Tandem Azide–Alkyne 1,3-Dipolar Cycloaddition/Electrophilic Addition: A Concise Three-Component Route to 4,5-Disubstituted Triazolyl-Nucleosides

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Abstract: A one-pot, three-component approach to a new family of 4,5-functionalized triazolyl-nucleosides is described. The method relies on the one-pot azide–alkyne 1,3-cycloaddition/electrophilic addition tandem reaction, which affords good yields of the corresponding 4,5-disubstituted nucleosides.

Key words: click, 3CR, tandem reaction, nucleosides

For many years, naturally occurring and synthetic analogues of nucleosides have attracted wide interest in view of the importance of their biological activity.[2] Recently, renewed interest in such analogues has also arisen because of their high potential value as biochemical probes and as building blocks in artificial DNA and RNA synthesis following the well-known phosphoramidite chemistry.[3] Among the bioactive nucleosides, those anchoring a five-membered heterocyclic ring are of particular interest. Thus, Ribavirin is a synthetic triazolyl-nucleoside endowed with a broad-spectrum of antiviral activity against many RNA and DNA viruses (Figure 1).[4] It is still the only small-molecule drug available to date for treatment of hepatitis C virus (HCV). Eicar is an imidazole nucleoside with potent antiviral and antitumor activity (Figure 1).[5] Mizoribine is another five-membered nucleoside produced by *Eupenicillium brefedianum*, with antibiotic, cytotoxic and immunosuppressive activity.[6] 4-Substituted triazolyl-nucleosides were recently reported in both carbocyclic[7] and acyclic series,[8] and some of these showed promising antiviral activities. However, only a few examples were reported in the 1,4,5-trisubstituted series and most of these involved multistep processes and have limited application scope. Ackermann described the synthesis of 1,4,5-trisubstituted triazole using an interesting sequential process.[9] Very recently, during the preparation of this manuscript, Zhang and co-workers reported a similar procedure using a CuI/NBS couple as both catalyst and iodination agent.[10]

We recently reported that azido-furanose and terminal alkynes undergo fast 1,3-dipolar cycloaddition under the cooperative effect of microwave activation and copper(I) catalysis, to give high yields of triazolyl-nucleoside cycloadducts.[11] Some of these displayed promising biological activity. As a continuation of our interest in the synthesis of new nucleoside analogues,[12] we describe herein a one-pot, three-component strategy for the synthesis of new triazolyl-nucleosides bearing two appended groups at positions 4 and 5 of the triazole ring (Scheme 1), which allows a new approach to the synthesis of Eicar and Mizoribine five-membered analogues. The methodology is highly efficient and involves, as the key step, a tandem azide–alkyne cycloaddition/electrophilic addition. We also report a short and expeditious synthesis of an Eicar analogue by applying this new synthetic strategy.

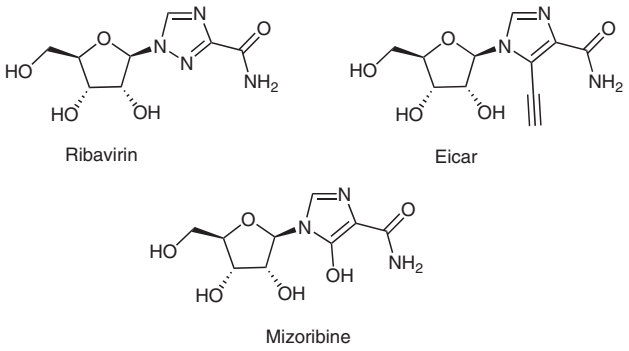
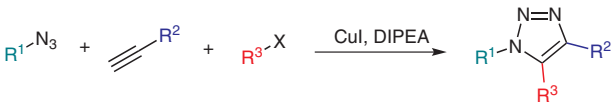


Figure 1 Structure of bioactive five-membered-ring nucleosides

Based on the remarkable discovery of copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition,[13] we envisioned, following our previous procedure, that the targeted 4,5-disubstituted triazolyl-nucleosides could be obtained through trapping of the triazolyl-copper intermediate I by electrophiles during the reaction (Scheme 2).[14] Therefore, the main challenge in this investigated one-pot reaction was to overcome the concomitant proteolysis reaction of I leading to 5-H-triazole.



