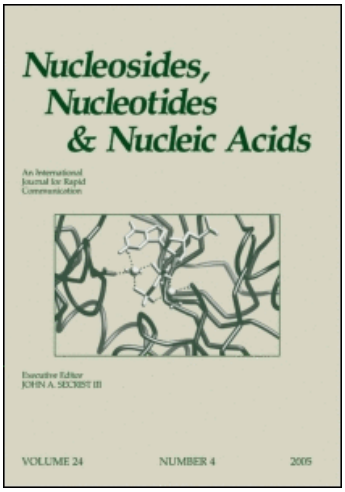

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EFFICIENT SYNTHESIS OF [2-^{15}N]GUANOSINE AND 2′-DEOXY[2′-^{15}N]GUANOSINE DERIVATIVES USING *N*-(*tert*-BUTYLDIMETHYLSILYL)[^{15}N]PHTHALIMIDE AS A ^{15}N-LABELING REAGENT

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□ *Nucleophilic aromatic substitution of 9-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)-6-chloro-2-fluoro-9*H*-purine with* N-(tert-*butyldimethylsilyl)[^{15}N]phthalimide in the presence of a catalytic amount of CsF at room temperature in DMF efficiently afforded the 6-chloro-2-[^{15}N]phthalimidopurine derivative, which was subsequently converted to the [2-^{15}N]guanosine derivative. The 2′-deoxy[2′-^{15}N]guanosine derivative was also efficiently synthesized through a similar procedure.*

Keywords Nucleosides bearing ^{15}N-labeled exocyclic amino groups; [2-^{15}N]Guanosine; 2-Deoxy[2′-^{15}N]guanosine

INTRODUCTION

NMR studies of ^{15}N-labeled oligonucleotides have provided useful insights into nucleic acid structure, drug binding and nucleic acid–protein interactions.[1–12] We reported an efficient method for the synthesis of nucleosides bearing ^{15}N-labeled exocyclic amino groups using [^{15}N]phthalimide and potassium [^{15}N]phthalimide. [4-^{15}N]Cytidine, 2′-deoxy[4-^{15}N]cytidine, [6-^{15}N]adenosine, and 2′-deoxy[6-^{15}N]adenosine derivatives were efficiently synthesized by substitution of their respective azolyl derivatives with [^{15}N]phthalimide in the presence of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[13,14] [2-^{15}N]Guanosine and 2′-deoxy[2-^{15}N]guanosine were synthesized by substitution of their respective 2-fluoroinosine derivatives with potassium [^{15}N]phthalimide. These

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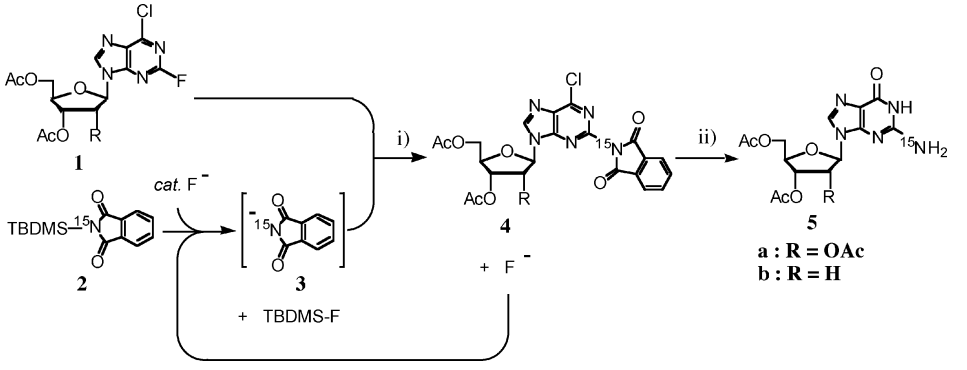
reactions took place at 90°C for 36–48 h in DMF to afford the N^2-phthaloyl[2-^{15}N]guanosine (62%) and 2′-deoxy-N^2-phthaloyl[2-^{15}N]guanosine (56%) derivatives, respectively.[15] Further investigations were then employed in an effort to develop a synthetic route toward the synthesis of [2-^{15}N]guanosine and 2′-deoxy[2-^{15}N]guanosine derivatives under mild conditions. Nucleophilic aromatic substitution of 6-chloro-2-fluoropurine derivatives **1**, prepared from guanine derivatives with potassium [^{15}N]phthalimide took place between room temperature and 60°C to afford the respective 6-chloro-2-[^{15}N]phthalimidopurine derivatives **4** (37–64%), which were subsequently converted to [2-^{15}N]guanine derivatives by alkaline hydrolysis.[15] Introduction of the chloro group as an electron-withdrawing group at the 6-position of the guanine moiety enhanced the reactivity at the 2-position, although this also resulted in the formation of 6-substituted by-products such as 2-fluoro-6-[^{15}N]phthalimidopurine derivatives **6** (5–27%) and 2,6-di[^{15}N]phthalimidopurine derivatives **7** (4–10%). Finally, investigations were performed with a view to improving the selectivity of substitution at the 2-position. Herein we report on the syntheses of [2-^{15}N]guanosine and 2′-deoxy[2-^{15}N]guanosine derivatives **5** using *N*-(*tert*-butyldimethylsilyl)[^{15}N]phthalimide (**2**)[16] as a ^{15}N-labeling reagent.

