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Efficient Sonogashira Coupling of Unprotected Halonucleosides in Aqueous Solvents Using Water-Soluble Palladium Catalysts

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A variety of applications of *C*-alkynylated nucleosides has prompted the continuing development of efficient synthetic methods for their preparation. We report an efficient and environmentally benign Sonogashira coupling reaction for alkynylation of unprotected halonucleosides in an aqueous solvent. The combination of $Pd(OAc)_2$, CuI, and TXPTS [trisodium tri(2,4-dimethyl-5-sulfonatophenyl)phosphane] provided an effective catalyst for the alkynylation of 8-bromopurines and 5-iodouridine in H_2O/CH_3CN (1:1) in yields ranging from 42 to 98%.

Introduction

Synthesis of non-natural nucleosides has attracted significant interest due to their crucial roles in biochemical systems.[1] Modified nucleosides containing alkynyl groups on the purine or pyrimidine base have received interest as potential anticancer and antiviral drugs,[2] as fluorescent[3] or spin-active[4] labels, and as methods to stabilize DNA duplex and triplex structures.[5] 5-Alkynyl-substituted uridine derivatives have received particular attention because this substitution does not impart any significant conformational changes in oligonucleotides incorporating the modified uridine base.[6] The importance of *C*-alkynylated nucleosides and nucleotides has prompted continuing efforts to develop efficient synthetic methods for alkynylation of nucleosides.

Palladium-catalyzed coupling reactions have provided powerful synthetic methods for the *C*-modification of nucleosides.[7] Because nucleosides are insoluble in typical organic solvents, the hydroxy groups are often protected to make the nucleoside more lipophilic prior to the coupling reaction. The protecting groups must then be removed after the coupling reaction, which results in a lower overall yield and increased waste production. Direct couplings of unprotected nucleosides in high polarity solvents in which they are soluble would provide a more atom-economical methodology. Alkynylations of unprotected pyrimidines, such as 5-iodouridine (5-IdU), are well precedented using DMF as the solvent.[7a] Examples of alkynylation of unprotected 8-halopurine nucleosides are less common, however.[8] 8-Bromoguanosine (8-BrG) and 8-bromo-2′-deoxyguanosine (8-BrdG) have proven particularly challenging with reported examples often requiring either harsh conditions (110 °C),[8f] long reaction times,[8g] or high copper (50 mol-%) and alkyne (4 equiv.) loadings.[8i]

Water-soluble palladium catalysts have received significant interest due to the potential environmental and economic benefits of doing catalysis in aqueous-organic biphasic systems.[9] Although there is a significant body of literature on the use of hydrophilic catalyst systems for cross-coupling of hydrophobic substrates, the use of aqueous solvents for homogeneous cross-coupling reactions of biomolecules has received less attention. Casalnuovo[10] initially reported the Suzuki and Sonogashira couplings of unprotected nucleosides, nucleotides, and amino acids using $Pd(TPPMS)_3$ [TPPMS = sodium diphenyl(3-sulfonatophenyl)phosphane] as the catalyst. Moderate to good yields were obtained for Sonogashira couplings of 5-iodopyrimidine nucleosides with alkynes, but no examples of purine alkynylations were reported. This methodology received limited attention until recently, however.

We[11] and others[12] have shown that palladium catalysts derived from water-soluble phosphanes are active catalysts for Suzuki couplings of 8-halopurine and 5-iodopyrimidine nucleosides under mild conditions. Sonogashira alkynylations of 5-IdU,[3d,12g] 6-chloropurine nucleosides,[12c] 7-iodo-7-deazapurine nucleosides and nucleotides[12e] and 8-bromo-2′-deoxyadenosine (8-BrdA)[12f] using catalysts derived from Pd/TPPTS [TPPTS = trisodium tri(3-sulfonatophenyl)phosphane, Figure 1] have been reported. To the best of our knowledge, there are no examples of alkynylation of 8-bromoguanosine derivatives under these conditions, however. The 8-bromopurines are less reactive in Pd-catalyzed cross-coupling reactions than 6-halopurines or 5-halopyrimidines due to the halogen being attached to the electron rich azole ring. 8-Bromoguanosines have proven to be particularly challenging substrates in our experience.[11b]

The Pd/TXPTS catalyst system showed high activity for Suzuki couplings of halonucleosides in aqueous solvent sys-

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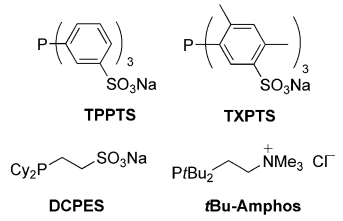
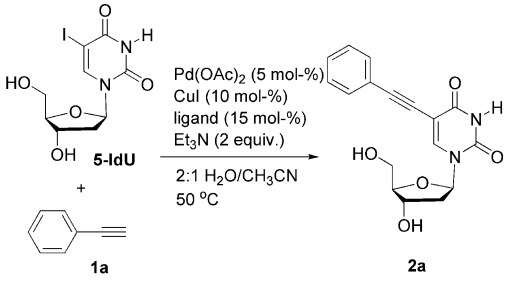


