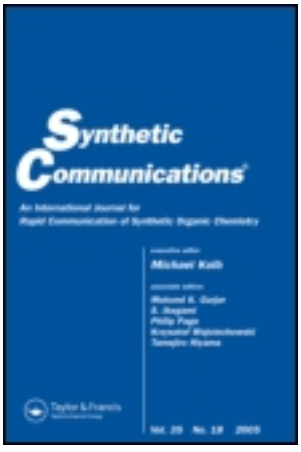

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Benzoyl Cyanide: A Mild and Efficient Reagent for Benzoylation of Nucleosides

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Abstract: Efficient benzoylation of various nucleosides has been accomplished in pyridine with a catalytic amount of DMAP and benzoyl cyanide under mild conditions.

Keywords: Benzoyl cyanide, nucleosides, DMAP, mild conditions

Protecting groups play a pivotal role in the synthesis of nucleic acids, polypeptides, oligosaccharides, and natural products. One of the most frequently used protecting groups for the blocking of hydroxyl and amino functionalities of a compound is a benzoyl group. The classical method for benzoylation of hydroxyl and amino groups is the treatment of the substrate with benzoyl chloride/benzoic anhydride[1] in the presence/absence of pyridine. A majority of these benzoylation reactions requires extended time periods, elevated temperatures or time-consuming work-up procedures. Further, acid chlorides and

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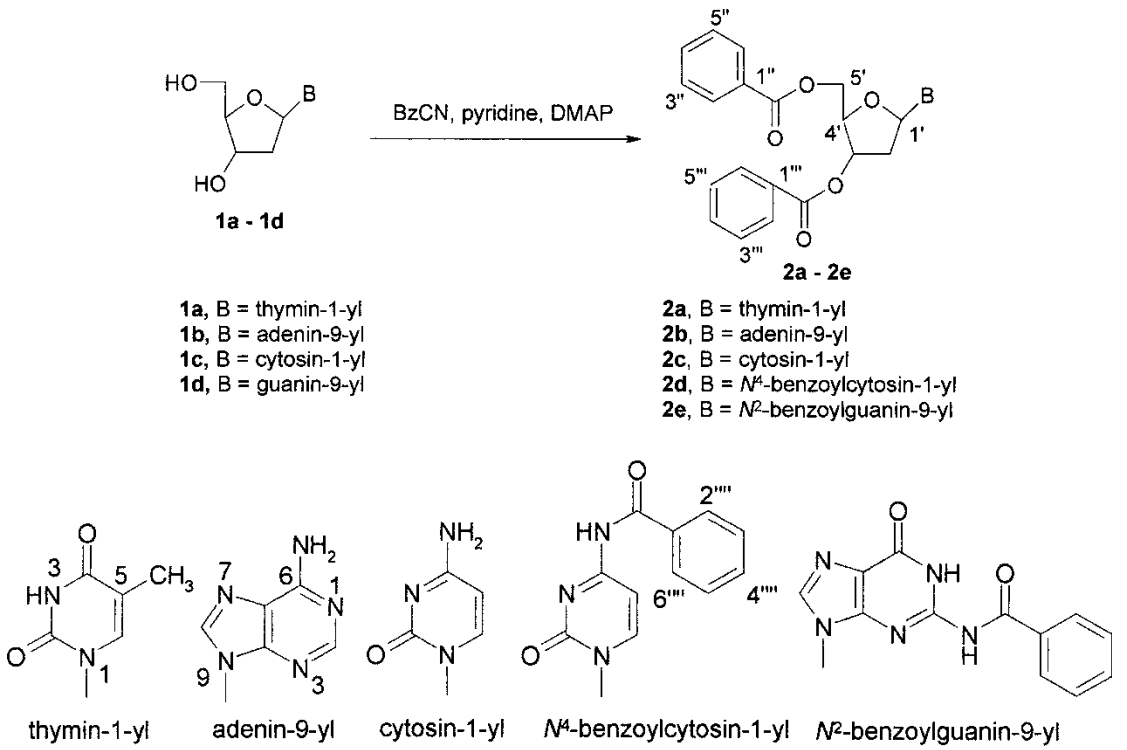
acid anhydrides, because they are reactive species, often lead to the formation of undesired products because of nonselective acylations.

