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Synthesis of Deuterated 1,2,3-Triazoles

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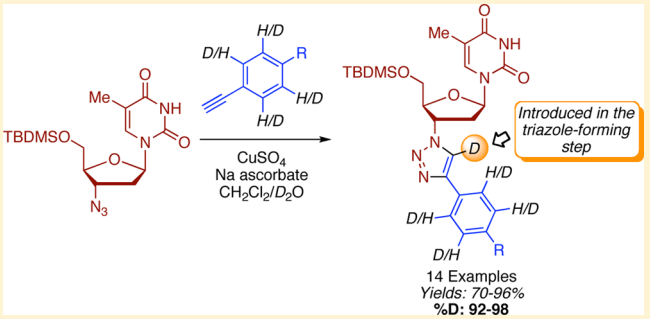
Supporting Information

ABSTRACT: The copper-catalyzed azide−alkyne cycloaddition (CuAAC) is a highly effective method for the selective incorporation of deuterium atom into the C-5 position of the 1,2,3-triazole structure. Reactions of alkynes and azides can be conveniently carried out in a biphasic medium of CH_2Cl_2/D_2O, using the $CuSO_4$/Na ascorbate system. The mildness of the method renders it applicable to substrates of relatively high complexity, such as nucleosides. Good yields and high levels of deuterium incorporation were observed. A reaction conducted in equimolar H_2O and D_2O showed 2.7 times greater incorporation of hydrogen atom as compared to deuterium. This is consistent with the H^+ and D^+ ion concentrations in H_2O and D_2O, respectively. With appropriately deuterated precursors, partially to fully deuterated triazoles were assembled where the final deuterium atom was incorporated in the triazole-forming step.



INTRODUCTION

The Huisgen ligation of azides and alkynes is an exceptionally atom-economical reaction leading to the formation of 1,2,3-triazoles.[1] However, the thermal process is not regioselective, resulting in the formation of 1,4- and 1,5-disubstituted 1,2,3-triazoles. The copper-catalyzed azide−alkyne cycloaddition (CuAAC) has emerged as an outstanding procedure for access to 1,4-disubstituted 1,2,3-triazoles, in a regioselective manner.[2−4]

The mechanism of the copper-catalyzed reaction of azides and terminal alkynes has been actively investigated[5−8] and several notable factors have emerged. Under catalytic conditions, the reaction is second order in Cu^I, either due to the involvement of one Cu each with the azide and the alkyne,[6,7] or due to the involvement of two Cu centers with the alkyne.[5] There has also been a question of the involvement of alkyne with π-coordinated copper versus a copper acetylide.[6−8] In this regard, the experimental evidence suggests intermediacy of Cu-acetylides from terminal alkynes. This is because the CuAAC reaction of PhC≡C−D with $PhCH_2N_3$ in *t*-BuOH/H_2O gave only the C-5 *protio triazole*,[8] consistent with a prior observation.[6] Therefore, CuAAC reactions of alkynes with a terminal deuterium atom are unlikely to lead to C-5 deuterated triazoles under aqueous conditions. However, aqueous conditions produce faster reactions.[7] To our knowledge, use of alkynes with a terminal deuterium atom in azide−alkyne cycloadditions is rare, and their use would be limited to processes where the deuterium will not be lost. In one example, an alkyne with a terminal deuterium atom has been employed in a thermal intramolecular reaction so as to control the cycloaddition regiochemistry and to ensure retention of the heavier isotope.[9]

A review of the literature indicated that although deuteration of 1,2,3-triazoles has been accomplished, procedures for C-5 deuteration are not particularly simple as compared to the CuAAC approach. For instance, C-5 deuterated triazoles can be obtained from alkynyl aluminum[10] or copper[11] intermediates or via lithiation of the triazole (Scheme 1).[12] Notably, the isolated alkynyl copper intermediate in Scheme 1 did not undergo ligation with azide in the absence of $MeCO_2H(D)$.[11] In a

Scheme 1. Known Syntheses of Deuterated Triazoles

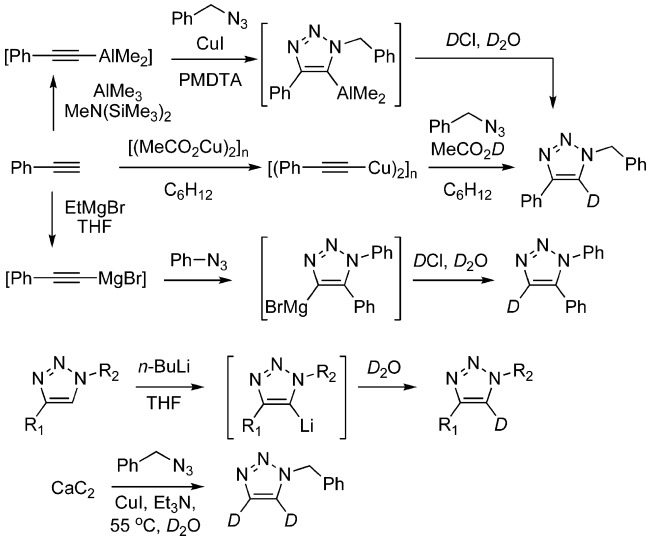


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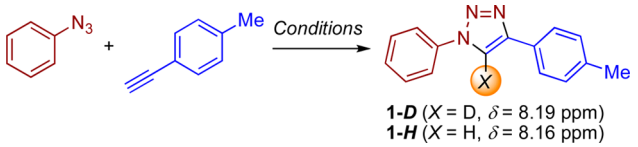
Table 1. Conditions Tested for the One-pot Triazole Formation and Deuteration[a]



1-*D* (*X* = D, δ = 8.19 ppm)
1-*H* (*X* = H, δ = 8.16 ppm)

entry	solvent, catalytic system, reaction time	product: result[b,c]
1[d,e]	1:1 CH_2Cl_2/D_2O, 2 equiv alkyne, 5 mol % $CuSO_4$, 10 mol % Na ascorbate, 12 h	**1-*D***: 60% yield, 80% D incorporation, reaction was incomplete[f]
2[g,h]	1:1 CH_2Cl_2/D_2O, 2 equiv alkyne, 7 mol % $CuSO_4$, 15 mol % Na ascorbate, 12 h	**1-*D***: 65% yield, 95% D incorporation, reaction was incomplete[i]
3[g,h]	1:1 CH_2Cl_2/D_2O, 2 equiv alkyne, 10 mol % $CuSO_4$, 20 mol % Na ascorbate, 12 h	**1-*D***: 75% yield, 96% D incorporation
4[g,h]	1:1 CH_2Cl_2/D_2O, 2 equiv alkyne, 10 mol % $CuSO_4$, 20 mol % Na ascorbate (dried from D_2O), 12 h	**1-*D***: 74% yield, 96% D incorporation
5[g,h]	1:1 CH_2Cl_2/D_2O, 1 equiv alkyne, 10 mol % $CuSO_4$, 20 mol % Na ascorbate (dried from D_2O), 12 h	**1-*D***: reaction was incomplete (ca. 80% azide consumed)[j]
6[g,h]	1:1 CH_3CN/D_2O, 2 equiv alkyne, 10 mol % $CuSO_4$, 20 mol % Na ascorbate (dried from D_2O), 24 h	**1-*D***: reaction was incomplete (<5% conversion)[j]
7	1:1 CH_3CN/H_2O, 2 equiv alkyne, 10 mol % $CuSO_4$, 20 mol % Na ascorbate, 5 d	**1-*H***: reaction was incomplete (<5% conversion)[j]
8	1:1 CH_2Cl_2/H_2O, 2 equiv alkyne, 20 mol % CuCl, 48 h	**1-*H***: reaction was incomplete[k]