Figure 1. Water-soluble phosphanes screened for coupling of 5-IdU and phenylacetylene.

tems.[11a] We have also shown that this catalyst system gives higher activity in the Sonogashira coupling of simple aryl bromides than catalysts derived from TPPTS.[13] Based on these results, we have applied the Pd/TXPTS catalyst system to the aqueous-phase Sonogashira coupling of unprotected halonucleosides. We report an efficient and environmentally benign methodology for alkynylation of nucleosides using water-soluble palladium catalysts.

Results and Discussion

A series of water-soluble phosphanes (Figure 1) were screened for their ability to provide active palladium catalysts in a model Sonogashira coupling of unprotected 5-iodouridine (5-IdU) and phenylacetylene [**1a**, Equation (1)]. The TPPTS and TXPTS ligands had both provided effective catalysts for the Suzuki coupling of halonucleosides,[11a] while *t*Bu–Amphos provided effective catalysts for the Sonogashira coupling of simple aryl bromides.[14] Reactions were carried out in 2:1 H_2O/CH_3CN at 50 °C using a catalyst system derived from $Pd(OAc)_2$ (5 mol-%), CuI (10 mol-%), and the phosphane ligand (15 mol-%) in the presence of triethylamine (2 equiv.).



(1)

The *t*Bu–Amphos/Pd catalyst system showed the fastest initial formation of product. An aliquot taken immediately after addition of the alkyne showed 30% conversion (Figure 2). Complete consumption of 5-IdU occurred within 30 min, but the product selectivity was low as only approximately 60% conversion to product occurred. The TXPTS/Pd system gave approximately 90% conversion of 5-IdU to the desired product **2a** within 1.5 hours. The TPPTS catalyst system gave slow conversion to product with approximately 75% conversion after 6 hours. The catalyst derived from DCPES gave very slow conversion to product (13% after 6 h). At longer reaction times, slow loss of **2a** was observed in some cases due to the formation of small amounts of uncharacterized side products.

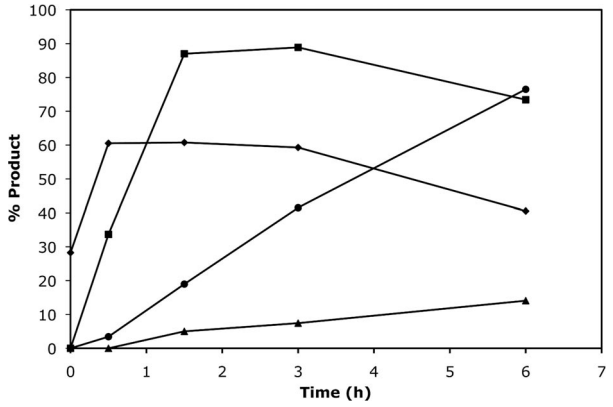
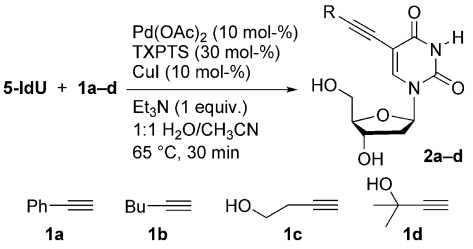


Figure 2. The variation of relative peak areas (%) of the products of Sonogashira couplings of 5-IdU and phenylacetylene with TPPTS(●), TXPTS (■), DCPES (▲), and *t*Bu–Amphos (♦); see also Equation (1).

The superior performance of TXPTS is consistent with our previous results in the Suzuki coupling of halonucleosides.[11a] Although *t*Bu–Amphos provides superior catalysts to TPPTS and TXPTS for the Suzuki and Sonogashira couplings of simple aryl bromides,[14] it was found to give lower activity catalysts in the Suzuki coupling of halonucleosides.[11a] In our previous studies, increased ligand cone angle correlated well with improved catalyst efficiency.[13–15] Therefore increased steric demand of TXPTS (cone angle: 206°) compared to TPPTS (165°) may account for the increased catalyst activity by promoting formation of the low-coordinate LPd^0 active species. The more electron rich *t*Bu–Amphos apparently gives a catalyst system that leads to undesired side products with 5-IdU. The *t*Bu–Amphos ligand may also be more easily displaced by the nucleoside base leading to inactive catalyst species.[11b]

