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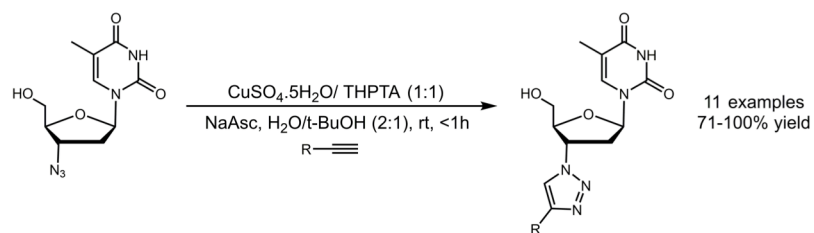
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Graphical Abstract

Efficient access to 3'-deoxy-3'-(4-substituted-1,2,3-triazolyl)-thymidine derivatives *via* ligand-promoted CuAAC

Laura Garlatti, Raphaël Huet and Karine Alvarez



Efficient access to 3'-deoxy-3'-(4-substituted-1,2,3-triazol-1-yl)-thymidine derivatives via ligand-promoted CuAAC

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ABSTRACT

Herein we describe an efficient and rapid access to 3'-deoxy-3'-(4-substituted-1,2,3-triazol-1-yl)-thymidine derivatives using 1,3-dipolar cycloaddition reaction catalyzed by copper(I). Innovative conditions allow us to generate target compounds in a one-pot reaction mixing 3'-azido-3'-deoxythymidine, alkyne, copper sulfate pentahydrate, sodium ascorbate and tris(benzyltriazolylmethyl)amine in a water/tert-butanol solvent mixture. Rapid treatment of the reaction and subsequent flash purification chromatography afforded pure compounds in an overall yield of **71-100%**. All eleven synthesized compounds were identified on the basis of their spectral data analysis (¹H, ¹³C, 2D NMR and high-resolution mass spectra).

Keywords:

3'-Azidothymidine;

1,2,3-triazolynucleosides;

CuAAC;

Click Chemistry;

Antiviral;

3'-deoxy-3'-(4-substituted-1,2,3-triazol-1-yl)-thymidine;

Introduction

In the past 20 years, the copper(I)-catalyzed Huisgen–Sharpless–Meldal 1,3-dipolar cycloaddition reaction^{1–3} (CuAAC) to form 1,4-disubstituted triazole heterocycles by reaction of azides and alkynes have attracted much attention. The click chemistry reaction offers several advantages: a high chemoselectivity, stereospecificity and often fast kinetics. CuAAC is wide in scope, simple to perform and can be conducted in benign solvents.

This reaction has opened new horizons for medicinal chemists by giving access to molecular diversity under mild, fast and efficient conditions that are readily set up and often biocompatible. Among the applications of click chemistry, antiviral development has been widely explored, in particular nucleoside analogues as essential molecules of current therapeutic strategies. Retrovir®⁴ (3'-azido-3'-deoxythymidine, AZT), still approved against HIV infection, alone or in combination in highly active anti-retroviral therapies (HAART), is a model compound that continues to be explored with more than 200 publications since 2019 (PubMed data). Despite significant progress in the design of anti-HIV drugs, the remaining issues (*i.e.* toxicity, resistance, weak activity) emerging from its use led to an increasing interest of synthesizing more relevant nucleoside analogues that can also be repositioned against other retroviruses or to treat various pathologies^{5,6}. With an azido group replacing the 3'-OH of the deoxyribose, AZT is a suitable candidate to be readily transformed into 1,4 or 1,5 triazolyl nucleoside analogues by a 1,3-dipolar cycloaddition. Although most of the reported derivatives did not show any activity against few viruses⁷, some have demonstrated potent activities^{8–12} against HIV-1. The first AZT-derived 1,2,3-triazole active against HIV-1 was reported in 2013 by Sirovolu V. *et al.*¹³ with a noticeable sub-micromolar activity. The resulting structure-activity relationship (SAR) studies highlighted that antiviral activity is observed when a bulky aromatic ring is introduced on C4 and/or C5 position of the triazolyl moiety (Figure 1). These promising results have demonstrated that the reported efforts put into the synthesis and biological evaluation of AZT analogues are worthwhile and must be pursued.