During the course of the multistep synthetic protocol, particularly in nucleic-acid chemistry, often selective manipulation of hydroxyl and amino groups or different hydroxyl groups using mild protecting groups is required.[2–5] For example, protected nucleosides are required for the synthesis of oligonucleotides. To synthesize these compounds, selective manipulation of hydroxyl groups over amino groups of nucleobases and *vice versa* are required under mild conditions. Among various mild benzoylating agents, benzoyltetrazole[6] and acyl cyanides[7–11] have emerged as reagents of choice because of their chemoselectivity. Our ongoing interest in acylation reactions[12,13] encouraged us to expand and thoroughly investigate the applications of BzCN as a benzoylation reagent. Herein, we describe our results on benzoylation of ribo- and 2′-deoxyribonucleosides using BzCN as benzoylating agent.

Because unprotected nucleosides are soluble in pyridine at high concentrations, pyridine was chosen as the solvent of choice. Furthermore, we decided to use DMAP as a catalyst because of its known beneficial effects.[14] Thymidine (**1a**) was treated with BzCN[15–17] in the presence of pyridine and DMAP followed by usual workup to give white crystalline 3′,5′-di-*O*-benzoylthymidine (**2a**) in 94% yield (Scheme 1 and Table 1). The benzoylation of 2′-deoxyadenosine (**1b**) under similar conditions afforded 3′,5′-di-*O*-benzoyl-2′-deoxyadenosine (**2b**) in 93% yield. Interestingly, BzCN showed chemoselectivity toward the hydroxyl groups of sugar moiety over the C^6 amino group in **1b**. However, benzoylation of 2′-deoxycytidine (**1c**) under similar conditions with 2.2 equivalents of BzCN led to the formation of 3′,5′-di-*O*-benzoyl-2′-deoxycytidine (**2c**) and N^4,$O^{3'}$, $O^{5'}$-tribenzoyl-2′-deoxycytidine (**2d**) in 79.3 and 17.2% yields, respectively. Use of excess of BzCN (8.0 equivalents) led to the formation of perbenzoylated product **2d** in 96.5% yield (Scheme 1); benzoylation of **1c** carried out with 2.3 to 7.9 equivalents of BzCN led to the formation of inseparable mixtures. Benzoylation of 2′-deoxyguanosine (**1d**) under similar conditions led to the formation of multiple products with a major amount of starting material. The slow reaction of **1d** could be attributed to its poor solubility in pyridine at 40°C. The perbenzoylation of **1d** was accomplished with 6.0 equivalents of BzCN at 115°C, furnishing N^2,$O^{3'}$,$O^{5'}$-tribenzoyl-2′-deoxyguanosine (**2e**) in 89% yield.

Next, we extended the benzoylation study with ribonucleosides (Scheme 2 and Table 2). Benzoylation of 5-methyluridine (**3a**) furnished the expected 2′,3′,5′-tri-*O*-benzoyl-5-methyluridine (**4a**; 89%). On the other hand, benzoylation of adenosine (**3b**) led to the formation of 2′,3′,5′-tri-*O*-benzoyladenosine (**4b**) as a major product and N^6,$O^{2'}$,$O^{3'}$,$O^{5'}$-tetrabenzoyladenosine (**4c**) as a minor product (Scheme 2). Treatment of cytidine (**3c**) and guanosine (**3d**) with excess of BzCN furnished the anticipated perbenzoylated N^4,$O^{2'}$,$O^{3'}$, $O^{5'}$-tetrabenzoylcytidine (**4d**; 92.0%) and N^2,$O^{2'}$,$O^{3'}$,



Scheme 1.

Table 1.