Scheme 1 The proposed click–electrophilic addition tandem process

In our previously reported work,[11a] we observed that the rate of the 1,3-dipolar cycloaddition reaction between azido-ribose and terminal alkynes was significantly increased when acetic acid or silica gel were used in the reaction. This acceleration could be explained by the

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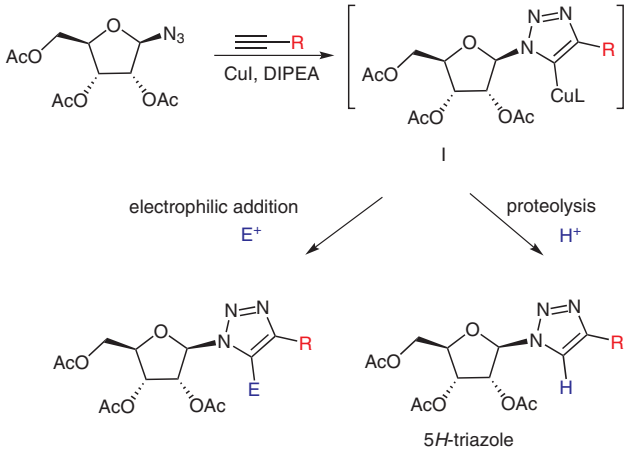


Scheme 2 Electrophilic addition vs proteolysis key steps

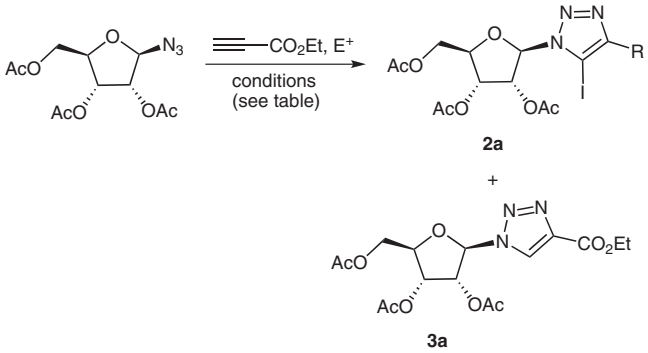
protonation of the triazolyl-copper intermediate I (proteolysis step, Scheme 2). Therefore, in this present work, in order to increase the efficiency of the electrophilic addition vs proteolysis (E^+ vs H^+) all sources of H^+ were avoided (acids and protic solvents).

As a model reaction, we investigated the reactivity of azido-ribose **1**, ethyl propiolate and various sources of I^+ (Table 1). First, condensation of azido-ribose **1** with ethyl propiolate, in the presence of CuI/DIPEA and iodine (1 equiv), produced the desired 5-iodo-triazolyl adduct **2a**, together with triazole **3a**, resulting from a concomitant proteolysis, in 85% combined yield and 1:3 ratio in favor of **3a** (**2a/3a** = 25:75; Table 1, entry 1).[15] Although the yield of **2a** was low, this result showed that the one-pot transformation was feasible, and prompted us to undertake a deeper study in order to increase the ratio of **2a**. Different conditions were then evaluated for this transformation, including the nature of solvent, source of I^+, stoichiometry and the use of additives. Thus, increasing the amount of I_2 from one to three equivalents resulted in an increased ratio in favor of **2a** (**2a/3a** = 70:30; Table 1, entry 3). The low efficiency observed in the production of **2a** is thus due to the slow iodonium addition step. The best results were obtained using iodine/iodosobenzene diacetate (I_2/IBD) or iodine/cerium(IV) ammonium nitrate (I_2/CAN) couples, both of which gave high yields of the desired compound **2a**, while minimizing the formation of **3a** (Table 1, entries 8 and 9). CAN and IBD were used as oxidizing agents in order to generate more reactive iodonium species.[16] We found that tetrahydrofuran and dichloromethane were both effective as solvents in this multi-component process. Furthermore, the ratio of DIPEA/I_2 was crucial in this transformation, since DIPEA served as a base, copper ligand and HI quencher (HI acid released from I_2).[17] Therefore, when I_2 was used, an excess of DIPEA was required in order to avoid proteolysis (HI). This result was also confirmed by using *N*-iodosuccinimide (NIS) instead of I_2. Under these conditions, only 1.5 equivalents of DIPEA were required to achieve complete transformation of **1** into **2a** (Table 1, entry 11). We also briefly explored the effect of changing the ligand/base from DIPEA to Et_3N or pyridine and confirmed the efficiency of DIPEA over the latter two (Table 2, entries 3, 6 and 7).