Although the use of copper greatly improved the 1,3-dipolar cycloaddition (10^7 to 10^8 rate acceleration), some CuAAC reactions still proceed relatively slowly. To improve reaction efficiency and reduce duration, temperature increase and microwave irradiation have proven to be effective. However, harsh reaction conditions are limiting, especially with labile substrates that may not resist. The discovery of polydentate *N*-donor molecules capable of stabilizing Cu(I) species by chelation (Figure 2) allowed to bypass these limitations.^{14,15} The resulting protection of catalytic species from air oxidation permit to maintain its concentration in solution, enabling the reaction to process efficiently at room temperature (RT) with impressive reaction rates. The tris(triazolylmethyl)amine ligands have been successfully used for multiple purposes¹⁶ like organic synthesis¹⁷, polymer and material science¹⁸, nucleic acid labelling in living media¹⁹ or bio-conjugation.²⁰ TBTA (tris((1-benzyl-4-triazolyl)methyl)amine) and THPTA (tris(benzyltriazolylmethyl)amine) are the most commonly-used polydentate *N*-donor ligands (Figure 2). According to literature, THPTA is far superior to TBTA in aqueous media, due to its higher water solubility and efficiency to protect Cu(I) species towards air oxidation.

Herein, we wanted to assess the use of THPTA for the synthesis of 3'-deoxy-3'-(4-substituted-1,2,3-triazol-1-yl)-thymidine derivatives in order to propose a mild, fast and

efficient CuAAC reaction in aqueous media. First, optimization of the reaction was conducted using AZT and phenylacetylene to produce compound **1**. To further expand the scope of the newly optimized method, ten 3'-deoxy-3'-(4-substituted-triazol-1-yl)-thymidine derivatives **2–11** were synthesized (Figure 3) varying alkyne substrate by substituted phenylacetylenes (*i.e.* phenoxymethyl, dioxolane, dimethoxy, nitrile, methyl ester, dimethylaniline, benzyl alcohol, tert-butyl and trifluoromethyl) or hex-5-ynol. The structures of all synthesized compounds **1–11** were identified on the basis of their spectral data analysis (¹H, ¹³C, 2D spectra, and high-resolution mass spectra (HRMS)).

Results and Discussion

The synthesis of compound **1** was first described in 1989 by Wigerinck *et al.*²¹. AZT was reacted in ethanol with a large excess of phenylacetylene and without copper catalysis resulting in an extended reaction time (144h). In 2008, the use of CuBr/ligand catalytic system reported by Wang *et al.*²² shortened the reaction time to 4.5h and allowed the reaction to be conducted in water at RT to yield 93% of the product. In 2010, Van Poecke *et al.*⁵ reported the synthesis of compound **1** at RT using a general Cu(II)/sodium ascorbate system resulting to 72% yield with a 24h reaction time. The same year, the use of microwave irradiation (20 min at 125°C) explored by Lin *et al.*²³ greatly improved the reaction rate and led to 84% yield. More recently, compound **1** was obtained with 83% yield by Alencar *et al.*¹¹ by heating the reaction media at 100°C during 2h.