In the course of these studies, slow decomposition of 5-IdU was observed under the reaction conditions. For example, heating a mixture of 5-IdU, $Pd(OAc)_2$, TPPTS, and Et_3N at 80 °C resulted in a loss of 34 and 77% of the initial 5-IdU after 5 and 14 hours, respectively. Therefore, the catalyst loading was raised to 10 mol-% Pd to ensure that the coupling reaction occurred at a faster rate than the decomposition. 5-IdU was coupled with alkynes **1a**–**d** using 10 mol-% $Pd(OAc)_2$, 10 mol-% CuI, 30 mol-% TXPTS, 1 equiv. of triethylamine at 65 °C in 1:1 H_2O/CH_3CN [Equation (2)]. Optimal yields were obtained when the al-



(2)

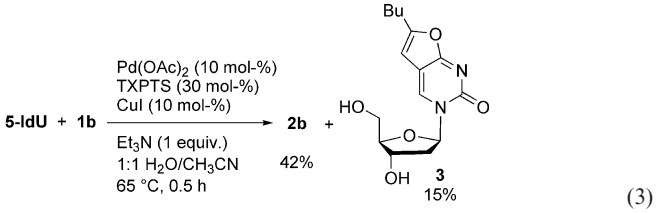
kyne was added in 3 portions during the course of the reaction, which limited loss of alkyne to homocoupling. The reactions reached completion within 30 min. Product **2a** derived from phenylacetylene was isolated in 71% yield under these conditions (Table 1). In comparison, repeating this reaction with *t*Bu–Amphos as the ligand gave **2a** in 43% yield.

Table 1. Sonogashira coupling of 5-IdU.

Entry	Alkyne	Product	Yield [%][a]
1	**1a**	**2a**	71
2	**1a**	**2a**	43[b]
3	**1b**	**2b**	42
4	**1c**	**2c**	55[c]
5	**1d**	**2d**	84

[a] Average isolated yield from two or more trials. Reactions carried out under conditions in Equation (2). [b] *t*Bu–Amphos used as the ligand. [c] Product coeluted with residual 5-IdU (18 wt.-%) as determined by ^{1}H NMR spectroscopy. Reported yield of **2c** obtained after subtracting mass of 5-IdU contaminant.

In contrast to the high yields achieved with phenylacetylene, reactions of 5-IdU with simple alkyl-substituted alkynes (**1b** and **1c**) gave lower yields (42 and 55%, respectively) of isolated products (entries 3–4). The more sterically hindered alkyne **1d** gave an 84% yield of **2d**, though. With the unhindered alkynes (**1b** and **1c**), formation of a cyclized byproduct was observed. In the case of 1-hexyne, the desired product **2b** and byproduct **3** were isolated in 42 and 15% yield, respectively [Equation (3)]. The formation of this cyclized byproduct is commonly observed in alkynylation of 5-IdU.[16] The rearrangement is catalyzed by metal ions, such as Cu^{I} and Pd^{II}. This rearrangement process appears to be competitive in the case of the sterically undemanding alkynes **1b** and **1c**, while the more hindered **1a** and **1d** do not undergo rearrangement to a significant extent over the course of the reaction.



(3)

The alkynylation conditions were further optimized for the 8-bromopurines (Table 2). Reactions of 8-BrdA and phenylacetylene were performed with varying CuI loadings ranging from 2–10 mol-% (entries 1–3) at room temperature. The conversion to product increased when the CuI loading was increased from 2 to 10 mol-%. This result is opposite to that seen in the Sonogashira coupling of simple aryl bromides using TXPTS/$Pd(OAc)_2$ where the reaction was most efficient when no copper cocatalyst was used.[13] An increase in conversion was observed when the TXPTS loading was increased from 10 mol-% to 15 mol-%, but further increases in the ligand loading had no significant effect (entries 4–7). The optimal 15 mol-% loading of TXPTS suggests that one equivalent of TXPTS is required for each metal center (5 mol-% Pd + 10 mol-% Cu). At least one equivalent of triethylamine was required (entries 8–11), but higher concentrations of base did not affect the catalyst performance.

Table 2. Optimization of the conditions for the coupling of 8-bromopurines and phenylacetylene.[a]

Entry	Substrate	CuI [mol-%]	TXPTS [mol-%]	Et_3N [equiv.]	*T* [°C]	Time [h]	*S*/*P*[b]
1	8-BrdA	2	25	2	r.t.	10	68:32
2	8-BrdA	5	25	2	r.t.	10	59:41
3	8-BrdA	10	25	2	r.t.	10	52:48
4	8-BrdA	10	10	2	r.t.	14	71:29
5	8-BrdA	10	15	2	r.t.	14	49:51
6	8-BrdA	10	20	2	r.t.	14	44:56
7	8-BrdA	10	25	2	r.t.	14	48:52
8	8-BrdG	10	30	0	65	1	99:1
9	8-BrdG	10	30	1	65	1	9:91
10	8-BrdG	10	30	2	65	1	10:90
11	8-BrdG	10	30	3	65	1	14:86

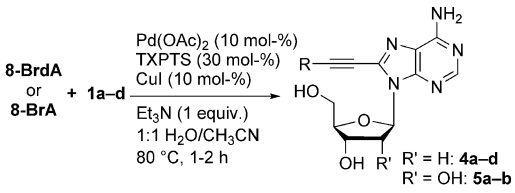
[a] Reactions were run under the conditions above using 5 mol-% $Pd(OAc)_2$ for 8-BrdA and 10 mol-% for 8-BrdG. [b] Substrate/product ratios based on HPLC peak areas. Peak areas were not adjusted for molar absorptivity of the substrates and products.