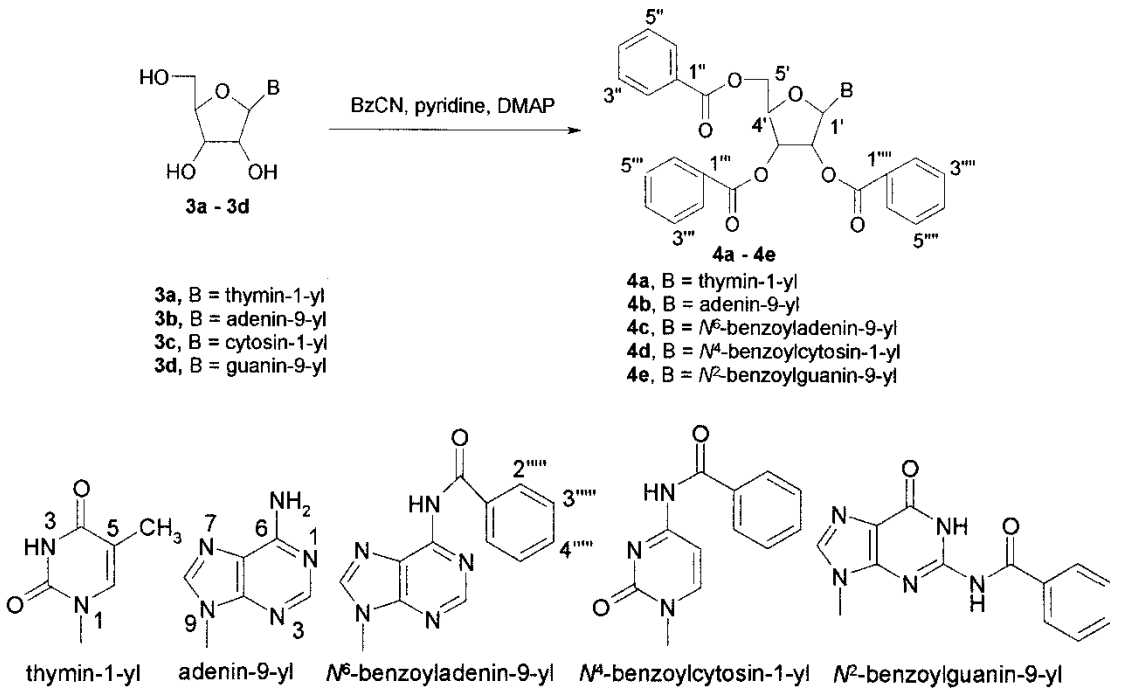
Starting compd.	BzCN (equiv.)	Reaction time/temperature	Product (s)	Yield (%)
1a	2.5	5 h/40°C	**2a**	94.0
1b	2.1	6 h/40°C	**2b**	93.0
1c	2.2	2 h/40°C	**2c**	79.3*
			2d	17.2*
1c	8.0	2 h/40°C	**2d**	96.5*
1d	6.0	4 h/115°C	**2e**	89.0

*The yields reported are on the basis of LC-MS analysis data.

$O^{5'}$-tetrabenzoylguanosine (**4e**; 88.5%). The high chemoselectivity observed in **1b** when treated with 2.1 equivalent of BzCN encouraged us to treat various nucleosides (**1c**, **1d**, **3b–d**) under similar conditions. Contrary to our expectations, all attempts to accomplish *O*-benzoylation with restricted amounts (~2–3 equivalents) of BzCN resulted in the formation of complex mixtures of *O*- and *N*-benzoylated products.

The structures of benzoylated nucleosides, *i.e.*, compounds **2a–e** and **4a–e**, were unambiguously established on the basis of their spectral analysis (IR, ^{1}H and ^{13}C NMR and LC-MS) and comparison of their melting points and/or spectral data with those reported in the literature;[18–25] melting points/physical states of known compounds **2c**, **2d**, and **4e** were not mentioned in their earlier reports.[20,21,25] The observed mp of **4a** and **4d** are not in good agreement with mp reported in the literature; however, their spectral data (^{1}H and ^{13}C NMR spectral data) match well with the reported data.[23] Further, different mp of compounds **4b** and **4c** have been reported by different authors[23–25] (see Experimental); our observed mp is in agreement with one of them in each case. We report herein the ^{1}H and ^{13}C NMR spectral data of all the benzoylated nucleosides.