In this study, our aim was to find new conditions allowing a fast and efficient synthesis of compound **1** at RT in aqueous media. First, optimization of the CuAAC reaction was conducted at RT, using AZT and phenylacetylene to produce compound **1** (Scheme 1) using various conditions. Results are summarized in Table 1. Several parameters were optimized when phenylacetylene and sodium ascorbate equivalents were fixed at 1.1 and 0.45 respectively. The ideal molar ratio of Cu(II) was assessed (1–10%). DMSO and t-BuOH as organic co-solvents were evaluated to ensure good solubility of most hydrophobic reagents in the reaction media. The efficiency of the reaction with either PPh₃, a catalytic auxiliary that improves the proximity of the reactants²⁴, or THPTA as an accelerating ligand was investigated. In the first place, the reaction was done “on water” without any co-solvent and with 1% of copper. (Entry 1). However, only 24% conversion was reached in 48h, highlighting the need of a co-solvent to solubilize hydrophobic components in the media. Thus, the reaction was then performed using a H₂O/DMSO (1:1) mixture and allowed to double the conversion to reach 50% yield (Entry 2). As expected, the molar ratio of Cu(II) influenced drastically the conversion of the reaction as an increased percentage from 1% to 10% doubled the conversion from 50 to 100% in 48h (Entry 3). With the aim of reducing reaction time the efficacy of the catalytic auxiliary PPh₃ was assessed in DMSO. Starting with 1% of copper and 10% of PPh₃, 85% conversion was achieved in 48h but the reaction didn't reach full completion (Entry 4). Even with 10% of copper, the conversion barely exceeded 90% (Entry 5). Moreover, precaution must be taken with PPh₃ as the Staudinger reaction may reduce the azide into the corresponding amine, partially inhibiting the reaction. In our case, with only 10% of catalytic auxiliary no side reaction was noticed. In order to further improve the reaction and implement a simple work-up protocol, while maintaining substrates solubility, we decided to replace DMSO by t-BuOH. To minimize the co-solvent proportion, a H₂O/t-BuOH (2:1) mixture was tested, as described in literature. The reaction time

has been halved but remained too long (20h) (Entry 6). To shorten it, the polydentate *N*-donor ligand THPTA was evaluated and full conversion has been achieved in only 30 min (200 times shorter) in both binary solvent mixtures (Entry 7 and 8), testifying to the highly valuable effect of this ligand. To summarize, the best conditions were obtained a 10% pre-mixed solution of CuSO₄·5H₂O and THPTA in a 1:1 ratio, with 45% of sodium ascorbate and 1.1 equivalents of phenylacetylene in a H₂O/*t*-BuOH (2:1) mixture. The reaction proceeds efficiently at RT in a very short time.

To expand the diversity of 3'-deoxy-3'-(4-substituted-triazol-1-yl)-thymidine derivatives, ten novel compounds (**2-11**) were synthesized using the optimized conditions (Figure 3). Reaction times and isolated yields obtained are gathered in Table 2. All reactions were completed in 30 to 60 min, in good to excellent yields (71 to 100%). No significant differences of reactivity were observed when using alkynes with various electronic properties. However, for the bulkiest and electron-rich substituted

phenylacetylenes (ie. *tert*-butyl and phenoxyethyl) a longer reaction time of 60 min was required. This observation correlates with the ones established previously in literature, where electron-poor alkynes react faster than the electron-rich, the latter being considered as “inactivated”.

Regarding the work-up of the reaction, we wanted to implement a simple protocol that allows a fast and quantitative recovery of target compounds. Previous work-up procedures reported in literature included either pesky water evaporation *in vacuo* at high temperature or time-consuming lyophilization. To find a more convenient procedure, different liquid-liquid extraction solvents were evaluated (eg. EtOAc, DCM, CHCl₃/*i*PrOH (3:1)) and CHCl₃/*i*PrOH (3:1) mixture allowed a total recovery of the compounds. As THPTA is water-soluble, a simple liquid-liquid extraction allowed to get rid of it and ensured the requisite elimination of complexed Cu(I) species as demonstrated by the

Table 1. Optimization of the reaction conditions with compound **1** as model product ^a

Entry	Solvent	CuSO ₄ ·5H ₂ O (mol%)	PPh ₃ (mol%)	THPTA (mol%)	Time (h)	Conversion ^b (%)
1	H ₂ O	1	-	-	48	24
2	H ₂ O/DMSO (1:1)	1	-	-	48	50
3	H ₂ O/DMSO (1:1)	10	-	-	48	100
4	H ₂ O/DMSO (1:1)	1	10	-	48	85
5	H ₂ O/DMSO (1:1)	10	10	-	48	>90
6	H ₂ O/ <i>t</i> -BuOH (2:1)	10	10	-	20	>99
7	H ₂ O/ <i>t</i> -BuOH (2:1)	10	-	10	0.5	100
8	H ₂ O/DMSO (1:1)	10	-	10	0.5	100

^aOptimization carried out on a 50 mg scale

^bDetermined by HPLC-MS

specific blue-colored aqueous layer. After drying and evaporation of the organic layer, the crude was immediately engaged in a flash chromatography purification to afford compounds **1-11** in 71 to 100% yields.