In contrast to Zhang's work[10] and as shown in Table 1, in our case, reactions using I_2 worked well (Table 1, entries 1–7) and dichloromethane was found to be an efficient solvent since it also gave good yields of **2a** (Table 1).

With these optimized reaction conditions in hand, the scope and limitations of this methodology were explored with various alkynes, azido-sugars and electrophiles (Table 2). It should be noted that we used CuCl/NCS and CuBr/NBS couples as sources of Cl^+ and Br^+, respectively. In general, all reactions of NIS, NBS and NCS with various azido-sugars (α- and β-deoxy-ribose, D- and L-ribose and pyranose series) were clean and the 4,5-disubstituted triazolyl nucleosides were obtained in good yields (Table 2).

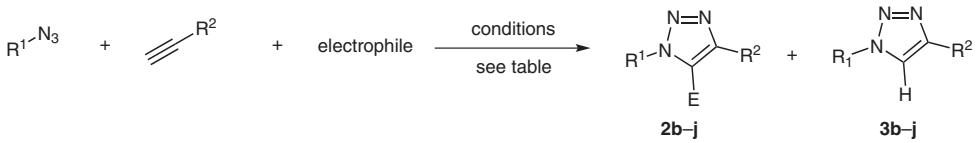
Table 1 Survey of the Reaction Conditions

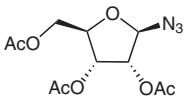
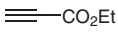
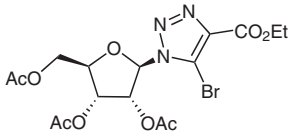
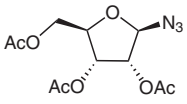
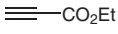
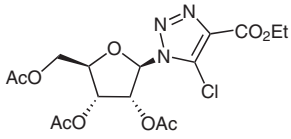
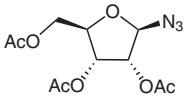
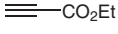
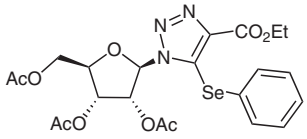
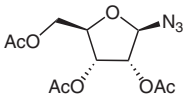
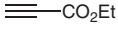
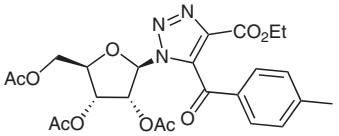
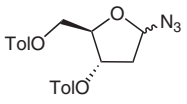
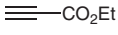
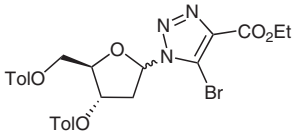
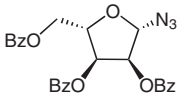
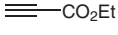
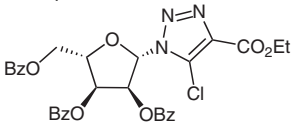
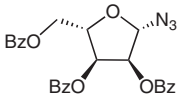
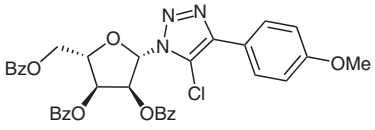
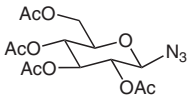
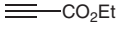
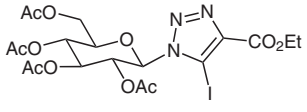
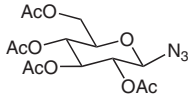
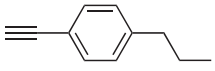
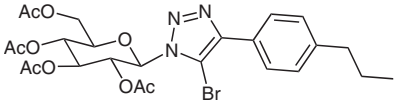


