentenyl)-O^6-(2-(p-nitrophenyl)ethyl)guanine, 5

To a suspension of **3** (3.42 g, 10.0 mmol), 4-hydroxycyclopentene (1.00 g, 12.0 mmol) and triphenylphosphine (3.15 g, 12.0 mmol) in 50 mL of dry dioxane

was added dropwise DEAD (1.9 mL, 12.0 mmol) in 10 mL of dry dioxane at 0°C under nitrogen. The mixture was stirred at room temperature overnight to yield a clear solution. The solvent was removed and the residue was purified by flash column chromatography (80% EtOAc-hexane) to give 2.86 g (70%) of **5** as white crystalline solid. ^{1}H NMR (300 MHz) δ 2.58 (s, 3H), 2.65 (dd, J = 3.6, 15.6, 2H), 3.00 (dd, J = 8.1, 15.9, 2H), 3.31 (t, J = 6.9, 2H), 4.78 (t, J = 6.9, 2H), 5.19-5.28 (m, 1H), 5.92 (s, 2H), 7.49 (d, J = 8.7, 2H), 7.83 (br s, 2H), 8.16 (d, J = 8.7, 2H); ^{13}C NMR (75.5 MHz) δ 25.0, 34.8, 39.9, 52.9, 66.5, 117.7, 123.6, 128.9, 129.9, 139.9, 145.7, 146.8, 151.8, 152.7, 160.5, 171.2; MS *m/z* 409 (M+1, 100); HRMS calcd for $C_{20}H_{21}N_6O_4$ 409.1624, found 409.1643.

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