Using the optimized conditions [10 mol-% $Pd(OAc)_2$, 10 mol-% CuI, 30 mol-% TXPTS, and 1 equiv. of triethylamine in 1:1 H_2O/CH_3CN], 8-BrdA and 8-BrdG were coupled with alkynes **1a**–**d** [Table 3, Equations (4) and (5)]. These reactions were run at 80 °C to ensure complete conversion to product. Sonogashira couplings of 8-BrdA were completed in 1–2 hours to give the desired product (**4a**–**d**) in excellent yields (entries 1–4). Both phenylacetylene and alkyl-substituted alkynes gave excellent yields of product with no formation of side products. 8-Bromoadenosine (8-BrA) gave somewhat lower yields when coupled with **1a** and **1b** (entries 5–6) than were obtained with the deoxy analog (8-BrdA). Sonogashira couplings of 8-BrdG were completed under similar conditions to generate the desired products (**6a**–**d**) in excellent yields (entries 7–10). In the Suzuki coupling at room temperature, 8-BrdG significantly inhibits the Pd/TXPTS catalyst system,[11b] but there was little difference in the reactivity of 8-BrdA and 8-BrdG at the higher temperatures used in these reactions.

Table 3. Sonogashira couplings of 8-bromopurine nucleosides.

Entry	Nucleoside	**1**	Product	Yield [%][a]
1	8-BrdA	**1a**	**4a**	88
2	8-BrdA	**1b**	**4b**	89
3	8-BrdA	**1c**	**4c**	98
4	8-BrdA	**1d**	**4d**	98
5	8-BrA	**1a**	**5a**	53
6	8-BrA	**1b**	**5b**	74
7	8-BrdG	**1a**	**6a**	86
8	8-BrdG	**1b**	**6b**	85
9	8-BrdG	**1c**	**6c**	85
10	8-BrdG	**1d**	**6d**	84

[a] Average isolated yield from two or more trials. Reactions were run under conditions in Equations (4) and (5).



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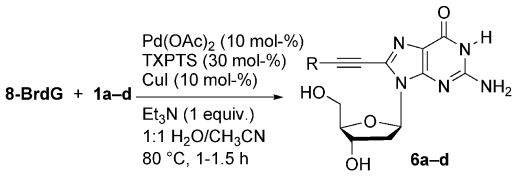

(5)

Conclusions

The catalyst derived from TXPTS and $Pd(OAc)_2$ provides an effective catalyst for the Sonogashira coupling of 8-halopurine nucleosides and 5-IdU under mild conditions in aqueous solvents from which the product nucleoside adducts can easily be recovered. The TXPTS ligand was found to give superior results to the more commonly used TPPTS as well as hydrophilic trialkylphosphanes, such as *t*Bu–Amphos. The TXPTS catalyst system showed good generality with 8-halopurine nucleosides for both aryl- and alkyl-substituted alkyne substrates. In the coupling with 5-IdU, the competitive cyclization of the alkyne adduct led to lower yields of product with sterically undemanding alkynes. This methodology represents the first example of Sonogashira coupling of unprotected 8-bromopurine nucleosides in an aqueous solvent system.

Experimental Section

General Procedure for Sonogashira Coupling of Halonucleosides and Alkynes: Palladium acetate (6.9 mg, 0.03 mmol), TXPTS (58.7 mg, 0.09 mmol), CuI (5.7 mg, 0.03 mmol), and the halonucleoside (0.3 mmol) were assembled in a round-bottomed flask sealed with a seputm in a nitrogen-filled glove box. After removal of the flask from the glove box, deoxygenated 1:1 water/acetonitrile (3 mL) was added, followed by addition of triethylamine (30.5 mg, 0.3 mmol). The reaction mixture was placed in an oil bath at 80 °C for 8-BrdA and 8-BrdG or at 65 °C for 5-IdU. The alkyne (0.6 mmol) was then added in three portions at 0, 15, and 25 min. The reaction mixture was stirred at 80 or 65 °C until RP-TLC (1:2 water/methanol) or RP-HPLC showed complete conversion (0.5–2 h). The reaction mixture was diluted with 10 mL of a mixture of 1:1 water/methanol and neutralized with 10% aqueous HCl solution. The solvent was evaporated and the crude product purified using reverse- or normal-phase silica gel.