Entry	Ratio alkyne/CuI/DIPEA[a] (equiv)	Source of I^+ (equiv)	Solvent	Yield (%)[b]	Ratio **2a/3a**[c]
1	2:2:5	I_2 (1)	CH_2Cl_2	85	25:75
2	2:2:5	I_2 (2)	CH_2Cl_2	93	40:60
3	2:2:5	I_2 (3)	CH_2Cl_2	92	70:30
4	2:2:5	I_2 (3)	THF	90	68:32
5	2:2:5	I_2 (3)	toluene[d]	32[e]	70:30
6	2:2:5 (pyridine)	I_2 (3)	CH_2Cl_2	35[e]	65:35
7	2:2:5 (Et_3N)	I_2 (3)	CH_2Cl_2	68	70:30
8	1.2:1.2:5	I_2 / IBD (2:1)	CH_2Cl_2	92	90:10
9	1.2:1.2:5	I_2 / CAN (2:1)	THF	95	>95:5
10	1.2:1.2:1.5	NIS (1)	CH_2Cl_2	65	60:40
11	1.2:1.2:1.5	NIS (3)	CH_2Cl_2	82	90:10

[a] DIPEA: *N*,*N*-diisopropylethylamine.
[b] Combined isolated yield. In general, reactions were complete after 1 h.
[c] Ratio based on ^1H NMR of the crude product.
[d] Reaction time = 16 h.
[e] The starting material was recovered.

Table 2 Extension of the Three-Component Procedure



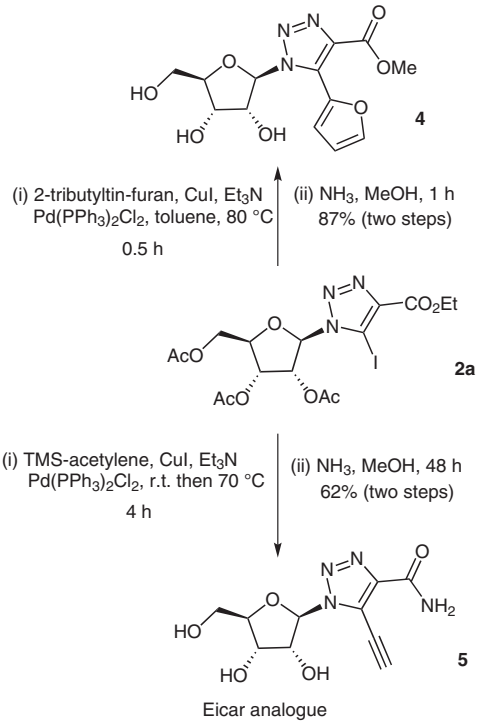
Entry[a]	Azide	Alkyne	E^+	Conditions (equiv)	Time (h)	Product	Ratio **2/3**[b], Yield (%)[c]
1			NBS	CuBr, DIPEA (1.2:1.2)	1	 **2b**	75:25 (85)
2			NCS	CuCl, DIPEA (1.2:1.2)	2	 **2c**	70:30 (82)
3[d]			PhSeBr	CuI, DIPEA (1.2:3)	1	 **2d**	30:70 (74)
4[d,e]			4-Me-C_6H_4COCl	CuI, DIPEA (2:5)	0.5	 **2e**	>95:5 (91)
5	 α/β = 2:3		NBS	CuBr, DIPEA (1.2:1.2)	1	 **2f** (α/β = 2:3)	68:32 (83)
6			NCS	CuCl, DIPEA (1.2:1.2)	1	 **2g**	70:30 (86)
7[d]			NCS	CuCl, DIPEA (2:5)	16	 **2h**	50:50 (60)
8			I_2, CAN (2:1)	CuI, DIPEA (1.2:5)	1	 **2i**	>95:5 (92)
9			NBS	CuBr, DIPEA (1.2:1.2)	8	 **2j**	30:70 (58)

[a] Reactions were performed at r.t. in CH_2Cl_2 (azide/alkyne/E^+ = 1:1.2:3).
[b] Based on ^1H NMR of the crude product.
[c] Combined isolated yield.
[d] Alkyne (2 equiv) was used.
[e] The reaction was performed in THF with E^+ (5 equiv).