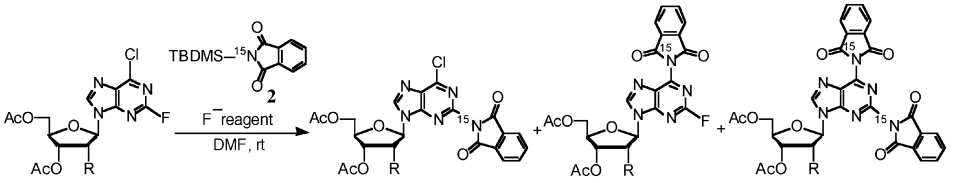
RESULTS AND DISCUSSION

We developed a synthetic route for the preparation of [2′-^{15}N]-guanosine and 2′-deoxy[2-^{15}N]guanosine derivatives **5** through nucleophilic aromatic substitution of 6-chloro-2-fluoropurine derivatives **1** with *N*-(*tert*-butyldimethylsilyl)[^{15}N]phthalimide (**2**) in the presence of a catalytic amount of a desilylating agent to afford the 6-chloro-2-[^{15}N]phthalimidopurine derivatives **4** as shown in Scheme 1. The high



SCHEME 1 Conditions: i) DMF, rt (see Table 1), ii) 1. sodium 2-cyanoethoxide/THF, 45°C, 1 h; 2. Ac_2O/pyridine/DMF, rt, 2 h; 3. 0.5 M $NH_2NH_2 \cdot H_2O$/1:4 AcOH-pyridine, rt, 30 min; 4. Ac_2O/pyridine. rt, 1 h.

TABLE 1 Nucleophilic Aromatic Substitution of 6-Chloro-2-fluoropurine Derivatives **1** with *N*-(*tert*-Butyldimethylsilyl)[^{15}N]phthalimide (**2**) in the Presence of Desilylating Reagents



Entry	Compound	**2** (equiv)	Desilylating (F^-) reagent (equiv)	Time (h)	Yield (%) **4**	**6**	**7**	Recovery (%) of [^{15}N]phthalimide based on **2**
1	**1a**	2.0[a]	TBAF (0.05 + 0.05)[b]	12 + 12	57[d]	19[d]	—	
2	**1a**	2.0[a]	CsF (0.05 + 0.05)[c]	12 + 12	84[d]	4[d]	—	
3	**1a**	2.0	CsF (0.05 + 0.05)[c]	12 + 12	85	4	—	42
4	**1a**	2.0[a]	CsF (0.1)	24	73[d]	—	—	
5	**1a**	1.5[a]	CsF (0.05 + 0.05)[c]	12 + 12	58[d]	—	—	
6	**1b**	2.0	CsF (0.05 + 0.05 + 0.05)[c]	12 + 12 + 4	79	4	—	49

[a]Reaction of **1a** with non-labeled *N*-TBDMS-phthalimide.