[a]Reactions were conducted at room temperature with 0.2 M azide in anhydrous CH_2Cl_2 or in CH_3CN. [b]Where reported, yield is of isolated and purified product. [c]%D incorporation was assessed from the residual H-5 resonance in the ^{1}H NMR spectra. Deuterium resonances are referenced to the ^{2}H resonance of $CDCl_3$ (δ = 7.24 ppm). [d]D_2O contained 98% D (not a freshly opened sample). [e]$CuSO_4{\cdot}5H_2O$ was heated with a heat gun until the color changed from blue to gray. [f]Phenyl azide (10%) was recovered. [g]D_2O contained 99.8% D. [h]$CuSO_4{\cdot}5H_2O$ was heated at 120 °C, under vacuum, until the color changed from blue to gray. [i]Phenyl azide (8%) was recovered. [j]Assessed by ^{1}H NMR. [k]Assessed by TLC.

complementary reaction, a magnesiated alkyne yielded the C-4 deuterated triazole.[13] Dideuterotriazoles can be made from acetylene gas generated in situ from CaC_2, in the presence of Et_3N/D_2O.[14]

Despite the widespread application of the CuAAC reaction and its possible use for the deuteration of triazoles, we were surprised to find the absence of a general method for this purpose.[15] In the broader context, the importance of isotopic labeling is well-recognized, for example, in mechanistic and biosynthetic considerations, mass spectrometry applications, and in metabolism studies, to name a few. The 1,2,3-triazolyl moiety is also prominent in medicinal chemistry, where it has been likened to an amide linkage, with the N-3 atom serving as a hydrogen-bond acceptor and the C-4 atom the hydrogen-bond donor.[16−18] However, in contrast to amides, the triazole ring is chemically and biologically robust. These considerations have led to the design of bioactive entities containing a 1,2,3-triazolyl ring.[16,17] Additionally, "heavy drugs", namely pharmaceuticals that contain one or more deuterium atom(s) in place of hydrogen(s), have received increased attention due to the positive attributes gained upon deuteration.[19] On the basis of these overall considerations, a method to deuterated triazoles is likely to be of broad relevance. Herein we report a simple, mild, and general route to deuterated 1,2,3-triazoles wherein introduction of the deuterium atom at the C-4 position occurs in the triazole-forming step.

RESULTS AND DISCUSSION

Of importance to the success of the approach would be the formation of Cu-acetylides as intermediates in CuAAC reactions. It has been proposed that π-coordination of Cu^I increases the acidity of the alkynyl proton, rendering the formation of Cu-acetylides feasible in aqueous media.[7] This implies that terminal alkynes can be directly utilized since the alkynyl proton would be lost early in the process. Azide coordination to the Cu center occurs after formation of the Cu-acetylide.[7] These mechanistic considerations supported our one-pot triazole-forming, deuteration strategy.

In recent work[20] with the CuAAC reactions of 6-azido purine nucleosides we had encountered a significant problem that is not typical in the reactions of simpler azides. That is, the azido group underwent competing reduction in the presence of aqueous $CuSO_4$/Na ascorbate.[20] To remedy this, we resorted to a biphasic reaction medium, which suppressed the undesired azide reduction and gave good to excellent product recoveries. This led us to reason that use of biphasic reaction conditions with cheap, commercially available D_2O as one phase, should allow for capture of a deuterium atom by the C-4 cuprated intermediates formed in the CuAAC while suppressing other undesired processes.

With these considerations we conducted a series of initial optimization reactions (Table 1). We opted to desiccate $CuSO_4{\cdot}5H_2O$ in order to increase the extent of deuterium incorporation by eliminating as much water as possible. Entry 1 in Table 1 indicates proof of principle. Here, simply drying the $CuSO_4{\cdot}5H_2O$ with a heat gun, use of D_2O with 98% D, and use of low catalyst load, gave a respectable product yield and %D incorporation, but the reaction was incomplete. Use of better conditions (more rigorously dried $CuSO_4$ and D_2O with 99.8% D), gave excellent D incorporation, but again the reaction remained incomplete (entry 2). Complete reaction, with 96% D incorporation was achieved by increasing the amounts of $CuSO_4$ and Na ascorbate (entry 3). In this case %D incorporation was evaluated in two ways. Use of CH_2Cl_2 as an internal NMR standard indicated 96% D whereas assessment by comparison of the residual H-5 to other product resonances indicated 94% D. In an attempt to further improve the extent of D incorporation, a reaction was carried out under conditions of entry 3, except that Na ascorbate was evaporated from D_2O under vacuum prior to its use in the reaction. Under these conditions (entry 4), practically no further improvement in %D incorporation was observed and product yield remained essentially unchanged. Next, the amount of alkyne was lowered

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so as to reduce the amount of a proton source, but here incomplete reaction was observed (entry 5).

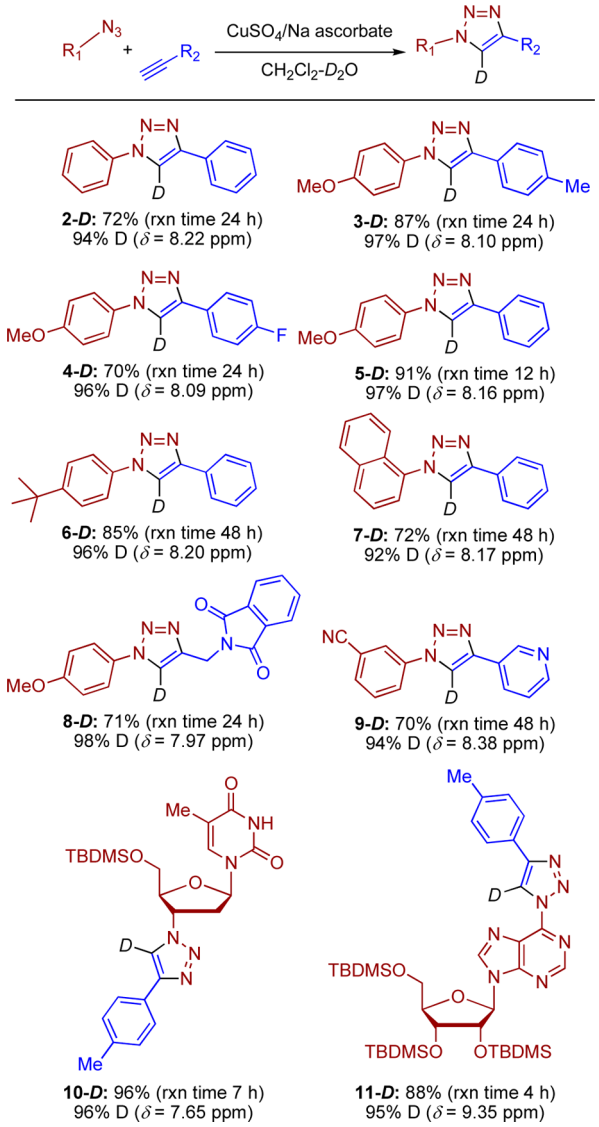
Attempts were then made to evaluate whether a water-miscible solvent offered any advantage. Use of CH_3CN led to less than 5% product formation in 24 h (entry 6). Surprised by this result, we conducted a reaction with H_2O rather than with D_2O, over an extended period. Again, less than 5% product formation was observed in 5 days (entry 7, a repeat of this experiment gave a comparable result). A prior report documents the failure of azide−alkyne ligation reactions with $CuSO_4{\cdot}5H_2O$/Na ascorbate in CH_3CN/H_2O, DMSO/H_2O, EtOH/H_2O, *t*-BuOH/H_2O, and other solvent combinations.[21] In that study, the superiority of the CH_2Cl_2/H_2O system led the authors to propose a rate-enhancing influence of this solvent combination on the CuAAC reactions.[21] Finally, in comparison to the $CuSO_4$/Na ascorbate system (entries 3 and 4), CuCl was inferior at catalyzing this reaction (entry 8).