As we previously observed, the rate of the 1,3-dipolar cycloaddition step was increased with more polar alkynes (polar transition state) since aryl-alkynes required longer reaction times and led to moderate yields compared to those obtained with ethyl propiolate (Tables 2, 6 *vs* 7 and 8 *vs* 9).[11] Interestingly, we found that the three-component reaction was also applicable to other electrophiles. Thus, when PhSeBr was used in the reaction, the desired 5-phenylselenide-substituted triazole **2d** was obtained in moderate yield, which is probably due to the low reactivity of the electrophile (Table 2, entry 3). Fortunately, the three-component, one-pot reaction of azido-ribose **1**, ethyl propiolate and toluoyl chloride, which was used as the electrophile, led to 5-toluoyl-triazolyl-nucleoside **2e** in excellent yield (Table 2, entry 4).[18]

In summary, we have developed an efficient, one-pot, three-component synthesis of 4,5-disubstituted triazolyl-nucleosides using a tandem process based on copper-catalyzed 1,3-dipolar cycloaddition and trapping with electrophiles. This methodology offers access to various triazoles functionalized at positions 1, 4 and 5. Generally moderate to good yields were obtained. Moreover, the process is compatible with many functional groups and offers several possibilities for further post-synthetic transformations. For example, the iodo-derivative **2a** was subjected to palladium cross-coupling reactions in order to evaluate its reactivity (Scheme 3). Thus, treatment of **2a** with 2-tributyltin-furan under Stille conditions followed by treatment with ammonia in methanol for one hour in order to induce acetyl group cleavage/*trans*-esterification (OEt to OMe) reactions, afforded the free nucleoside **4** in 87% overall yield.[19] In a similar way, the new Eicar analogue **5**[20] was prepared in 62% overall yield through Sonogashira coupling between **2a** and TMS-protected acetylene, and subsequent aminolysis (NH_3, MeOH, 48 h); this approach efficiently allowed three transformations in one operation, i.e., acetyl, TMS-cleavage and ester into amide conversion.

Taken together, our results illustrate the efficiency of the given synthetic methodology for the supply of a variety of 4,5-disubstituted triazolyl nucleosides for further biophysical and biological applications. The evaluation of the antiviral activity of these analogues is under investigation.