In summary, we have demonstrated that BzCN is an efficient and mild benzoylating agent for a variety of compounds. Compared to the traditional benzoylation reagents such as benzoyl chloride or benzoic anhydride, use of BzCN has certain advantages. Most important, the by-product formed during benzoylation with BzCN is hydrogen cyanide,[17] which, being volatile, is easily removed, thus simplifying the reaction workup. For example, benzoylated nucleosides were isolated in a pure state by pouring the reaction mixtures into water and filtering the precipitated products. This protocol eliminates the tedious and expensive silica-gel column-chromatographic step for the isolation of the final products. We believe that the generality and simplicity of this reaction would encourage the use of BzCN as a reagent of choice for benzoylation in nucleic acid chemistry under mild conditions.



Scheme 2.

Table 2.

Starting compd.	BzCN (equiv.)	Reaction time/temperature	Product (s)	Yield (%)
3a	5.0	3 h/40°C	**4a**	89.0
3b	6.0	5 h/40°C	**4b**	71.5*
			4c	11.0*
3c	6.8	7 h/40°C	**4d**	92.0
3d	7.0	7 h/115°C	**4e**	88.5*

*The yields reported are on the basis of LC-MS analysis data.

EXPERIMENTAL

Melting points were determined on a Mettler FP 62 instrument or in a sulfuric-acid bath. The IR spectra were recorded on a Perkin-Elmer model 2000 FT-IR spectrometer by making KBr disc for solid samples and thin films for oils. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 Avance spectrometer at 300 and 75 MHz, respectively, using TMS as internal standard. The chemical shift values are on δ scale and the coupling constants (J) are in Hz. The LC-MS analysis was carried out on Agilent Ion Trap instrument. All nucleosides were coevaporated twice with pyridine and dried in vacuum desiccators prior to benzoylation. Analytical TLCs were performed on precoated Merck silica-gel $60F_{254}$ plates; the spots were detected either under UV light or by charring with 4% alcoholic H_2SO_4.

General Experimental Procedure for Benzoylation of Nucleosides with BzCN

The anhydrous compound (1 mmol) was dissolved in dry pyridine (5 ml, 20 ml in case of dG and G) followed by the addition of DMAP (10 mg) and BzCN (2.1–8.0 equivalents). The reaction mixture was allowed to stir at 40°C (115°C in the cases of dG and G) and the progress of the reaction followed by TLC. Upon completion, the reaction was poured over crushed ice under vigorous stirring and the precipitate filtered under vacuum, washed with water and petroleum ether, and dried to afford the corresponding benzoylated compounds. The melting points and ^{1}H and ^{13}C NMR data of benzoylated nucleosides are given below.

3′,5′-Di-*O*-benzoylthymidine (**2a**) (18): White solid (423 mg; 94%); mp 180–182°C (lit.[18] mp 192–193°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (3 H, s, C5-CH_3), 2.34 (1 H, p, $J = 5.4$ Hz C-2′H_a), 2.72 (1 H, dd, $J = 5.4$ Hz and 14.8 Hz, C-2′H_b), 4.54 (1 H, d, $J = 2.1$ Hz, C-4′H), 4.70 (1 H, dd, $J = 3.0$ Hz and 15.9 Hz, C-5′H_a), 4.79 (1 H, dd, $J = 3.0$ Hz and 15.9 Hz,