Having completed these initial studies, we next focused on evaluating the generality of this regioselective deuteration. Product structures, yields, and %D incorporation are shown in Table 2.

As can be seen from Table 2, generally good-excellent product yields were obtained, with excellent D incorporation (92−98%). From a medicinal chemistry perspective, compounds **1-*D*** to **7-*D*** are structurally very similar to resveratrol analogues that have shown more potent cytotoxic and antiproliferative activity than resveratrol.[22] Compound **9-*D*** is a deuterated version of a highly active nicotinic acetylcholine receptor modulator.[23] Although a 54% yield of the protio analogue **9-*H*** is reported in the literature,[23] under our conditions both **9-*H*** and **9-*D*** were obtained in 70% yield. Even the more complex nucleoside substrates gave high yields and showed excellent D incorporation. The 96% yield of **10-*D*** compares very favorably to the microwave-mediated CuAAC reactions of AZT.[24] Protio triazolyl nucleoside analogues such as **10-*D***, derived from AZT, have proven to be excellent substrates for thymidine kinase of the pathogen *Ureaplasma parvum*.[24] We have previously shown that the C-6 azido purine nucleoside precursor to **11-*D*** exhibits significant azide-tetrazole equilibrium and is prone to facile reduction under CuAAC conditions.[20] However, as seen here, this substrate reacted smoothly. These results clearly indicate that the reaction conditions are generally very effective for a broad range of substrates.

In comparing protonation to deuteration, the former should be a more facile reaction due to the difference in the O−H and O−D bond energies.[25] To assess the relative difference in protonation versus deuteration when both processes compete in the triazole-forming-deuteration reactions, two reactions of phenyl azide with 4-ethynyltoluene were conducted in parallel. One reaction was with D_2O (99.8%) only and the other was with equimolar H_2O/D_2O (99.8%). By ^{1}H NMR analysis, using CH_2Cl_2 as an internal standard, the amount of **1-*H*** formed in the reaction with only D_2O was estimated to be 4%, whereas in the H_2O/D_2O reaction **1-*H*** was formed to an extent of 73% (77% observed − 4% formed in the control experiment). The isolated product yields from the two reactions were comparable, 75% for the D_2O reaction and 76% in the H_2O/D_2O reaction. The ratio of **1-*H*/1-*D*** formed in the latter experiment was 2.7. It is therefore plausible that the greater proportion of **1-*H*** as compared to **1-*D*** results from a more rapid protonation of the cuprated triazole. This could be a contributing factor toward the amounts of the protio products

Table 2. Generality of the Triazole Deuteration Protocol[a−e]



[a]Reactions were conducted at room temperature with 0.2 M azide and 2 mol equiv of alkyne. [b]Yields are of isolated and purified products. [c]% D incorporation was assessed from the residual H-5 resonance in the ^{1}H NMR spectra. Deuterium resonances are referenced to the ^{2}H resonance of $CDCl_3$ (δ = 7.24 ppm). [d]Syntheses of compounds **2-*D*** to **10-*D*** were performed using 10 mol % $CuSO_4$ (0.048 M in 99.8% D_2O) and 20 mol % Na ascorbate (0.096 M in 99.8% D_2O). [e]Synthesis of **11-*D*** was performed using 5 mol % $CuSO_4$ (0.048 M in 99.8% D_2O) and 10 mol % Na ascorbate (0.096 M in 99.8% D_2O).

formed in these reactions, which exceed what would be predicted based solely upon the deuterium content of the D_2O used.

Although monodeuteration reactions proceeded efficiently, we were curious to assess the ability to build poly- and fully deuterated molecules by this general methodology, where final deuteration of the triazole occurred in the CuAAC step. Therefore, using the optimized conditions, the synthesis of three compounds was undertaken (Scheme 2). For this, phenyl azide-D_5[26−28] and ethynylbenzene-D_5[29−32] were synthesized from bromobenzene-D_5 (99% D).

Reaction of phenyl azide-D_5 with 4-ethynyltoluene yielded **12-D_6**, whereas reaction of TBDMS-protected AZT with

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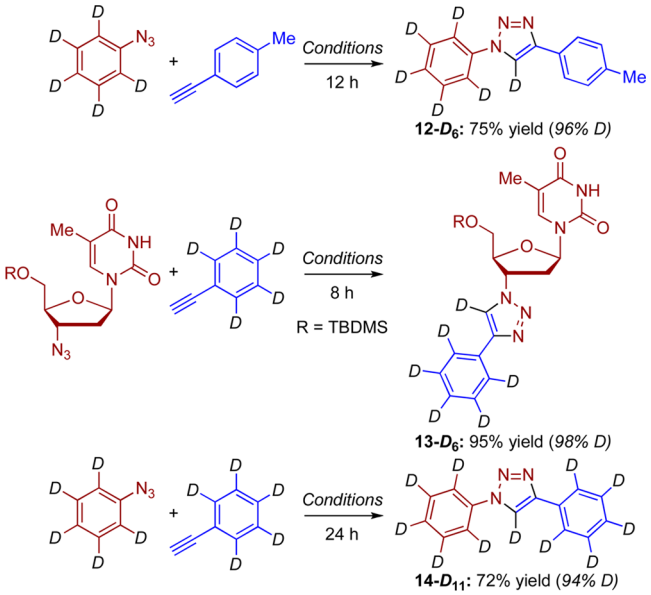
Scheme 2. Synthesis of Poly- and Fully-deuterated 1,2,3-Triazoles



ethynylbenzene-D_5 gave **13-*D*$_6$**, a more extensively deuterated analogue of **10-*D***. Finally, reaction of phenyl azide-D_5 with ethynylbenzene-D_5 gave **14-*D*$_{11}$**, which is a fully deuterated version of **2-*D***. %D incorporation in **12-*D*$_6$** and **13-*D*$_6$** was assessed from the residual H-5 triazolyl resonances in the ^{1}H NMR spectra. In the case of **14-*D*$_{11}$**, this assessment was done with CH_2Cl_2 as an internal standard.