[b]The reaction was performed in the presence of Molecular Sieves 4 A (0.5 g/1 mmol of **1**). The commercially available 1 M tetrabutylammonium fluoride (TBAF)/THF solution, containing H_2O (~5 wt.%), was added portionwise after drying over Molecular Sieves 3 A for 12 h.

[c]Cesium fluoride (CsF) was added portionwise.

[d]Non-labeled phthalimidopurine derivative.

regioselectivity to the 2-position of the base moiety can be expected in the nucleophilic aromatic substitution, since this reaction system was designed to gradually generate the imido anion **3**.

Nucleophilic aromatic substitution of the 6-chloro-2-fluoropurine derivative **1a** with the ^{15}N-labeling reagent **2** in the presence of tetrabutylammonium fluoride (TBAF) or cesium fluoride (CsF) as a desilylating agent in DMF at room temperature was performed and the results are summarized in entries 1–5 of Table 1. When TBAF was used as the desilylation agent, the reaction remained incomplete with decomposition of the reagent **2** (entry 1 of Table 1). Possible contamination with H_2O from the TBAF solution could account for the aforementioned result. The most favorable result was obtained when using CsF as the desilylating agent (entries 2 and 3 of Table 1). Nucleophilic aromatic substitution of 6-chloro-2-fluoropurine derivative **1a** with the ^{15}N-labeling reagent **2** (2 equiv) in the presence of CsF (0.05 + 0.05 equiv) as a desilylating agent at room temperature for 24 h in DMF efficiently afforded the 6-chloro-2-[^{15}N]phthalimidopurine derivative **4a** in 85% yield (entry 3 of Table 1). In this reaction, formation of the 2,6-di[^{15}N]phthalimidopurine derivative **7** was not detected, while a small amount of the 2-fluoro-6-[^{15}N]phthalimidopurine derivative **6** (4% yield) was detected as a by-product, and [^{15}N]phthalimide was recovered in 42% yield based on the ^{15}N-labeling reagent **2**. The portionwise addition of CsF

was effective in this reaction (entries 2, 3, and 4 of Table 1). When the amount of ^{15}N-labeling reagent **2** was reduced from 2.0 to 1.5 equiv, the reaction remained incomplete (entry 5 of Table 1).

Next, the reaction of 2′-deoxyribofuranose derivative **1b** and the ^{15}N-labeling reagent **2** was carried out under similar conditions used for obtaining good results in the reaction of ribofuranose derivative **1a** and the ^{15}N-labeling reagent **2**. Nucleophilic aromatic substitution of the 6-chloro-2-fluoropurine derivative **1b** with the ^{15}N-labeling reagent **2** (2 equiv) in the presence of CsF (0.05 + 0.05 + 0.05 equiv) as a desilylating agent at room temperature for 28 h in DMF efficiently afforded the 6-chloro-2-[^{15}N]phthalimidopurine derivative **4b** in 79% yield (entry 6 of Table 1). With the 2′-deoxyribofuranose derivative **1b**, it was necessary to add CsF to 0.05 equivalent excess relative to the ribofuranose derivative **1a** since the reactivity of the 2′-deoxyribofuranose derivative **1b** was lower than the ribofuranose derivative **1a**.