C-5′H_b), 5.66 (1 H, d, $J = 6.3$ Hz, C-3′H), 6.47 (1 H, dd, $J = 2.9$ Hz and 5.4 Hz, C-1′H), 7.26 (1 H, s, C-6H), 7.46–7.51 (4 H, m, C-3″H, C-3‴H, C-5″H, and C-5‴H), 7.60–7.64 (2 H, m, C-4″H and C-4‴H), 8.03–8.08 (4 H, m, C-2″H, C-2‴H, C-6″H, and C-6‴H) and 8.76 (1 H, s, NH);^{13}C NMR (75 MHz, $CDCl_3$): δ 12.50 (CH_3), 38.38 (C-2′), 64.68 (C-5′), 75.37 (C-3′), 83.04 (C-4′), 85.31 (C-1′), 112.10 (C-5), 128.97, 129.15, 129.39, 129.71, 129.87, and 130.18 (C-1″, C-1‴, C-2″, C-2‴, C-3″, C-3‴, C-5″, C-5‴, C-6″, and C-6‴), 134.07 and 134.09 (C-4″ and C-4‴), 134.74 (C-4), 150.64 (C-2), 163.74 (C-6), 166.35 and 166.41 (2 × ester CO); HRMS $[M + H]^+$ calcd. for $C_{24}H_{22}N_2O_7$ 451,1505; found 451,1521.

3′,5′-Di-*O*-benzoyl-2′-deoxyadenosine (**2b**) (19): White solid (427 mg; 93%); mp 116–120°C (lit.[19] mp 105–107°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (1 H, dd, $J = 5.1$ Hz and 13.8 Hz, C-2′H_a), 3.17 (1 H, p, $J = 7.2$ Hz, C-2′H_b), 4.67–4.81 (3 H, m, C-4′H and C-5′H), 5.79 (2 H, br s, -NH_2), 5.84 (1 H, br d, $J = 5.9$ Hz, C-3′H), 6.54 (1 H, t, $J = 6.9$ Hz, C-1′H), 7.41–7.51 (4 H, m, C-3″H, C-3‴H, C-5″H, and C-5‴H), 7.55–7.65 (2 H, m, C-4′H, and C-4‴H), 7.98–8.10 (5 H, m, C-8H, C-2″H, C-2‴H, C-6″H, and C-6‴H), 8.32 (1 H, s, C-2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.34 (C-2′), 64.73 (C-5′), 75.85 (C-3′), 83.44 (C-4′), 85.38 (C-1′), 129.09, 129.12, 130.20 and 130.34 (C-5, C-2″, C-2‴, C-3″, C-3‴, C-5″, C-5‴, C-6″, and C-6‴), 133.89 and 134.19 (C-4″ and C-4‴), 139.21 (C-1″ and C-1‴); 151.03 (C-6); 153.70 (C-2 and C-8), 156.09 (C-4), 166.45 and 166.68 (2 x ester CO); HRMS $[M + H]^+$ calcd. for $C_{24}H_{21}N_5O_5$ 460,1621; found 460,1636.

3′,5′-Di-*O*-benzoyl-2′-deoxycytidine (**2c**) (20): White solid (345 mg; 79.3%); mp 202–205°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (2 H, brs, NH_2), 2.16–2.28 (1 H, m, C-2′H_a), 2.89–2.93 (1 H, m, C-2′H_b), 4.56 (1 H, d, $J = 2.1$ Hz, C-4′H), 4.68–4.69 (2 H, brs, C-5′H), 5.59 (1 H, d, $J = 6.0$ Hz, C-5H), 5.65 (1 H, d, $J = 6.0$ Hz, C-3′H), 6.40 (1 H, t, $J = 6.5$ Hz, C-1′H), 7.42–7.49 (4 H, m, C-3″H, C-3‴H, C-5″H, and C-5‴H), 7.56–7.65 (3 H, m, C-6H, C-4″H, and C-4‴H), and 7.99 and 8.05 (4 H, 2d, 2 H each, $J = 7.5$ Hz each, C-2″H, C-2‴H, C-6″H, and C-6‴H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.20 (C-2′), 64.80 (C-5′), 75.53 (C-3′), 83.12 (C-4′), 87.19 (C-1′), 95.29 (C-5), 128.92, 129.00, 129.54, 129.76, 129.92, and 130.16 (C-2″, C-2‴, C-3″H, C-3‴H, C-5″H, C-5‴H, C-6″H and C-6‴H), 133.86 and 133.96 (C-1″, C-1‴, C-4″ and C-4‴), 140.50 (C-6), 156.02 (C-4), 166.10, 166.41 and 166.50 (C-2 and 2 × ester CO); HRMS $[M + H]^+$ calcd. for $C_{23}H_{21}N_3O_6$ 436,1509; found 436,1511.