CONCLUSIONS

In summary, a straightforward and mild procedure for regioselective C-5 deuteration of 1,2,3-triazoles has been developed via the CuAAC protocol, utilizing desiccated $CuSO_4$ and Na ascorbate. Cuprated triazoles formed in these reactions capture deuterium from cheap and readily available D_2O. Use of biphasic CH_2Cl_2/D_2O for these reactions eliminates certain problems, such as azide reduction encountered during the CuAAC reactions of azido nucleosides, and this combination is superior to CH_3CN/D_2O. Mono to fully deuterated compounds can be readily assembled via this methodology. It is foreseeable that this deuteration process can be coupled with the incorporation of other atomic isotopes, such as ^{13}C and/or ^{15}N, to yield multiply labeled compounds. All these factors contribute to the importance of the described chemistry. This simple deuteration method circumvents chemical manipulations of the triazole that may not be easily accomplished with molecules of increased complexity, and this is also likely to be of value in medicinal chemistry applications.

EXPERIMENTAL SECTION

General Experimental Considerations. Thin layer chromatography was performed on aluminum foil-backed TLC plates of 200 μm thickness and column chromatographic purifications were performed on 200−300 mesh silica gel. CH_2Cl_2 and MeCN were distilled over CaH_2, Et_2O was distilled over $LiAlH_4$ and then over Na. All other reagents were obtained from commercial sources and were used without further purification. Glassware used for reactions was dried at 150 °C in an oven and cooled in a desiccator. Melting points reported are of chromatographically purified materials and are uncorrected. ^{1}H NMR spectra were recorded at 500 MHz and are referenced to the residual solvent resonance. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ and are referenced to the solvent resonance. ^{2}H NMR spectra were recorded at 77 MHz using $CDCl_3$ as an internal standard. For this, first the ^{1}H NMR spectrum of $CDCl_3$ was recorded at 500 MHz and the residual protonated solvent resonance was set to δ 7.26 ppm. Next, the ^{2}H NMR spectrum of the same sample was recorded at 77 MHz, and this showed a resonance at δ 7.24 ppm. From this analysis, $CDCl_3$ was referenced to δ 7.24 ppm for all ^{2}H NMR experiments. The ^{19}F NMR spectrum was recorded at 282 MHz using $CFCl_3$ as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are in hertz (Hz). HRMS analyses were performed using a TOF analyzer, the ionization methods are provided in the compound characterization.

Synthesis of 3-Ethynylpyridine. *Step 1. Synthesis of 3-((Triisopropylsilyl)ethynyl)pyridine.* Following a literature procedure,[31] in a clean, dry, round-bottom flask equipped with a stirring bar, 3-bromopyridine (122 μL, 1.26 mmol) was dissolved in iPr_2NH (5 mL). TIPS-acetylene (336 μL, 1.512 mmol), $PdCl_2(Ph_3P)_2$ (44.0 mg, 0.063 mmol) and CuI (12.0 mg, 0.063 mmol) were added, and the reaction mixture was stirred and heated at 100 °C under a reflux condenser for 1 h, in a nitrogen atmosphere. The reaction mixture was diluted with EtOAc (20 mL) and filtered through Celite. The filtrate was washed with deionized H_2O (3 × 20 mL) and brine (15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material, by passing it through a short silica gel plug with initial elution using hexanes followed by 5% EtOAc in hexanes, gave 294 mg (90% yield) of TIPS-protected ethynylpyridine as a pale-yellow, viscous liquid. R_f (SiO_2/10% EtOAc in hexanes) = 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (s, 1H, H-2), 8.51 (d, 1H, H-6, J = 4.1 Hz), 7.73 (dt, 1H, H-4, J = 1.9, 7.8 Hz), 7.22 (dd, 1H, H-5, J = 4.9, 7.8 Hz), 1.13 (s, 21H, Si(iPr)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 148.8, 139.0, 123.0, 120.9, 103.8, 95.1, 18.7, 11.6. HRMS (ESI) calculated for $C_{16}H_{26}NSi$ $[M + H]^+$ 260.1829, found 260.1835.

Step 2. Synthesis of 3-Ethynylpyridine.[33] Following a literature procedure,[34] in a clean, dry, round-bottom flask equipped with a stirring bar, TIPS-protected ethynylpyridine (286 mg, 1.102 mmol) was dissolved in dry MeOH (15 mL). Powdered KOH (433 mg, 7.72 mmol) was added and the reaction mixture was stirred at 45 °C for 24 h. To the reaction mixture was added a saturated aqueous NH_4Cl solution and the mixture was extracted with Et_2O (3 × 15 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and carefully evaporated. Purification of the crude material on a short silica gel column using 10% Et_2O in hexanes yielded 51.0 mg (45% yield) of 3-ethynylpyridine as a white solid. R_f (SiO_2/20% Et_2O in hexanes) = 0.39. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H, H-2), 8.57 (d, 1H, H-6, J = 4.6 Hz), 7.77 (d, 1H, H-4, J = 7.8 Hz), 7.37 (t, 1H, H-5, J = 6.4 Hz), 3.22 (s, 1H, ≡CH).

Synthesis of Ethynylbenzene-*D*$_5$. *Step 1. Synthesis of Triisopropyl(phenylethynyl)silane-D_5.* Following a literature procedure,[31] in a clean, dry, round-bottom flask equipped with a stirring bar, bromobenzene-D_5 (500 mg, 3.085 mmol) was dissolved in iPr_2NH (12.5 mL). TIPS-acetylene (823 μL, 3.702 mmol), $PdCl_2(Ph_3P)_2$ (108.3 mg, 0.154 mmol) and CuI (29.4 mg, 0.154 mmol) were added, and the reaction mixture was stirred and heated under a reflux condenser at 100 °C for 1.5 h, in a nitrogen atmosphere. The reaction mixture was diluted with EtOAc (20 mL) and filtered through Celite. The filtrate was washed with deionized H_2O (3 × 20 mL) and brine (15 mL). The organic layer was separated, dried over anhydrous

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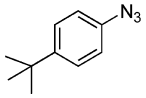
Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material, by passing it through a short silica gel plug using hexanes as the eluting solvent gave 500 mg (61% yield) of TIPS-protected ethynylbenzene as a colorless, viscous liquid. R_f (hexanes/SiO_2) = 0.70. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (s, 21H, Si(iPr)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.8 (t, J = 24.8 Hz), 128.0 (t, J = 24.0 Hz), 127.8 (t, J = 24.5 Hz), 123.6, 107.3, 90.6, 18.9, 11.6. ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.51, 7.33, 7.20. HRMS (ESI) calculated for $C_{17}H_{21}D_5Si$ $[M]^+$ 263.2112, found 263.2101.

Step 2. Synthesis of Ethynylbenzene-D_5.[30] By modifying a literature procedure,[32] in a clean, dry, 25 mL round-bottom flask equipped with a stirring bar, TIPS-protected ethynylbenzene-D_5 (700 mg, 2.656 mmol) was dissolved in dry Et_2O (11 mL) with stirring. A 1 M solution of n-$Bu_4N^+F^-$ in THF (3.2 mL, 3.2 mmol) was added and the mixture was stirred for 5 min. The mixture was concentrated under a stream of nitrogen gas and loaded onto a short silica gel column. Elution with hexanes, followed by careful rotary evaporation of the fractions containing the product using a water bath at ≤65 °C, gave 171 mg (61% yield) of ethynylbenzene-D_5 as a pale-yellow liquid. R_f (SiO_2/hexanes) = 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (s, 1H, ≡CH). ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.52, 7.38, 7.35.