^{15}N-Labeled compounds **4a** and **4b** were converted to [2-^{15}N]guanine derivatives **5a** and **5b** in 84 and 86% yields, respectively, according to the previously reported procedure.[15,17]

Thus, the syntheses of [2-^{15}N]guanosine and 2′-deoxy[2-^{15}N]guanosine derivatives **5** were efficiently accomplished by nucleophilic aromatic substitution of 6-chloro-2-fluoropurine derivatives **1** with *N*-(*tert*-butyldimethylsilyl)[^{15}N]phthalimide (**2**) in the presence of a catalytic amount of CsF as a desilylating agent to afford the 6-chloro-2-[^{15}N]-phthalimidopurine derivatives **4** and treatment with sodium 2-cyanoethoxide. The present investigation provides useful synthetic intermediates leading to the potential synthesis of oligonucleotides functionalized by ^{15}N-labels in the exocyclic amino group of guanosine and 2′-deoxyguanosine, in addition to those of adenosine, 2′-deoxyadenosine, cytidine, and 2′-deoxycytidine, as previously reported.[13,14]

EXPERIMENTAL

Column chromatography was performed on silica gel (Wakogel C-300, purchased from Wako Pure Chemicals, Co. Ltd.) by the use of methanol/chloroform, and hexane/ethyl acetate system. TLC was conducted on Merck silica gel F_{254} by developing with 1:9 methanol/chloroform or 1:4 hexane/ethyl acetate. Melting points were determined by a Yanaco micro-melting-point apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DRX 400 apparatus with $CDCl_3$ or DMSO-d_6 as an internal standard. ^{15}N-NMR spectra were recorded on a Brucker DRX 500-2 apparatus with liquid $^{15}NH_3$ as an external standard. Mass spectra were recorded on a Micromass Q-Tof Ultima API apparatus. Compounds **1a** and **1b** were prepared from guanosine and 2′-deoxyguanosine, respectively, as described previously.[15] Compounds **2** and non-labeled **2** were prepared according to the procedure described by Chun.[16]

***N*-(*tert*-Butyldimethylsilyl)[^{15}N]phthalimide (2).** To a stirred mixture of [^{15}N]phthalimide (2.96 g, 20 mmol, 99.7% ^{15}N-enriched, purchased from Shoko Co. Ltd.) in CH_2Cl_2 (20 mL) was slowly added triethylamine (5.6 mL, 40 mmol). The mixture was then refluxed for 6 h and cooled. The reaction solution was washed successively with 5% HCl solution (20 mL × 2) and H_2O (20 mL × 2). The organic layer was dried on $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **2** was obtained in 96% yield (5.05 g) as a white solid: mp 115–118°C; ^{1}H NMR (DMSO-d_6) δ 0.88 (s, 6H, -Si(CH_3)$_2$-C(CH$_3$)$_3$), 1.33 (s, 9H, -Si(CH$_3$)$_2$-C(CH_3)$_3$), 8.24–8.25 (m, 4H, Ph-*H* of the phthaloyl group); ^{15}N NMR (DMSO-d_6) δ 157.83; ESI-TOF Mass m/z calcd for $C_{14}H_{20}{}^{15}NO_2Si$ $(M + H)^+$, 263.1234; found, 263.1219.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-2-phthalimido-9*H*-purine (Non-labeled 4a). (Entry 1 of Table 1). To a stirred mixture of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-2-fluoro-9*H*-purine (**1a**) (0.83 g, 1.9 mmol), non-labeled **2** (1.00 g, 3.8 mmol), and Molecular Sieves 4 A (0.95 g) in DMF (7.8 mL) was added 1 M TBAF/THF solution (95 μL, 0.095 mmol, dried over Molecular Sieves 3A for 12 h) at room temperature. After 12 h, 1 M TBAF/THF solution (95 μL, 0.095 mmol) was added and the solution was stirred for a further 12 h. The resulting mixture was then quenched with H_2O (2 mL). Molecular Sieves was removed by filtration. The filtrate was diluted with chloroform (100 mL) and washed with H_2O (90 mL × 2). Following drying over anhydrous $MgSO_4$, the organic layer was evaporated to dryness, and the residue was subjected to chromatographic separation on a silica gel column using a hexane/ethyl acetate system to give non-labeled **4a** (0.61 g, 57%) and 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-fluoro-6-phthalimido-9*H*-purine (non-labeled **6a**) (0.20 g, 19%).