N^4,$O^{3'}$,$O^{5'}$-Tribenzoyl-2′-deoxycytidine (**2d**) (21): White solid (520 mg; 96.5%); mp 198–200°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26–2.36 (1 H, m, C-2′H_a), 3.10 (1 H, dd, $J = 4.4$ Hz and 14.2 Hz, C-2′H_b), 4.67–4.80 (3 H, m, C-4′H, and C-5′H), 5.64 (1 H, br d, $J = 5.7$ Hz, C-3′H), 6.40 (1 H, t, $J = 6.5$ Hz, C-1′H), 7.43–7.53 (7 H, m, C-5H, C-3″H, C-3‴H, C-3⁗H, C-5″H, C-5‴H, and C-5⁗H), 7.56–7.63 (3 H, m, C-4″H, C-4‴H, and

C-4‴″H), 7.88, 7.99, and 8.07 (6 H, 3d, 2H each, $J = 7.3$ Hz, 7.6 Hz, and 7.9 Hz, respectively, C-2″H, C-6″H, C-2‴H, C-6‴H, C-2⁗H, and C-6⁗H), 8.12 (1 H, s, C-6H) and 8.71 (1 H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.77 (C-2′), 65.55 (C-5′), 76.39 (C-3′), 85.00 (C-4′), 88.99 (C-1′), 98.16 (C-5), 128.91, 129.95, 130.08, 130.44, 130.63, 130.90 and 131.20 (C-2″, C-2‴, C-2⁗, C-3″H, C-3‴H, C-3⁗H, C-5″H, C-5‴H, C-5⁗H, C-6″H, C-6‴H, and C-6⁗H), 134.60, 134.99 and 135.05 (C-6, C-1″, C-1‴, C-1⁗, C-4″, C-4‴ and C-4⁗), 144.84 (C-4), 163.68 (C-2), and 167.38 and 167.44 (2 × ester CO and amidic CO); HRMS $[M + H]^+$ calcd. for $C_{30}H_{25}N_3O_7$ 540,1771; found 540,1794.

N^2,$O^{3'}$,$O^{5'}$-Tribenzoyl-2′-deoxyguanosine (**2e**) (22): White solid (516 mg; 89%); mp 210–215°C (lit[22] mp 214°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65–2.75 (1 H, m, C-2′H_a), 3.26–3.35 (1 H, m, C-2′H_b), 4.72 (2 H, d, $J = 6.9$ Hz, C-5′H), 5.12 (1 H, q, $J = 7.3$ Hz, C-4′H), 6.02 (1 H, s,C-3′H), 6.32 (1 H, t, $J = 6.4$ Hz, C-1′H), 7.37–8.16 (16 H, m, aromatic protons, and C-8H), 9.55 (1 H, s, N^1-H) and 12.01 (1 H, s, C-2NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.70 (C-2′), 63.65 (C-5′), 75.21 (C-3′), 82.64 (C-4′), 86.20 (C-1′), 123.27 (C-5), 128.45, 128.95, 128.99, 129.38, 129.96 and 130.11 (C-2″, C-2‴, C-2⁗, C-3″, C-3‴, C-3⁗, C-5″, C-5‴, C-5⁗, C-6″, C-6‴, and C-6⁗), 134.02 and 134.09 (C-4″, C-4‴, and C-4⁗), 138.95 (C-1″, C-1‴, and C-1⁗), 147.73 and 147.91 (C-4 and C-8), 155.83 (C-2), 166.36 (C-6), and 167.32 and 168.28 (2 × ester CO and amidic CO); HRMS $[M + H]^+$ calcd. for $C_{31}H_{25}N_5O_7$ 580,1832; found 580,1886.