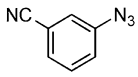
Synthesis of Azides. The C-6 azido purine ribonucleoside precursor[20] and 3′-azido-3′-deoxy-5′-*O*-(*t*-butyldimethylsilyl)-thymidine[35] were synthesized as described in the literature. Unless mentioned otherwise, all other azides were synthesized from the corresponding boronic acids.[36]

4-(*t*-Butyl)phenyl azide.[37]



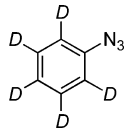
In a clean 10 mL round-bottom flask equipped with a stirring bar, 4-(*t*-butyl)phenylboronic acid (356 mg, 2 mmol) was dissolved in MeOH (6 mL). NaN_3 (156 mg, 2.4 mmol) and $CuSO_4{\cdot}5H_2O$ (50 mg, 0.2 mmol) were added to the reaction mixture, and the mixture was stirred in an open flask at room temperature for 16 h. The solvent was evaporated under reduced pressure and EtOAc (10 mL) was added. The mixture was extracted with H_2O (10 mL) and the aqueous layer was back extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the crude material on a short silica gel plug using hexanes yielded 311.5 mg (89% yield) of the title compound as an orange-red liquid. R_f (SiO_2/hexanes) = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, 2H, Ar−H, J = 8.6 Hz), 6.98 (d, 2H, Ar−H, J = 8.6 Hz), 1.32 (s, 9H, *t*-Bu). 4-(*t*-Butyl)phenyl azide has previously been synthesized by diazotization of 4-*t*-butylaniline.[37]

***m*-Azidobenzonitrile.**[38]



Following a literature procedure,[39] in a clean, dry, round-bottom flask equipped with a stirring bar, 3-aminobenzonitrile (200 mg, 1.69 mmol) was dissolved in dry MeCN (4 mL) and cooled to 0 °C. To the stirring solution, *t*-butyl nitrite (300 μL, 2.54 mmol) was added dropwise, followed by dropwise addition of Me_3SiN_3 (270 μL, 2.03 mmol). The mixture was warmed to room temperature and stirred for 2 h. This reaction mixture was diluted with EtOAc (15 mL) and washed with deionized H_2O (3 × 15 mL), and brine (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the crude material on a silica gel column using 5% EtOAc in hexanes yielded 190 mg (78% yield) of the title compound as a brown solid. R_f (SiO_2/10% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49−7.42 (m, 2H), 7.29−7.26 (m, 2H). *m*-Azidobenzonitrile has previously been synthesized by diazotization of *m*-cyanoaniline.[38]

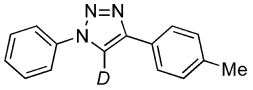
Phenyl azide-D_5.[27]



Following a literature procedure,[28] in a clean, dry, round-bottom flask equipped with a stirring bar, bromobenzene-D_5 (400 mg, 2.468 mmol) was dissolved in 7:3 EtOH/H_2O (4.8 mL). *N*,*N*′-Dimethylethylenediamine (40 μL, 0.37 mmol), NaN_3 (321 mg, 4.936 mmol), Na ascorbate (24.4 mg, 0.123 mmol), and CuI (47 mg, 0.247 mmol) were added, and the mixture was stirred and heated at 100 °C under a reflux condenser for 2 h, in an argon atmosphere. The mixture was cooled to room temperature, and diluted with Et_2O (20 mL) and deionized H_2O (10 mL). The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the crude material on a short silica gel column using hexanes yielded 261 mg (85% yield) of the title compound as a yellow liquid. R_f (SiO_2/hexanes) = 0.50. ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8, 129.2 (t, J = 24.2 Hz), 124.3 (t, J = 24.2 Hz), 118.6 (t, J = 24.2 Hz). ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.29, 7.08, 6.98. Phenyl azide-D_5 has previously been synthesized by diazotization of aniline-D_5.[27]

General Procedure for the Synthesis of Deuterated Triazoles (1-*D* to 14-D_{11}). In a clean, oven-dried, 10 mL round-bottom flask equipped with a stirring bar, was placed the appropriate azide (0.335 mmol) in 1.6 mL of dry CH_2Cl_2. To this stirring mixture the appropriate alkyne (0.67 mmol) was added. In a separate vial $CuSO_4{\cdot}5H_2O$ (8.4 mg, 0.0335 mmol, 10 mol %) was heated at 120 °C under vacuum until the color changed from blue to gray. Using this desiccated $CuSO_4$, a 0.048 M solution was prepared in a glovebag by the addition of D_2O (99.8% D, 0.7 mL), and this solution was transferred to the reaction mixture. To the reaction mixture a 0.096 M solution of Na ascorbate (13.3 mg in 0.7 mL of 99.8% D_2O, 20 mol %) was added. The reaction mixture was sealed and stirred in a nitrogen atmosphere at room temperature until TLC showed consumption of azide. The organic layer of the reaction mixture was separated and the aqueous layer was back extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by chromatography on a silica gel column. See compound headings below for details.

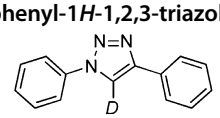
5-Deutero-1-phenyl-4-(*p*-tolyl)-1*H*-1,2,3-triazole (1-*D*).[12a]



Chromatography using hexanes followed by 20% EtOAc in hexanes gave 59.5 mg (75% yield) of **1-*D*** as an off-white solid. Mp = 156−158 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82−7.79 (m, 4H, Ar−H), 7.55 (t, 2H, Ar−H, J = 7.4 Hz), 7.46 (t, 1H, Ar−H, J = 7.3 Hz), 7.28 (d, 2H, Ar−H, J = 7.4 Hz), 2.41 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.7, 138.5, 137.5, 129.9, 129.8, 128.8, 127.8, 126.1, 120.7, 117.2 (t, J = 30.4 Hz), 21.4. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.19. HRMS (ESI) calculated for $C_{15}H_{13}DN_3$ $[M + H]^+$ 237.1245, found 237.1248.

Assessment of %D Incorporation Using an External Standard. CH_2Cl_2 (16 μL, 0.25 mmol) was added to a solution of the product (11.8 mg, 0.05 mmol) in $CDCl_3$ (0.5 mL). The ^{1}H NMR spectrum of this solution was acquired and the resonances were integrated. The signal at δ 5.30 ppm (CH_2Cl_2) was set to 10 whereby the signal at δ 8.16 ppm (residual triazolyl C5−H) integrated to 0.04. Thus, the %D incorporation in the reaction was estimated to be 4%.

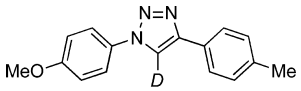
5-Deutero-1,4-diphenyl-1*H*-1,2,3-triazole (2-*D*).



dx.doi.org/10.1021/jo301146j | J. Org. Chem. 2012, 77, 8896−8904

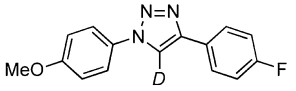
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 53.5 mg (72% yield) of **2-*D*** as a white solid. Mp = 183−185 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, 2H, Ar−H, J = 8.1 Hz), 7.80 (d, 2H, Ar−H, J = 7.8 Hz), 7.55 (t, 2H, Ar−H, J = 7.8 Hz), 7.48−7.45 (m, 3H, Ar−H), 7.37 (t, 1H, Ar−H, J = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6, 137.4, 130.6, 130.0, 129.1, 128.9, 128.6, 126.2, 120.8, 117.6 (s, J = 28.1 Hz). ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.22. HRMS (ESI) calculated for $C_{14}H_{11}DN_3$ $[M + H]^+$ 223.1089, found 223.1086.