Scheme 3 Post-synthetic transformations of **2a**

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References and Notes

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(15) **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.97 (s, 3 H, Ac), 2.07 (s, 6 H, Ac), 4.07 (dd, *J* = 12.3, 4.2 Hz, 1 H, H-5′), 4.25–4.50 (m, 4 H, H-4′, H-5′ and CH_2 ester), 5.72 (t, *J* = 5.5 Hz, 1 H, H-3′), 6.07 (dd, *J* = 5.5, 3.1 Hz, 1 H, H-2′), 6.12 (d, *J* = 3.1 Hz, 1 H, H-1′). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 20.4, 20.5, 20.6, 61.6, 62.5, 70.9, 73.9, 81.5, 90.3, 142.2, 159.9, 169.2, 169.4, 170.4. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{21}N_3O_9I$: 526.0322; found: 526.0317.
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(17) With excess of I_2 as electrophile the reaction was sluggish when only one equivalent of DIPEA was used.
(18) **Typical procedure:** To a solution of azido-sugar (1 mmol) in CH_2Cl_2 (10 mL) were successively added alkyne (1.1 equiv), electrophile (3 equiv), CuX (CuI, CuBr or CuCl, 1.1 equiv) and DIPEA (see Table 1 and Table 2). The reaction mixture was stirred at r.t. until the reaction was complete as indicated by TLC. The mixture was filtered through Celite and the solvent was removed. The crude product was purified by flash silica gel chromatography (cyclohexane–EtOAc, 9:1→1:1) to afford the desired 1,4,5-trisubstituted triazoles.
Analytical data for selected compounds:
2d: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.97 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 4.05 (dd, *J* = 13.1, 5.1 Hz, 1 H, H-5′), 4.25–4.40 (m, 4 H, H-4′, H-5′ and CH_2 ester), 5.72 (t, *J* = 5.5 Hz, 1 H, H-3′), 5.88 (dd, *J* = 5.2, 3.0 Hz, 1 H, H-2′), 6.27 (d, *J* = 3.0 Hz, 1 H, H-1′), 7.17–7.25 (m, 3 H, H-Ar), 7.31–7.40 (m, 2 H, H-Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 20.5, 20.6, 20.8, 61.7, 62.7, 71.0, 74.3, 81.2, 88.9, 128.3, 128.7, 129.9, 132.6, 136.8, 160.3, 169.2, 169.5, 170.7, 172.0. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{26}N_3O_9Se$: 556.0834; found: 526.0829.
2e: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.96 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 2.37 (s, 3 H, CH_3Ph), 3.99 (dd, *J* = 12.3, 4.5 Hz, 1 H, H-5′), 4.07 (q, *J* = 7.1 Hz, 2 H, CH_2 ester), 4.17 (dd, *J* = 12.3, 3.3 Hz, 1 H, H-5′), 4.31 (dd, *J* = 7.9, 4.5 Hz, 1 H, H-4′), 5.59 (t, *J* = 4.7 Hz, 1 H, H-3′), 6.07 (m, 2 H, H-1′ and H-2′), 7.23 (d, *J* = 8.1 Hz, 2 H, H-Ar), 7.59 (d, *J* = 8.1 Hz, 2 H, H-Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 20.3, 20.4, 20.6, 21.9, 61.6, 62.5, 70.8, 73.7, 81.7, 89.4, 129.7, 133.7, 137.6, 138.8, 146.5, 159.4, 169.1, 169.4, 170.4, 185.4. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{28}N_3O_{10}$: 518.1775; found: 518.1781.
2h: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 4.61 (dd, *J* = 12.2, 4.9 Hz, 1 H, H-5′), 4.78 (dd, *J* = 12.2, 3.7 Hz, 1 H, H-5′), 4.94 (dd, *J* = 10.9, 5.3 Hz, 1 H, H-4′), 6.35 (dd, *J* = 7.0, 5.1 Hz, 1 H, H-3′), 6.40 (d, *J* = 2.0 Hz, 1 H, H-1′), 6.50 (dd, *J* = 5.1, 2.0 Hz, 1 H, H-2′), 7.00 (d, *J* = 8.9 Hz, 2 H, H-Ar), 7.30–7.65 (m, 9 H, H-Ar), 7.85–8.10 (m, 8 H, H-Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4, 63.7, 71.9, 75.1, 81.2, 88.2, 114.3, 121.5, 128.1, 128.5, 128.6, 128.7, 130.0, 133.3, 133.7, 134.0, 142.3, 160.1, 165.2, 166.3. MS (ES): *m/z* = 75.8 [M + Na].
(19) To a solution of **2a** (1 mmol) in toluene (10 mL) were successively added 2-(tributylstannyl)furan (2 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (5 mol%) and Et_3N (1 equiv). The reaction mixture was stirred for 30 min at 80 °C. After the reaction was complete (^{1}H NMR monitoring), the mixture was filtered through Celite and the solvent was removed. The crude product was purified by flash silica gel chromatography (cyclohexane–EtOAc, 9:1→1:1) to afford the desired compound in 95% isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.00 (s, 3 H, Ac), 2.09 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 4.11 (dd, *J* = 12.1, 4.4 Hz, 1 H, H-5′), 4.30–4.50 (m, 4 H, H-4′, H-5′ and CH_2 ester), 5.82 (t, *J* = 6.2 Hz, 1 H, H-3′), 6.17 (dd, *J* = 5.2, 2.9 Hz, 1 H, H-2′), 6.39 (d, *J* = 2.9 Hz, 1 H, H-1′), 6.60 (dd, *J* = 3.4, 1.8 Hz, 1 H, H-furan), 7.45 (d, *J* = 3.4 Hz, 1 H, H-furan), 7.66 (d, *J* = 1.8 Hz, 1 H, H-furan). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4, 20.6, 20.8, 61.6, 62.9, 71.2, 74.4, 81.4, 89.7, 112.4, 117.6, 139.0, 145.3, 151.5, 157.9, 160.8, 169.4, 169.5, 170.7. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{24}N_3O_{10}$: 466.1462; found: 466.1456. This compound was then dissolved in MeOH (8 mL) and the solution was saturated with ammonia at 0 °C and stirred for 1 h at r.t. The crude product was evaporated and purified by flash silica gel chromatography (CH_2Cl_2–MeOH, 9:1) to afford nucleoside **4** in 91% yield. Free nucleoside **4**: ^{1}H NMR (200 MHz, CD_3OD): δ = 3.60 (dd, *J* = 12.1, 5.6 Hz, 1 H, H-5′), 3.75 (dd, *J* = 12.2, 3.7 Hz, 1 H, H-5′), 3.88 (s, 3 H, OMe), 4.13 (dd, *J* = 9.2, 5.5 Hz, 1 H, H-4′), 4.51 (t, *J* = 5.4 Hz, 1 H, H-3′), 4.87 (t, *J* = 1.7 Hz, 1 H, H-2′), 6.17 (d, *J* = 2.9 Hz, 1 H, H-1′), 6.69 (dd, *J* = 3.4, 1.8 Hz, 1 H, H-furan), 7.36 (d, *J* = 3.4 Hz, 1 H, H-furan), 7.82 (d, *J* = 1.8 Hz, 1 H, H-furan). ^{13}C NMR (50 MHz, CD_3OD): δ = 52.6, 63.3, 72.2, 76.0, 87.3, 93.3, 113.0, 118.0, 139.8, 147.0, 159.0, 161.7, 162.2. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{15}N_3O_7Na$: 348.0808; found: 348.0807.
(20) The Eicar analogue **5** was prepared using standard Sonogashira coupling to give the protected nucleoside intermediate: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.27 (s, 9 H, TMS), 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.02 (s, 3 H, Ac), 2.09 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 4.12 (dd, *J* = 12.9, 5.4 Hz,