2′,3′,5′-Tri-*O*-benzoyl-5-methyluridine (**4a**) (23): White solid (507 mg; 89%); mp 155–160°C (lit[23] mp 98.0–99.5°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (3 H, s, CH_3), 4.64–4.68 (2 H, m, C-5′H), 4.89 (1 H, d, $J = 10.8$ Hz, C-4′H), 5.75 (1 H, t, $J = 6.0$ Hz, C-3′H), 5.90 (1 H, d, $J = 3.6$ Hz, C-2′H), 6.42 (1 H, d, $J = 6.3$ Hz, C-1′H), 7.16 (1 H, s, C-6H), 7.36–8.15 (15 H, m, aromatic protons) and 8.48 (1 H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.43 (CH_3), 65.27 (C-5′), 72.82 (C-3′), 74.74 (C-4′), 82.01 (C-2′), 88.35 (C-1′), 113.56 (C-6), 129.92, 130.23, 130.63, 131.02, 131.21, 131.30, 135.13, 136.18 (C-1″, C-1‴, C-1⁗,C-2″, C-2‴, C-2⁗, C-3″, C-3‴, C-3⁗, C-4″, C-4‴, C-4⁗, C-5″, C-5‴, C-5⁗, C-6″, C-6‴, C-6⁗, and C-5), 151.55 (C-2), 164.42 (C-4), 166.69, 166.77 and 167.35 (3 × ester CO); HRMS $[M + H]^+$ calcd. for $C_{31}H_{26}N_2O_9$ 571,1717; found 571,1736.

2′,3′,5′-Tri-*O*-benzoyladenosine (**4b**) (23,24): White solid (414 mg; 71.5%); mp 92–96°C (lit[23] mp 90–94°C, lit[24] mp 246–247°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.69–4.91 (3 H, m, C-4′H, and C-5′H), 5.87 (2 H, s, NH_2), 6.29 (1 H, d, $J = 4.5$ Hz, C-3′H), 6.39–6.42 (2 H, m, C-1′H, and C-2′H), 7.33–7.46 (6 H, m, C-3″H, C-3‴H, C-3⁗H, C-5″H, C-5‴H, and C-5⁗H), 7.51–7.57 (3 H, m, C-4″H, C-4‴H, and C-4⁗H), 7.93–8.10 (7 H, m, C-8H, C-2″H, C-2‴H, C-2⁗H, C-6″H, C-6‴H and C-6⁗H) and 8.28 (1 H, s, C-2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.00 (C-5′), 71.90 (C-3′), 74.42 (C-4′), 81.08 (C-2′), 87.33 (C-1′), 120.58 (C-5), 128.88,

128.92, 129.18, 129.81, 130.14, 130.20, 130.23, 133.75, 134.03, 134.11 and 139.52 (C-1″, C-1‴, C-1⁗,C-2″, C-2‴, C-2⁗, C-3″, C-3‴, C-3⁗, C-4″, C-4‴, C-4⁗, C-5″, C-5‴, C-5⁗, C-6″, C-6‴, and C-6⁗), 150.24 (C-6), 153.78 (C-4 and C-8), 155.93 (C-2), and 165.51, 165.68, and 166.54 (3 × ester CO); HRMS $[M + Na]^+$ calcd. for $C_{31}H_{25}N_5O_7$ 602,1652; found 602,1731.

N^6,$O^{2'}$,$O^{3'}$,$O^{5'}$-Tetrabenzoyladenosine (**4c**) (23,25): White solid (75 mg; 11%); mp 116–120°C (lit[23] mp 88–92°C, lit[25] mp 128.5–129.2°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72 (1 H, dd, $J = 3.9$ Hz and 12.1 Hz, C-5′H_a), 4.84 (1 H, q, $J = 4.1$ Hz, C-4′H), 4.91 (1 H, dd, $J = 4.0$ Hz and 12.0 Hz, C-5′H_b), 6.26 (1 H, t, $J = 5.3$ Hz, C-3′H), 6.37 (1 H, t, $J = 5.4$ Hz, C-2′H), 6.45 (1 H, d, $J = 4.8$ Hz, C-1′H), 7.38–8.25 (22 H, m, aromatic protons, C-2H, and C-8H), and 9.66 (1 H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.91 (C-5′), 71.89 (C-3′), 74.58 (C-4′), 81.22 (C-2′), 87.53 (C-1′), 119.80 (C-5), 128.72, 128.93, 128.97, 130.12, 130.23, 130.25, 130.34, 131.01, 133.42, 133.83, 134.10 and 134.19 (C-1″, C-1‴, C-1⁗, C-1⁗′, C-2″, C-2‴, C-2⁗, C-2⁗′, C-3″, C-3‴, C-3⁗, C-3⁗′,C-4″, C-4‴, C-4⁗, C-4⁗′,C-5″, C-5‴, C-5⁗, C-5⁗′, C-6″, C-6‴, C-6⁗, and C-6⁗′), 142.33 (C-6), 149.80 (C-4), 152.95 (C-8), 156.20 (C-2), and 165.57, 165.97, 166.58, and 171.03 (3 × ester CO and amidic CO).