Non-labeled compound **4a** was a glass:[15] ^{1}H NMR ($CDCl_3$) δ 2.09, 2.10, 2.14 (3 s, 9H, COCH_3 × 3), 4.42–4.49 (m, 3H, H-4′, 5′, and 5″), 5.61 (dd, 1H, $J_{2',3'}$ = 5.5 Hz, $J_{3',4'}$ = 3.9 Hz, H-3′), 5.87 (dd, 1H, $J_{1',2'}$ = 5.6 Hz and $J_{2',3'}$ = 5.5 Hz, H-2′), 6.27 (d, 1H, $J_{1',2'}$ = 5.6 Hz, H-1′), 7.82–8.01 (m, 4H, Ph-*H* of the phthaloyl group), and 8.37 (s, 1H, H-8). Non-labeled compound **6a** was a glass[15]: ^{1}H NMR ($CDCl_3$) δ 2.11, 2.17, 2.18 (3s, 9H, COCH_3 × 3), 4.41–4.49 (m, 3H, H-4′, 5′, and 5″), 5.59 (dd, 1H, $J_{2',3'}$ = 5.5 Hz and $J_{3',4'}$ = 3.9 Hz, H-3′), 5.87 (dd, 1H, $J_{1',2'}$ = 6.1 Hz and $J_{2',3'}$ = 5.5 Hz, H-2′), 6.26 (d, 1H, $J_{1',2'}$ = 6.1 Hz, H-1′), 7.83–8.03 (m, 4H, Ph-*H* of the phthaloyl group), and 8.30 (s, 1H, H-8).

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-2-[^{15}N]phthalimido-9*H*-purine (4a). (Entry 3 of Table 1). To a stirred mixture of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-2-fluoro-9*H*-purine (**1a**) (1.32 g, 3.1 mmol) and **2** (1.61 g, 6.2 mmol) in DMF (12.4 mL) was added CsF (25 mg, 0.16 mmol) at room temperature. After 12 h, CsF (25 mg, 0.16 mmol)

was added and the solution was stirred for a further 12 h. The resulting mixture was then quenched with H_2O (3 mL). The solution was diluted with chloroform (150 mL) and washed with H_2O (90 mL × 2). Following drying over anhydrous $MgSO_4$, the organic layer was evaporated to dryness, and the residue was subjected to chromatographic separation on a silica gel column using a hexane/ethyl acetate system to give **4a** (1.46 g, 85%), 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-fluoro-6-[^{15}N]phthalimido-9*H*-purine (**6a**) (0.07 g, 4%), and [^{15}N]phthalimide (0.39 g, 42% based on **2**).

Compound **4a** was a glass:[15] ^{1}H NMR ($CDCl_3$) δ 2.08, 2.10, 2.13 (3 s, 9H, COCH_3 × 3), 4.43–4.47 (m, 3H, H-4′, 5′, and 5″), 5.61 (dd, 1H, $J_{2',3'} = 5.5$ Hz, $J_{3',4'} = 3.9$ Hz, H-3′), 5.86 (dd, 1H, $J_{1',2'} = 5.6$ Hz and $J_{2',3'} = 5.5$ Hz, H-2′), 6.27 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′), 7.82–8.00 (m, 4H, Ph-*H* of the phthaloyl group), and 8.37 (s, 1H, H-8); ^{15}N NMR ($CDCl_3$): δ 176.87 (N^2). ESI-TOF Mass m/z calcd for $C_{24}H_{21}ClN_4{}^{15}NO_9$ $(M + H)^+$, 559.0998; found, 559.1018.