5-(2-Phenyl-1-ethyn-1-yl)-2′-deoxyuridine (2a):[17] Using the general procedure, 5-IdU (102.6 mg, 0.290 mmol) was coupled with phenylacetylene (62.5 mg, 0.60 mmol). Product **2a** (67.7 mg, 71.2%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 11.69 (br. s, 1 H), 8.40 (s, 1 H), 7.49–7.47 (m, 2 H), 7.42–7.40 (m, 3 H), 6.14 (dd, J = 6.5, 6.5 Hz, 1 H), 5.27 (d, J = 4.5 Hz, 1 H), 5.17 (t, J = 4.8 Hz, 1 H), 4.29–4.25 (m, 1 H), 3.69–3.65 (m, 1 H), 3.62–3.58 (m, 1 H), 2.19–2.16 (m, 2 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 161.3, 149.3, 143.8, 131.0, 128.6, 128.5, 122.3, 98.1, 91.7, 87.5, 84.8, 82.4, 69.8, 60.7, 48.5, 40.1 ppm.

5-(1-Hexyn-1-yl)-2′-deoxyuridine (2b):[18] Using the general procedure, 5-IdU (108.4 mg, 0.306 mmol) was coupled with 1-hexyne (50.8 mg, 0.60 mmol). The product **2b** (39.6 mg, 42.0%) along with **3** was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.54 (br. s, 1 H), 8.11 (s, 1 H), 6.12 (dd, J = 6.8, 6.8 Hz, 1 H), 5.23 (d, J = 4.5 Hz, 1 H), 5.08 (t, J = 5.0 Hz, 1 H), 4.24–4.22 (m, 1 H), 3.80–3.78 (m, 1 H), 3.63–3.59 (m, 1 H), 3.58–3.54 (m, 1 H), 2.36 (t, J = 7.0 Hz, 2 H), 2.13–2.10 (m, 2 H), 1.51–1.45 (m, 2 H), 1.42–1.36 (m, 2 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 161.7, 149.4, 142.5, 99.0, 93.1, 87.5, 84.5, 72.7, 70.1, 60.9, 48.5, 30.2, 21.3, 18.4, 13.4 ppm, one was obscured by solvent.

6-Butyl-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)furano[2,3-*d*]-pyrimidin-2-one (3):[16a] (14.5 mg, 15.4%) isolated as byproduct with **2b**. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 8.67 (s, 1 H), 6.43 (s, 1 H), 6.16 (dd, J = 6.1, 6.1 Hz, 1 H), 5.28 (d, J = 4.3 Hz, 1 H), 5.12 (t, J = 5.4 Hz, 1 H), 4.25–4.20 (m, 1 H), 3.92–3.89 (m, 1 H), 3.70–3.57 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 2.40–2.34 (m, 1 H), 2.08–2.00 (m, 1 H), 1.64–1.55 (m, 2 H), 1.39–1.29 (m, 2 H), 0.90 (t, J = 7.38 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 171.1, 158.2, 153.7, 136.6, 106.2, 99.6, 88.0, 87.3, 69.6, 60.7, 41.1, 28.4, 26.9, 21.4, 13.5 ppm.

5-(4-Hydroxy-1-butyn-1-yl)-2′-deoxyuridine (2c):[16a] Using the general procedure, 5-IdU (137.3 mg, 0.3877 mmol) was coupled with 3-butyn-1-ol (0.0578 mg, 0.800 mmol). Adduct **2c** (77.0 mg, 67.0%) was obtained from the crude product by column chromatography using normal phase silica gel eluted with 95:5 acetone/MeOH. The product co-eluted with 5-IdU (88:12 **2c**/5-IdU, mol/mol) as determined by NMR spectroscopy. Yield of **2c** was 63.4 mg (55.2%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.56 (br. s, 1 H), 8.12 (s, 1 H), 6.12 (dd, J = 6.7, 6.7 Hz, 1 H), 5.22 (d, J = 4.3 Hz, 1 H), 5.07 (t, J = 5.0 Hz, 1 H), 4.83 (t, J = 5.6 Hz, 1 H), 4.25–4.22 (m, 1 H), 3.81–3.78 (m, 1 H), 3.63–3.51 (m, 4 H), 2.50 (t, J = 7.0 Hz, 2 H), 2.12–2.08 (m, 2 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 161.7, 149.3, 142.8, 98.8, 90.9, 87.4, 84.5, 73.3, 70.1, 60.9, 59.6, 23.3 ppm, one carbon resonance obscured by solvent.