N^4,$O^{2'}$,$O^{3'}$,$O^{5'}$-Tetrabenzoylcytidine (**4d**) (23): White solid (606 mg; 92%); mp 170–175°C (lit[23] mp 206.5–208.0°C). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 4.70–4.88 (3 H, m, C-4′H, and C-5′H), 5.84 (1 H, t, $J = 5.2$ Hz, C-3′H), 5.92 (1 H, t, $J = 5.5$ Hz, C-2′H), 6.46 (1 H, d, $J = 4.5$ Hz, C-1′H), 7.35–8.12 (22 H, m, aromatic protons, and C-5H, C-6H), and 8.95 (1 H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 64.42 (C-5′), 71.53 (C-3′), 74.76 (C-4′), 79.18 (C-2′), 92.74 (C-1′), 97.71 (C-5), 129.08, 129.29, 130.12 and 130.19 (C-2″, C-2‴, C-2⁗, C-2⁗′, C-3″, C-3‴, C-3⁗, C-3⁗′, C-5″, C-5‴, C-5⁗, C-5⁗′, C-6″, C-6‴, C-6⁗, and C-6⁗′), 133.41, 134.10, 134.39 and 134.49 (C-6, C-1″, C-1‴, C-1⁗, C-1⁗′, C-4″, C-4‴, C-4⁗, and C-4⁗′), 147.75 (C-4), 164.50 (C-2), and 165.40, 166.01, and 166.25 (3 × ester CO and amidic CO); HRMS $[M + Na]^+$ calcd. for $C_{37}H_{29}N_3O_9$, 682,1801; found 682,1901.

N^2,$O^{2'}$,$O^{3'}$,$O^{5'}$-Tetrabenzoylguanosine (**4e**) (25): White solid (619 mg; 88.5%); mp 130–135°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76–4.85 (3 H, m, C-4′H, and C-5′H), 6.17 (1 H, brs, C-3′H), 6.45 (1 H, brs, C-2′H), 6.93 (1 H, brs, C-1′H), 7.26–8.17 (21 H, m, aromatic protons, and C-8H), 9.50 (1 H, s, N^1-H), and 11.93 (1 H, s, C-2NH); ^{13}C NMR (75 Mz, $CDCl_3$): δ 61.93 (C-5′), 71.18 (C-3′), 74.69 (C-4′), 79.74 (C-2′), 88.46 (C-1′), 122.86 (C-5), 128.42, 128.84, 128.97, 129.03, 129.40, 129.65, 130.17 and 130.22 (C-2″, C-2‴, C-2⁗, C-2⁗′, C-3″, C-3‴, C-3⁗, C-3⁗′, C-5″, C-5‴, C-5⁗, C-5⁗′, C-6″, C-6‴, C-6⁗, and C-6⁗′), 131.76, 134.04, 134.21, 134.29, and 139.37 (C-2, C-1″, C-1‴, C-1⁗, C-1⁗′, C-4″, C-4‴, C-4⁗, and C-4⁗′), 147.38 and 147.89 (C-4 and C-8), 155.69 (C-6), 165.55, 166.43, 166.72,

and 167.72 (3 × ester CO and amidic CO); HRMS $[M + Na]^+$ calcd. for $C_{38}H_{29}N_5O_9$ 722,1863, found 722,1981.

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