1 H, H-5′), 4.32–4.52 (m, 4 H, H-4, H-5′ and CH_2 ester), 5.73 (t, *J* = 6.2 Hz, 1 H, H-3′), 5.90 (dd, *J* = 5.2, 2.8 Hz, 1 H, H-2′), 6.16 (d, *J* = 2.8 Hz, 1 H, H-1′). ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.6, 14.3, 20.4, 20.5, 20.7, 61.5, 62.6, 70.7, 74.1, 81.1, 88.8, 113.6, 124.6, 140.6, 159.6, 169.2, 169.4, 170.6. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_9Si$: 496.1751; found: 496.1746.

Methanolysis of this intermediate as described above (MeOH, NH_3, 48 h) led to the free nucleoside **5**: ^{1}H NMR (200 MHz, CD_3OD): δ = 3.40 (s, 1 H, H-alkyne), 3.60 (dd, *J* = 12.1, 5.7 Hz, 1 H, H-5′), 3.74 (dd, *J* = 12.1, 3.8 Hz, 1 H, H-5′), 4.11 (dd, *J* = 9.3, 5.4 Hz, 1 H, H-4′), 4.45 (t, *J* = 5.4 Hz, 1 H, H-3′), 4.75 (t, *J* = 3.4 Hz, 1 H, H-2′), 6.09 (d, *J* = 3.4 Hz, 1 H, H-1′). ^{13}C NMR (50 MHz, CD_3OD): δ = 63.3, 72.2, 75.8, 87.4, 92.5, 94.5, 123.8, 144.3, 159.1, 163.3. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}N_4O_5$: 269.0886; found: 269.0882.