5-(3-Hydroxy-3-methyl-1-butyn-1-yl)-2′-deoxyuridine (2d): Using the general procedure, 5-IdU (105.2 mg, 0.2971 mmol) was coupled with 2-methyl-3-butyn-2-ol (0.0515 mg, 0.600 mmol). Adduct **2d** (77.1 mg, 83.6%) was obtained from the crude product by column chromatography using normal phase silica eluted with 2:8 acetone/ethyl acetate. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 11.49 (br. s, 1 H), 8.14 (s, 1 H), 6.12 (dd, J = 6.7, 6.7 Hz, 1 H), 5.40 (br. s, 1 H), 5.26 (br. s, 1 H), 5.12 (br. s, 1 H), 4.26–4.22 (m, 1 H), 3.81–3.78 (m, 1 H), 3.65–3.55 (m, 2 H), 2.14–2.11 (m, 2 H), 1.42 (s, 6 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 161.4, 149.4, 143.1, 98.5, 98.3, 87.5, 84.6, 73.0, 70.0, 63.6, 60.9, 40.0, 31.5 ppm. HRMS-EI (m/z): [M – H$_2$O]$^+$ calcd. for $C_{14}H_{15}N_2O_5$, 292.1059; found, 292.1059.

8-(2-Phenyl-1-ethyn-1-yl)-2′-deoxyadenosine (4a): Using the general procedure, 8-BrdA (99.0 mg, 0.30 mmol) was coupled with phenylacetylene (62.5 mg, 0.60 mmol). Adduct **4a** (92.8 mg, 88.0%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 8.18 (s, 1 H), 7.71–7.50 (m, 5 H), 7.65 (br. s, 2 H), 6.54 (dd, J = 6.8, 7.6 Hz, 1 H),

5.37 (d, J = 4.7 Hz, 1 H), 5.34–5.31 (m, 1 H), 4.54–4.49 (m, 1 H), 3.93–3.90 (m, 1 H), 3.72–3.66 (m, 1 H), 3.55–3.48 (m, 1 H), 3.20–3.12 (m, 1 H), 2.31–2.25 (m, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 156.0, 153.3, 148.5, 132.7, 131.8, 130.3, 129.0, 119.8, 119.5, 94.2, 88.2, 84.9, 78.5, 71.1, 62.1, 37.7 ppm. HRMS-EI (m/z): [M]$^+$ calcd. for $C_{18}H_{17}N_5O_3$, 351.1331; found, 351.1322.

8-(1-Hexyn-1-yl)-2′-deoxyadenosine (4b): Using the general procedure, 8-BrdA (99.0 mg, 0.299 mmol) was coupled with 1-hexyne (61.0 mg, 0.51 mmol). Adduct **4b** (88.3 mg, 89.0%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 8.13 (s, 1 H), 7.53 (br. s, 2 H), 6.41 (dd, J = 8.3, 6.5 Hz, 1 H), 5.41 (dd, J = 7.9, 4.3 Hz, 1 H), 5.32 (d, J = 4.0 Hz, 1 H), 4.49–4.45 (m, 1 H), 3.91–3.88 (m, 1 H), 3.70–3.64 (m, 1 H), 3.53–3.46 (m, 1 H), 3.16–3.09 (m, 1 H), 2.59 (t, J = 14.0 Hz, 2 H), 2.20–2.14 (m, 1 H), 1.63–1.55 (m, 2 H), 1.51–1.41 (m, 2 H), 0.93 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ = 155.8, 152.9, 148.2, 133.3, 119.0, 97.5, 88.2, 85.1, 71.2, 70.2, 62.1, 37.5, 29.4, 21.3, 18.1, 13.3 ppm. HRMS-EI (m/z): [M]$^+$ calcd. for $C_{16}H_{21}N_5O_3$, 331.1644; found, 331.1653.

8-(4-Hydroxy-1-butyn-1-yl)-2′-deoxyadenosine (4c): Using the general procedure, 8-BrdA (101.4 mg, 0.307 mmol) was coupled with 3-butyn-1-ol (43.0 mg, 0.60 mmol). Adduct **4c** (93.7 mg, 98.0%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.15 (s, 1 H), 7.52 (br. s, 2 H), 6.44 (dd, J = 8.0, 6.8 Hz, 1 H), 5.40 (dd, J = 8.0, 4.0 Hz, 1 H), 5.33 (d, J = 4.0 Hz, 1 H), 5.05 (t, J = 5.5 Hz, 1 H), 4.41–4.47 (m, 1 H), 3.92–3.89 (m, 1 H), 3.70–3.64 (m, 3 H), 3.54–3.49 (m, 1 H), 3.15–3.10 (m, 1 H), 2.72–2.71 (t, J = 6.5 Hz, 2 H), 2.21–2.17 (m, 1 H) ppm. ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ = 156.4, 153.5, 148.8, 133.9, 119.6, 96.4, 88.8, 85.6, 71.8, 71.2, 62.8, 59.6, 38.2, 23.7 ppm. HRMS-EI (m/z): [M]$^+$ calcd. for $C_{14}H_{17}N_5O_4$, 319.1281; found, 319.1286.