Compound **6a** was a glass:[15] ^{1}H NMR ($CDCl_3$) δ 2.11, 2.16, 2.18 (3s, 9H, COCH_3 × 3), 4.42–4.49 (m, 3H, H-4′, 5′, and 5″), 5.60 (dd, 1H, $J_{2',3'} = 5.5$ Hz and $J_{3',4'} = 3.8$ Hz, H-3′), 5.88 (dd, 1H, $J_{1',2'} = 6.1$ Hz and $J_{2',3'} = 5.5$ Hz, H-2′), 6.26 (d, 1H, $J_{1',2'} = 6.1$ Hz, H-1′), 7.85–8.05 (m, 4H, Ph-*H* of the phthaloyl group), and 8.30 (s, 1H, H-8); ^{15}N NMR ($CDCl_3$) δ 170.20 (N^6). ESI-TOF Mass m/z calcd for $C_{24}H_{21}FN_4{}^{15}NO_9$ $(M + H)^+$, 543.1323; found, 543.1282.

9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)-6-chloro-2-[^{15}N]phthalimido-9*H*-purine (4b). (Entry 6 of Table 1). To a stirred mixture of 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)-6-chloro-2-fluoro-9*H*-purine (**1b**) (1.08 g, 2.9 mmol) and **2** (1.52 g, 5.8 mmol) in DMF (11.6 mL) was added CsF (23 mg, 0.15 mmol) at room temperature. After stirring for 12 h, CsF (23 mg, 0.15 mmol) was added to the solution. Furthermore, after 12 h, CsF (23 mg, 0.15 mmol) was added and the solution was stirred for 4 h. The resulting mixture was then quenched with H_2O (3 mL). The solution was diluted with chloroform (150 mL) and washed with H_2O (90 mL × 2). Following drying over anhydrous $MgSO_4$, the organic layer was evaporated to dryness, and the residue was subjected to chromatographic separation on a silica gel column using a hexane/ethyl acetate system to give **4b** (1.14 g, 79%), 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)-2-fluoro-6-[^{15}N]phthalimido-9*H*-purine (**6b**) (0.05 g, 4%), and [^{15}N]phthalimide (0.42 g, 49% based on **2**).

Compound **4b** was a glass:[15] ^{1}H NMR ($CDCl_3$) δ 2.09, 2.13 (2s, 6H, COCH_3 × 2), 2.72 (ddd, 1H, $J_{1',2'} = 6.0$ Hz, $J_{2',2''} = 13.7$ Hz, and $J_{2',3'} = 2.5$ Hz, H-2′), 2.95 (ddd, 1H $J_{1',2''} = 8.0$ Hz, $J_{2',2''} = 14.8$ Hz, and $J_{2'',3'} = 6.4$ Hz, H-2″), 4.32–4.41 (m, 3H, H-4′, 5′, and 5″), 5.40–5.42 (m, 1H, H-3′), 6.49 (dd, 1H, $J_{1',2'} = 6.0$ Hz and $J_{1',2''} = 8.0$ Hz, H-1′), 7.82–8.01 (m, 4H, Ph-*H* of the phthaloyl group), and 8.40 (s, 1H, H-8); ^{15}N NMR ($CDCl_3$) δ 178.08 (N^2). ESI-TOF Mass m/z calcd for $C_{24}H_{21}ClN_4{}^{15}NO_9$ $(M + H)^+$, 501.0943; found, 501.0937.

Compound **6b** was a glass:[15] ^{1}H NMR ($CDCl_3$) δ 2.09, 2.15 (2s, 6H, $COCH_3 \times 2$), 2.70 (ddd, 1H, $J_{1',2'} = 6.0$ Hz, $J_{2',2''} = 14.1$ Hz, and $J_{2',3'} = 2.4$ Hz, H-2′), 2.87–2.95 (m, 1H, H-2″), 4.36–4.40 (m, 3H, H-4′, 5′, and 5″), 5.41–5.43 (m, 1H, H-3′), 6.50 (dd, 1H, $J_{1',2'} = 6.0$ Hz and $J_{1',2''} = 8.1$ Hz, H-1′), 7.81–8.02 (m, 4H, Ph-*H* of the phthaloyl group), and 8.42 (s, 1H, H-8); ^{15}N NMR ($CDCl_3$) δ 170.22 (N^6). ESI-TOF Mass m/z calcd for $C_{24}H_{21}FN_4{}^{15}NO_9$ $(M + H)^+$, 485.1269; found, 485.1220.

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