5-Deutero-1-(4-methoxyphenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole (3-*D*).



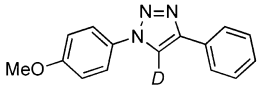
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 89.0 mg (87% yield) of **3-*D*** as a white solid. Mp = 174−176 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.26. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, 2H, Ar−H, J = 7.6 Hz), 7.67 (d, 2H, Ar−H, J = 8.6 Hz), 7.26 (d, 2H, Ar−H, J = 7.6 Hz), 7.02 (d, 2H, Ar−H, J = 8.6 Hz), 3.87 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 148.3, 138.4, 130.7, 129.7, 127.7, 125.9, 122.3, 117.5 (t, J = 28.9 Hz), 114.9, 55.8, 21.5. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.10. HRMS (ESI) calculated for $C_{16}H_{15}DN_3O$ $[M + H]^+$ 267.1351, found 267.1356.

5-Deutero-4-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (4-*D*).



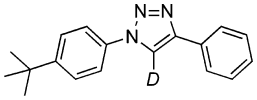
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 90.5 mg (70% yield) of **4-*D*** as an off-white solid. Mp = 184−186 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89−7.86 (m, 2H, Ar−H), 7.67 (d, 2H, Ar−H, J = 8.9 Hz), 7.14 (t, 2H, Ar−H, J = 8.6 Hz), 7.04 (d, 2H, Ar−H, J = 8.9 Hz), 3.88 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1 (d, J = 247.7 Hz), 160.3, 147.5, 130.8, 127.8 (d, J = 8.1 Hz), 127.0 (d, J = 3.2 Hz), 122.4, 117.6 (t, J = 28.9 Hz), 116.1 (d, J = 21.8 Hz), 115.1, 55.9. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.09. ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.8 (relative to $CFCl_3$). HRMS (ESI) calculated for $C_{15}H_{12}DFN_3O$ $[M + H]^+$ 271.1100, found 271.1105.

5-Deutero-1-(4-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole (5-*D*).



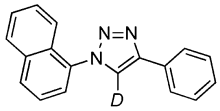
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 77.0 mg (91% yield) of **5-*D*** as a white solid. Mp = 166−169 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 2H, Ar−H, J = 7.8 Hz), 7.69 (d, 2H, Ar−H, J = 8.9 Hz), 7.46 (t, 2H, Ar−H, J = 7.6 Hz), 7.37 (t, 1H, Ar−H, J = 7.4 Hz), 7.04 (d, 2H, Ar−H, J = 8.9 Hz), 3.88 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 148.4, 130.9, 130.8, 129.1, 128.5, 126.1, 122.4, 117.8 (t, J = 28.3 Hz), 115.1, 55.9. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.16. HRMS (ESI) calculated for $C_{15}H_{13}DN_3O$ $[M + H]^+$ 253.1194, found 253.1199.

1-(4-(*t*-Butyl)phenyl)-5-deutero-4-phenyl-1*H*-1,2,3-triazole (6-*D*).



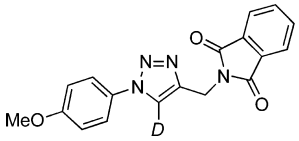
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 93.3 mg (85% yield) of **6-*D*** as an off-white solid. Mp = 153−156 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.46. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, 2H, Ar−H, J = 8.1 Hz), 7.70 (d, 2H, Ar−H, J = 8.5 Hz), 7.53 (d, 2H, Ar−H, J = 8.5 Hz), 7.44 (t, 2H, Ar−H, J = 7.6 Hz), 7.35 (dt, 1H, Ar−H, J = 1.0, 7.4 Hz), 1.38 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 148.3, 134.8, 130.5, 129.1, 128.5, 126.8, 126.0, 120.4, 117.8 (t, J = 28.9 Hz), 35.0, 31.5. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.20. HRMS (ESI) calculated for $C_{18}H_{19}DN_3$ $[M + H]^+$ 279.1715, found 279.1709.

5-Deutero-1-(naphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazole (7-*D*).



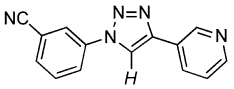
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 80.0 mg (72% yield) of **7-*D*** as a brown solid. Mp = 86−88 °C. R_f (SiO_2/25% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00−7.92 (m, 4H, Ar−H), 7.69 (d, 1H, Ar−H, J = 8.3 Hz), 7.59−7.49 (m, 4H, Ar−H), 7.46 (t, 2H, Ar−H, J = 7.7 Hz), 7.04 (dt, 1H, Ar−H, J = 1.0, 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.9, 134.5, 134.0, 130.6, 130.5, 129.1, 128.9, 128.6, 128.5, 128.1, 127.3, 126.1, 125.2, 123.7, 122.6, 122.2 (t, J = 28.6 Hz). ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.17. HRMS (ESI) calculated for $C_{18}H_{13}DN_3$ $[M + H]^+$ 273.1245, found 273.1247.

5-Deutero-1-(4-methoxyphenyl)-4-(*N*-phthalimidomethyl)-1*H*-1,2,3-triazole (8-*D*).



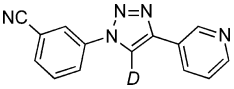
Chromatography using hexanes followed by 40% EtOAc in hexanes gave 80.0 mg (71% yield) of **8-*D*** as an off-white solid. Mp = 181−183 °C. R_f (SiO_2/50% EtOAc in hexanes) = 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, 2H, Ar−H, J = 3.1, 5.3 Hz), 7.72 (dd, 2H, Ar−H, J = 3.1, 5.3 Hz), 7.57 (d, 2H, Ar−H, J = 8.9 Hz), 6.97 (d, 2H, Ar−H, J = 8.9 Hz), 5.06 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 159.9, 143.3, 134.3, 132.2, 130.5, 123.6, 122.4, 121.1 (t, J = 28.8 Hz), 114.8, 55.8, 33.2. ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.97. HRMS (ESI) calculated for $C_{18}H_{14}DN_4O_3$ $[M + H]^+$ 336.1201, found 336.1204.