8-(3-Hydroxy-3-methyl-1-butyn-1-yl)-2′-deoxyadenosine (4d): Using the general procedure, 8-BrdA (102.0 mg, 0.3090 mmol) was coupled with 2-methyl-3-butyn-2-ol (51.5 mg, 0.600 mmol). Adduct **4d** (101.1 mg, 98.2%) was purified by column chromatography using normal phase silica gel eluted with a gradient of neat ethyl acetate to 1:4 MeOH/ethyl acetate. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.15 (s, 1 H), 7.57 (br. s, 2 H), 6.41 (dd, J = 7.9, 6.8 Hz, 1 H), 5.85 (s, 1 H), 5.41 (dd, J = 7.9, 4.3 Hz, 1 H), 5.35 (d, J = 4.0 Hz, 1 H), 4.52–4.47 (m, 1 H), 3.92–3.89 (m, 1 H), 3.72–3.66 (m, 1 H), 3.55–3.48 (m, 1 H), 3.14–3.07 (m, 1 H), 2.23–2.16 (m, 1 H), 1.52 (s, 6 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 155.9, 153.1, 148.3, 132.8, 119.2, 101.6, 88.3, 85.0, 71.2, 70.2, 63.7, 62.2, 37.7, 30.85, 30.83 ppm. HRMS-EI (m/z): [M]$^+$ calcd. for $C_{15}H_{19}N_5O_4$, 333.1437; found, 333.1437.

8-(2-Phenylethyn-1-yl)adenosine (5a):[8c] Using the general procedure, 8-BrA (103.9 mg, 0.299 mmol) was coupled with phenylacetylene (62.5 mg, 0.60 mmol). Adduct **5a** (58.1 mg, 53.1%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.18 (s, 1 H), 7.70–7.68 (m, 4 H), 7.56–7.52 (m, 3 H), 6.05 (d, J = 6.8 Hz, 1 H), 5.57 (dd, J = 8.4, 3.6 Hz, 1 H), 5.49 (d, J = 6.6 Hz, 1 H), 5.26 (d, J = 4.8 Hz, 1 H), 5.02 (dd, J = 12.2, 6.5 Hz), 4.21 (td, J = 5.1, 2.5 Hz, 1 H), 4.01 (dd, J = 5.7, 3.4 Hz, 1 H), 3.70 (dt, J = 12.2, 3.9 Hz, 1 H), 3.55 (ddd, J = 12.3, 8.4, 3.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 156.0, 153.3, 148.5, 133.2, 131.8, 130.3, 129.0, 119.8, 119.5, 94.2, 89.3, 86.6, 78.4, 71.6, 70.9, 62.1 ppm.

8-(1-Hexyn-1-yl)adenosine (5b):[8c] Using the general procedure, 8-BrA (109.6 mg, 0.316 mmol) was coupled with1-hexyne (73.9 mg, 0.90 mmol). Adduct **5b** (82.0 mg, 74.5%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.13 (s, 1 H), 7.57 (br. s, 2 H), 5.93 (d, J = 6.8 Hz, 1 H), 5.56 (dd, J = 8.6, 3.9 Hz, 1 H), 5.41 (d, J = 6.1 Hz, 1 H), 5.18 (d, J = 4.5 Hz, 1 H), 5.00 (dd, J = 11.8, 6.6 Hz, 1 H), 4.18 (td, J = 4.8, 2.3 Hz, 1 H), 3.96 (dd, J = 6.1, 3.9 Hz, 1 H), 3.67 (dt, J = 12.0, 3.9 Hz, 1 H), 3.52 (ddd, J = 12.3, 8.6, 4.1 Hz, 1 H), 2.58 (t, J = 6.9 Hz, 2 H), 1.62–1.54 (m, 2 H), 1.50–1.40 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 156.4, 153.5, 148.8, 134.5, 119.6, 97.9, 89.8, 87.0, 72.0, 71.5, 70.7, 62.7, 30.0, 21.8, 18.7, 13.8 ppm.

8-(2-Phenylethyn-1-yl)-2′-deoxyguanosine (6a):[8g] Using the general procedure, 8-BrdG (105.5 mg, 0.305 mmol) was coupled with phenylacetylene (62.5 mg, 0.60 mmol). Adduct **6a** (96.5 mg, 86.1%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 10.86 (br. s, 1 H), 7.65–7.62 (m, 2 H), 7.51–7.49 (m, 3 H), 6.61 (br. s, 2 H), 6.34 (dd, J = 7.2, 7.2 Hz, 1 H), 5.29 (d, J = 4.3 Hz, 1 H), 4.87 (t, J = 5.9 Hz, 1 H), 4.43–4.40 (m, 1 H), 3.83–3.79 (m, 1 H), 3.65–3.59 (m, 1 H), 3.54–3.48 (m, 1 H), 3.12–3.05 (m, 1 H), 2.21–2.15 (m, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 156.5, 154.4, 151.4, 132.1, 130.4, 129.5, 129.4, 121.0, 118.0, 93.1, 88.2, 84.0, 80.2, 71.5, 62.6, 37.8 ppm.