Table 2. Reaction times and isolated yields for synthesized compounds **1-11**

Compound	Reaction time (min)	Isolated yield ^a (%)
1	30	100
2	60	77
3	30	94
4	30	97
5	30	79
6	30	74
7	30	96
8	30	94
9	30	71
10	60	94
11	30	71

^aIsolated yields after flash chromatography purification

For all target compounds, a complete regioselectivity of the copper(I)-catalyzed-1,3-dipolar cycloaddition was observed. The unique formation of the 1,4-disubstituted triazoles was clearly confirmed by ¹H-NMR spectra. The characteristic chemical shift of the 1,4-disubstituted triazole proton is shifted downfield compared to the 1,5-disubstituted regioisomer²⁶ (about 8.50 ppm versus 8.20 ppm). All synthesized compounds followed this trend (8.56-8.99 ppm), excepting the compound **8** bearing an aliphatic chain on the triazole moiety. Indeed, in this specific case, the low chemical shift of 8.04 ppm observed is due to the absence of the strong deshielding effect of the phenyl ring. In addition, we noticed the splitting of the thymidine double bond proton singlet (H₆) into a “pseudo” doublet with a small coupling constant around 1 Hz for all compounds. The corresponding multiplicity is noted s* in the ¹H NMR description and an expansion of the relevant area is available for compound **4** (S9, Supporting Information). Although this peak is commonly reported as a singlet in literature, this phenomenon was previously described as the coupling between H₆ and -CH₃ protons of the thymidine ring. In some cases, the methylene peak at 1.82 ppm was also noticed as a “pseudo” doublet reinforcing this observation. A coupling between the 5'-OH proton and neighboring hydrogens was noticed for all compounds excepting for **1** and **7** where a broad singlet was observed. To further investigate the previous observations, 2D experiments were conducted on compound **2**. By the mean of a COSY experiment (S17, Supporting Information) we were able to confirm the slight coupling between H₆ and the thymidine -CH₃ proton as a clear correlation

was observed between both. Moreover, we noticed a correlation between the 5'-OH and the neighboring non-equivalent H₅ and H_{5'} protons. The expecting doublet of doublets is displayed as a pseudo triplet as the two resulting coupling constants may be equal in this particular case. The coupling observation was made possible thanks to the aprotic and polar DMSO-d₆ which removed of any acidic impurities is able to reduce the rate of proton exchange. As expected, other important correlations between the furanose protons were noticed: H_{1'} with H_{2'}, H_{3'} with H_{2'} and H_{4'}. Last but not least, a specific correlation was observed between aromatic protons and aliphatic -CH₂ protons of the phenoxyethyl moiety. Finally, ROESY spectra of compound 2 was acquired to complete structural data (S17, Supporting Information).

Conclusions

In summary, we propose here a turnkey method, that gives fast and convenient access to 3'-deoxy-3'-(4-substituted-1,2,3-triazol-1-yl)-thymidine derivatives by ligand-promoted CuAAC. Reactions are conducted at RT in a very short time, using Cu(I)-THPTA complex, in H₂O:*t*-BuOH solvent mixture. After reaction, a simple extraction work-up allows a quantitative recovery of target compounds before flash chromatography purification. By this way, ten novel AZT-derived 1,2,3-triazoles were generated. Their antiviral activity evaluation against HIV is under progress.

Declaration of Competing Interests

The authors declare no conflict of interest.

Acknowledgments

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Supplementary Material

Supplementary data (detailed synthetic procedures, spectroscopic 1D and 2D data, HPLC-MS and HRMS spectra for compounds **1-11**) associated with this article can be found, in the online version at

Artwork and Tables with Captions

Figure 1. Representative biologically active 1,4 or 1,5 - 3'deoxy-3'-(1,2,3-triazol-1-yl)-thymidine derivatives.