1-(3-Cyanophenyl)-4-(pyridin-3-yl)-1*H*-1,2,3-triazole (9-*H*).[23]



In a clean, oven-dried, 10 mL round-bottom flask equipped with a stirring bar, *m*-azidobenzonitrile (57 mg, 0.335 mmol) was dissolved in CH_2Cl_2 (1.6 mL). 3-Ethynylpyridine (69 mg, 0.67 mmol) was added to the flask, followed by $CuSO_4{\cdot}5H_2O$ (8.4 mg, 0.0335 mmol), Na ascorbate (13.3 mg, 0.067 mmol), and H_2O (1.4 mL). The mixture was stirred at room temperature for 48 h and then diluted with CH_2Cl_2 (5 mL). The aqueous layer was separated and back extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the crude material on a short silica gel plug by sequential elution with 10% EtOAc in hexanes followed by EtOAc, gave 58.0 mg (70% yield) of **9-*H*** as an off-white solid. Mp = 215−217 °C (lit. 214−216 °C[23]). R_f (SiO_2/EtOAc) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (br s, 1H, Ar−H), 8.68 (br s, 1H, Ar−H), 8.33 (s, 1H, Ar−H), 8.31 (d, 1H, Ar−H, J = 7.7 Hz), 8.15 (t, 1H, Ar−H, J = 1.5 Hz), 8.11 (ddd, 1H, Ar−H, J = 1.1, 2.1, 8.1 Hz), 7.79 (dt, 1H, Ar−H, J = 1.2, 7.8 Hz), 7.73 (t, 1H, Ar−H, J = 7.9 Hz), 7.47 (br s, 1H, Ar−H). ^{13}C NMR (125 MHz, CD_3OD, 55 °C): δ 150.2, 147.8, 146.8, 139.1, 135.2, 133.7, 132.5, 128.4, 126.1, 125.7, 125.1, 121.4, 118.7, 115.4.

1-(3-Cyanophenyl)-5-deutero-4-(pyridin-3-yl)-1*H*-1,2,3-triazole (9-*D*).

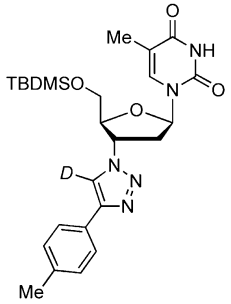


Chromatography using 10% EtOAc in hexanes followed by EtOAc gave 52.8 mg (70% yield) of **9-*D*** as an off-white solid. Mp = 218−220

dx.doi.org/10.1021/jo301146j | J. Org. Chem. 2012, 77, 8896−8904

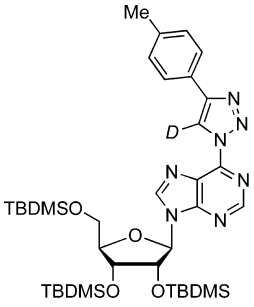
°C. R_f (SiO_2/EtOAc) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (br s, 1H, Ar−H), 8.73 (br s, 1H, Ar−H), 8.31 (d, 1H, Ar−H, J = 7.9 Hz), 8.15 (t, 1H, Ar−H, J = 1.6 Hz), 8.11 (ddd, 1H, Ar−H, J = 1.1, 2.2, 8.1 Hz), 7.79 (dt, 1H, Ar−H, J = 1.3, 7.7 Hz), 7.74 (t, 1H, Ar−H, J = 7.9 Hz), 7.47 (br s, 1H, Ar−H). ^{13}C NMR (125 MHz, CD_3OD, 55 °C): δ 150.2, 147.8, 146.8, 139.1, 135.2, 133.7, 132.5, 128.4, 126.1, 125.7, 125.1, 121.2 (t, J = 29.6 Hz), 118.7, 115.4. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.38. HRMS (ESI) calculated for $C_{14}H_9DN_5$ $[M + H]^+$ 249.0993, found 249.0997.

5′-*O*-(*t*-Butyldimethylsilyl)-3′-deoxy-3′-(5-deutero-4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)thymidine (10-*D*).



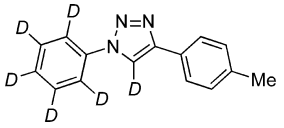
For this reaction 0.131 mmol of azide, 0.262 mmol of alkyne, 10 mol % of anhydrous $CuSO_4$ in 273 μL of D_2O, 20 mol % of Na ascorbate in 273 μL of D_2O, and 0.65 mL of dry CH_2Cl_2 were used. Chromatography using hexanes followed by 45% EtOAc in hexanes gave 63.0 mg (96% yield) of **10-*D*** as a white solid. Mp = 176−178 °C. R_f (SiO_2/75% EtOAc in hexanes) = 0.48. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.41 (br s, 1H, NH), 7.70 (d, 2H, Ar−H, J = 7.9 Hz), 7.49 (s, 1H, Ar−H), 7.22 (d, 2H, Ar−H, J = 7.9 Hz), 6.44 (t, 1H, H-1′, J = 6.5 Hz), 5.33 (app dt, 1H, H-3′, J_{app} = 4.6, 9.1 Hz), 4.49−4.47 (m, 1H, H-4′), 4.02 (dd, 1H, H-5′, J = 2.4, 11.6 Hz), 3.88 (dd, 1H, H-5′, J = 2.4, 11.6 Hz), 3.00 (app dt, 1H, H-2′, J_{app} = 5.9, 13.1 Hz), 2.63 (ddd, 1H, H-2′, J = 6.8, 8.5, 14.6 Hz), 2.37 (s, 3H, CH_3), 1.94, (s, 3H, CH_3), 0.93 (s, 9H, *t*-Bu), 0.13 and 0.12 (2s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 150.5, 148.6, 138.5, 135.5, 129.8, 127.7, 125.9, 118.5 (t, J = 28.7 Hz), 111.3, 85.8, 85.0, 62.9, 59.8, 38.8, 26.1, 21.4, 18.6, 12.7, −5.1, −5.2. ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.85. HRMS (ESI) calculated for $C_{25}H_{35}DN_5O_4Si$ $[M + H]^+$ 499.2594, found 499.2600.

6-[5-Deutero-4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-9-[2,3,5-tri-*O*-(*t*-butyldimethylsilyl)-*β*-D-ribofuranosyl]purine (11-*D*).



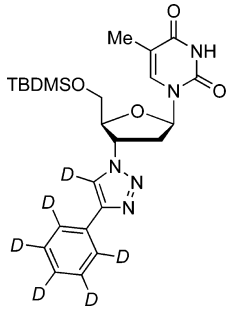
For this reaction 0.198 mmol of azide, 0.395 mmol of alkyne, 5 mol % of anhydrous $CuSO_4$ in 0.2 mL of D_2O, 10 mol % of Na ascorbate in 0.2 mL of D_2O, and 0.95 mL of CH_2Cl_2 were used. Chromatography using hexanes followed by 15% EtOAc in hexanes gave 131.0 mg (88% yield) of **11-*D*** as a pale-yellow solid. Mp = 89−91 °C. R_f (SiO_2/20% EtOAc in hexanes) = 0.28. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H, Ar−H), 8.65 (s, 1H, Ar−H), 7.91 (d, 1H, Ar−H, J = 8.0 Hz), 7.29 (d, 2H, Ar−H, J = 8.0 Hz), 6.24 (d, 1H, H-1′, J = 5.1 Hz), 4.68 (t, 1H, H-2′, J = 4.7 Hz), 4.35 (t, 1H, H-3′, J = 3.9 Hz), 4.20 (app q, 1H, H-4′, J_{app} = 3.0 Hz), 4.06 (dd, 1H, H-5′, J = 3.5, 11.4 Hz), 3.85 (dd, 1H, H-5′, J = 2.4, 11.4 Hz), 2.41 (s, 3H, CH_3), 0.99, 0.96, and 0.81 (3s, 27H, *t*-Bu), 0.19, 0.18, 0.13, 0.12, −0.02, and −0.21 (6s, 18H, Si-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5, 152.5, 148.5, 145.2, 145.0, 138.8, 129.8, 127.5, 126.4, 123.5, 119.5 (t, J = 26 Hz), 88.9, 86.1, 76.5, 72.3, 62.8, 26.4, 26.1, 25.9, 21.5, 18.8, 18.3, 18.1, −4.1, −4.3, −4.4, −4.6, −4.7, −5.1. ^{2}H NMR (77 MHz, $CHCl_3$): δ 9.35. HRMS (ESI) calculated for $C_{37}H_{60}DN_7O_4Si_3Na$ $[M + Na]^+$ 775.4048, found 775.4046.