8-(1-Hexyn-1-yl)-2′-deoxyguanosine (6b): Using the general procedure, 8-BrdG (104.2 mg, 0.301 mmol) was coupled with phenylacetylene (50.8 mg, 0.60 mmol). Adduct **6b** (89.0 mg, 85%) was obtained after elution of the crude product through RP-silica gel eluting with a gradient ranging from water to 40:60 water/methanol. ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 10.76 (br. s, 1 H), 6.48 (br. s, 2 H), 6.24 (dd, J = 7.9, 6.8 Hz, 1 H), 5.24 (d, J = 4.0 Hz, 1 H), 4.87 (t, J = 5.9 Hz, 1 H), 4.37–4.35 (m, 1 H), 3.80–3.77 (m, 1 H), 3.64–3.57 (m, 1 H), 3.52–3.45 (m, 1 H), 3.09–3.01 (m, 1 H), 2.52 (t, J = 6.8 Hz, 2 H), 2.22–2.05 (m, 1 H), 1.60–1.52 (m, 2 H), 1.48–1.38 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 156.2, 153.5, 150.4, 129.7, 116.7, 95.3, 71.1, 71.0, 62.1, 36.9, 29.5, 21.3, 18.2, 13.3 ppm. HRMS-EI (m/z): [M]$^+$ calcd. for $C_{16}H_{21}N_5O_4$, 347.1594; found, 347.1589.

8-(4-Hydroxy-1-butyn-1-yl)-2′-deoxyguanosine (6c): Using the general procedure, 8-BrdG (100.0 mg, 0.289 mmol) was coupled with 3-butyn-1-ol (43.4 mg, 0.60 mmol). Adduct **6c** (82.6 mg, 85.2%) was purified by column chromatography using normal phase silica gel eluted with 1:1 MeOH/ethyl acetate. ^{1}H NMR (360 MHz, [D$_6$]-DMSO): δ = 11.05 (br. s, 1 H), 6.61 (br. s, 2 H), 6.26 (dd, J = 7.4, 7.4 Hz, 1 H), 5.26 (br. s, 1 H), 5.02 (br. s, 2 H), 4.40–4.38 (m, 1 H), 3.82–3.78 (m, 1 H), 3.64–3.61 (m, 3 H), 3.53–3.49 (m, 1 H), 3.10–3.02 (m, 1 H), 2.66 (t, J = 6.84 Hz, 2 H), 2.12–2.06 (m, 1 H) ppm. ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ = 157.1, 154.6, 151.1, 130.1, 117.3, 94.0, 88.3, 84.2, 72.1, 71.6, 62.7, 59.6, 37.6, 23.8 ppm. HRMS-ESI (m/z): [M + H]$^+$ calcd. for $C_{14}H_{17}N_5O_5$, 336.1308; found, 336.1312.

8-(3-Hydroxy-3-methyl-1-butyn-1-yl)-2′-deoxyguanosine (6d): Using the general procedure, 8-BrdG (104.0 mg, 0.300 mmol) was coupled with 2-methyl-3-butyn-2-ol (51.5 mg, 0.60 mmol). Adduct **6d** (88.5 mg, 84.4%) was purified by column chromatography using normal phase silica gel eluted with a solvent gradient ranging from CH_2Cl_2 to 25:75 MeOH/CH_2Cl_2. ^{1}H NMR (360 MHz, [D$_6$]-DMSO): δ = 10.91 (br. s, 1 H), 6.64 (br. s, 2 H), 6.24 (dd, J = 7.2, 7.2 Hz, 1 H), 5.74 (s, 1 H), 5.27 (d, J = 4.3 Hz, 1 H), 4.91 (t, J =

5.9 Hz, 1 H), 4.25–4.38 (m, 1 H), 3.81–3.77 (m, 1 H), 3.68–3.62 (m, 1 H), 3.55–3.49 (m, 1 H), 3.09–3.02 (m, 1 H), 2.24–2.07 (m, 1 H), 1.49 (s, 6 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 155.9, 153.7, 150.6, 129.1, 117.0, 99.5, 87.6, 83.4, 71.1, 70.9, 63.6, 62.0, 37.0, 30.92, 30.90 ppm. HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd. for $C_{15}H_{19}N_5O_5$, 350.1464; found, 350.1458.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds in Tables S1 and S3.

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