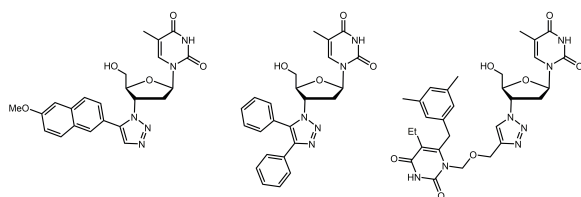
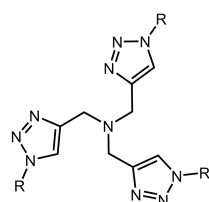
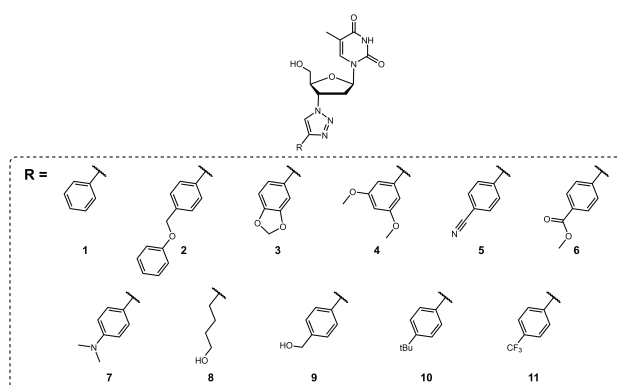


Figure 2. Structure of THPTA and TBTA, two tris(triazolylmethyl)amine ligands accelerating CuAAC reactions.



TBTA: R = Bn
THPTA: R = $-(\text{CH}_2)_3\text{OH}$

Figure 3. Structures of 3'-deoxy-3'-(4-substituted-1,2,3-triazol-1-yl)-thymidine derivatives **1-11**.



Scheme 1. Synthesis scheme of compound **1**.

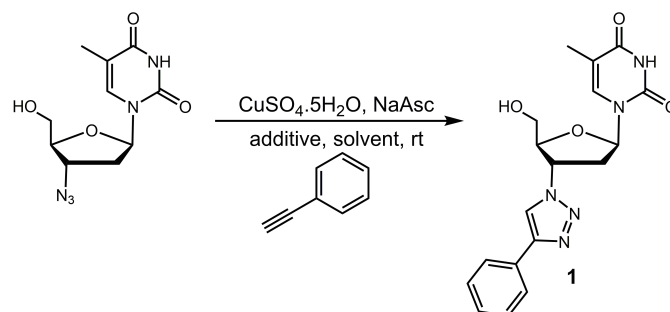


Table 1. Optimization of the reaction conditions with compound **1** as model product^a

Entry	Solvent	CuSO ₄ ·5H ₂ O (mol%)	PPh ₃ (mol%)	THPTA (mol%)	Time (h)	Conversion ^b (%)
1	H ₂ O	1	-	-	48	24
2	H ₂ O/DMSO (1:1)	1	-	-	48	50
3	H ₂ O/DMSO (1:1)	10	-	-	48	100
4	H ₂ O/DMSO (1:1)	1	10	-	48	85
5	H ₂ O/DMSO (1:1)	10	10	-	48	>90
6	H ₂ O/t-BuOH (2:1)	10	10	-	20	>99
7	H ₂ O/t-BuOH (2:1)	10	-	10	0.5	100
8	H ₂ O/DMSO (1:1)	10	-	10	0.5	100

^aOptimization carried out on a 50 mg scale^bDetermined by HPLC-MS**Table 2.** Reaction times and isolated yields for synthesized compounds **1-11**

Compound	Reaction time (min)	Isolated yield ^a (%)
1	30	100
2	60	77
3	30	94
4	30	97
5	30	79
6	30	74
7	30	96
8	30	94
9	30	71
10	60	94
11	30	71

^aIsolated yields after flash chromatography purification