5-Deutero-1-phenyl-D_5-4-(*p*-tolyl)-1*H*-1,2,3-triazole (12-D_6).



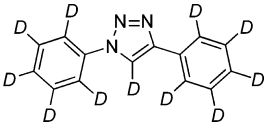
Chromatography using hexanes followed by 20% EtOAc in hexanes gave 60.5 mg (75% yield) of **12-D_6** as an off-white solid. Mp = 153−155 °C. R_f (SiO_2/50% EtOAc in hexanes) = 0.60. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, 2H, Ar−H, J = 7.8 Hz), 7.29 (d, 2H, Ar−H, J = 7.8 Hz), 2.42 (s, 3H, $-CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6, 138.5, 137.2, 129.8, 129.5 (t, J = 25.0 Hz), 128.4 (t, J = 25.0 Hz), 127.6, 126, 120.3 (t, J = 24.9 Hz), 117.2 (t, J = 29.4 Hz), 21.5. ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.19, 7.82, 7.58, 7.49. HRMS (ESI) calculated for $C_{15}H_8D_6N_3$ $[M + H]^+$ 242.1559, found 242.1553.

5′-*O*-(*t*-Butyldimethylsilyl)-3′-deoxy-3′-(5-deutero-4-(phenyl-D_5)-1*H*-1,2,3-triazol-1-yl)thymidine (13-D_6).



For this reaction 0.131 mmol of azide, 0.262 mmol of alkyne, 10 mol % of anhydrous $CuSO_4$ in 0.273 mL of D_2O, 20 mol % of Na ascorbate in 0.273 mL of D_2O, and 0.65 mL of dry CH_2Cl_2 were used. Chromatography using hexanes followed by 50% EtOAc in hexanes gave 61.0 mg (95% yield) of **13-D_6** as a white solid. Mp = 96−98 °C. R_f (SiO_2/50% EtOAc in hexanes) = 0.21. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.20 (br s, 1H, NH), 7.50 (s, 1H, Ar−H), 6.45 (t, 1H, H-1′, J = 6.5 Hz), 5.34 (app dt, 1H, H-3′, J_{app} = 4.6, 8.8 Hz), 4.49−4.51 (m, 1H, H-4′), 4.03 (dd, 1H, H-5′, J = 2.1, 11.5 Hz), 3.88 (dd, 1H, H-5′, J = 1.8, 11.5 Hz), 3.01 (ddd, 1H, H-2′, J = 5.2, 6.3, 14.0 Hz), 2.64 (ddd, 1H, H-2′, J = 6.5, 8.1, 14.3 Hz), 1.95 (s, 3H, CH_3), 0.94 (s, 9H, *t*-Bu), 0.14 and 0.13 (2s, 6H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 150.5, 148.4, 135.5, 130.1, 128.6 (t, J = 23.8 Hz), 128.1 (t, J = 23.0 Hz), 125.6 (t, J = 24.1 Hz), 118.7 (t, J = 28.8 Hz), 111.4, 85.6, 85.0, 62.8, 59.8, 38.9, 26.1, 18.6, 12.8, −5.1, −5.2. ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.87, 7.45. HRMS (ESI) calculated for $C_{24}H_{28}D_6N_5O_4Si$ $[M + H]^+$ 490.2751, found 490.2766.

5-Deutero-1,4-diphenyl-D_{10}-1*H*-1,2,3-triazole (14-D_{11}).



Chromatography using hexanes followed by 20% EtOAc in hexanes gave 58.4 mg (72% yield) of **14-D_{11}** as an off-white solid. Mp = 183−186 °C. R_f (SiO_2/50% EtOAc in hexanes) = 0.60. ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 137.2, 130.3, 129.5 (t, J = 24.3 Hz), 128.6 (t, J = 23.3 Hz), 128.5(t, J = 23.1 Hz), 128.1 (t, J = 21.8 Hz), 125.7 (t, J = 24.2 Hz), 120.3 (t, J = 25.2 Hz), 117.6 (t, J = 26.9 Hz). ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.23, 7.94, 7.83, 7.58, 7.49. HRMS (ESI) calculated for $C_{14}HD_{11}N_3$ $[M + H]^+$ 233.1716, found 233.1717.

Assessment of %D in **14-D_{11}.** CH_2Cl_2 (16 μL, 0.25 mmol) was added to the solution of **14-D_{11}** (11.7 mg, 0.05 mmol) in $CDCl_3$ (0.5 mL). The ^{1}H NMR spectrum of this solution was acquired and the resonances were integrated. The signal at δ 5.30 ppm (CH_2Cl_2) was set to 10 whereby the signal at δ 8.19 ppm (residual triazolyl C5−H) integrated to 0.06. Thus, the %D incorporation in the reaction was estimated to be 94%.

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Competitive Experiment using H_2O and D_2O. In a clean, oven-dried, 10 mL round-bottom flask equipped with a stirring bar, was placed phenyl azide (40.0 mg, 0.335 mmol) in dry CH_2Cl_2 (1.6 mL). To this stirring solution 4-ethynyltoluene (85 μL, 0.67 mmol) was added. In a separate vial $CuSO_4 \cdot 5H_2O$ (8.4 mg, 0.0335 mmol, 10 mol %) was heated at 120 °C under vacuum until the color changed from blue to gray. Using this dehydrated $CuSO_4$, a 0.048 M solution was prepared in a glovebag by the addition of D_2O (99.8% D, 0.7 mL) and this solution was transferred to the reaction mixture. To the reaction mixture a 0.096 M solution of Na ascorbate (13.3 mg in 0.7 mL of H_2O, 20 mol %) was then added. The reaction mixture was sealed and stirred under nitrogen gas at room temperature until TLC showed consumption of azide. The organic layer of the reaction mixture was separated and the aqueous layer was back extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by chromatography on a silica gel column to give 60 mg of an off-white solid. On the basis of the ^1H NMR analysis, this mixture contained 15.6 mg (19.7%) of **1-*D*** and 44.4 mg (56.3%) of **1-*H***. R_f (25% EtOAc in hexanes/SiO_2) = 0.34.

*Assessment of the Amounts of **1-H** and **1-D** in the Product Mixture.* CH_2Cl_2 (16 μL, 0.25 mmol) was added to a solution of the product mixture (11.8 mg, 0.05 mmol) in $CDCl_3$ (0.5 mL). The ^1H NMR spectrum of this solution was acquired and the resonances were integrated. The signal at δ 5.30 ppm (CH_2Cl_2) was set to 10 whereby the signal at δ 8.16 ppm (residual triazolyl C5−H) integrated to 0.77. On the basis of these values the amount of **1-*H*** was estimated at 9.058 mg (77%) and that of **1-*D*** was estimated as 2.741 mg (23%).

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for **1-*D*** to **14-D_{11}**, **9-*H***, as well as for other relevant intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): A patent application has been filed.

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