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Synthesis of geminal bis- and tristriazoles: exploration of unconventional azide chemistry†

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A range of geminal bis- and tristriazoles are presented. These rare and hardly studied compound classes were easily synthesized using ethyl 2,2-diazo-3-oxobutanoate as the common starting point. Firstly, CuAAC-reaction with an alkyne afforded the corresponding deacetylated bistriazoles. Upon further azidation yielding azido-methylenebistriazoles, a second CuAAC-functionalization then led to the creation of the geminal tristriazole compounds.

The generation of triazoles through the copper-catalyzed alkyne azide cycloaddition (CuAAC) reaction has become a major playground in many disciplines of science, ranging from chemical biology to material sciences.¹ Contemporary research in the field of small molecules containing azide functionalities is also boosted,² mainly due to their use as one reaction partner in the CuAAC, and several new methods for the simple azidation of compact chemical structures were reported over the last couple of years.³

We became involved into the question of how to azidate small molecules during our studies on oxidative functionalizations of 1,3-dicarbonyl compounds.⁴ In 2012, we demonstrated that 1,3-dicarbonyls can be azidated by use of IBX-SO₃K,⁵ sodium azide and catalytic amounts of sodium iodide in aqueous DMSO at room temperature.⁶ With this protocol, we were capable of creating several geminal diazides.[‡] A variant of this procedure also led to the synthesis of geminal triazides, highly energetic compounds that must be handled with caution.⁸ In the course of those projects, we realized that the di- and triazides can be converted into their corresponding geminal bis- and tristriazoles using cycloaddition reactions with alkynes.⁹ Besides our own reports, the two compound classes turned out to be somewhat neglected, and most previous reports on geminal bistriazoles

focused on geminal bis(benzotriazol-1-yl)methyl derivatives, as shown, for example, in the detailed studies by Katritzky and co-workers.^{10,11} Even more surprising, our review of the literature revealed only one example for a geminal tristriazole, *i.e.* tris(benzotriazo-1-yl)methane.¹²

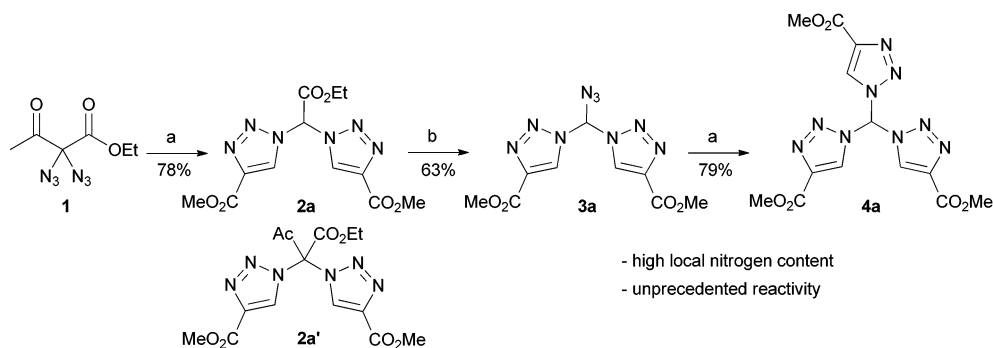
In this communication, we describe a unique approach toward geminal tristriazoles that does neither rely on the hazardous geminal triazides⁸ as starting materials nor on the nucleophilic substitution of chloroform,¹² a reaction that is highly limited in scope. We also show how azides (and triazoles) can dramatically alter the reactive behavior of adjacent functional groups and give rise to a whole new pool of unconventional disconnections that might become of interest for future reaction plannings.¹³

By pure serendipity, it was observed that CuAAC reaction with geminal diazide **1** under standard conditions does not result in the formation of the expected bistriazole **2a'**. To our surprise, triazole formation was, with this particular substrate, always accompanied by deacetylation, and **2a** [¹⁵N-NMR (DMSO) –13.3, –20.3, –134.4 ppm] was isolated as the only product when reaction time was prolonged (Scheme 1). The molecular structure of **2a** was unequivocally confirmed by X-ray crystallography (Fig. 1); the two triazole rings are oriented in a perpendicular way. In contrast to **2a'**, bistriazole **2a** had a position with an additional hydrogen where a further functionalization could be anticipated. Indeed, the electron-withdrawing nature of the triazole groups activates this position, and azidation was possible by use of our standard azidation protocol with IBX-SO₃K, sodium azide and catalytic amounts of sodium iodide.⁶ Now, the door was open to the synthesis of tristriazoles, and **3a** [¹⁵N-NMR (DMSO) –17.6, –20.0, –127.2, –143.0, –152.8, –293.6 ppm] was transformed into the symmetric tristriazole **4a** [¹⁵N-NMR (DMSO) –16.4, –19.3, –134.4 ppm] through standard cycloaddition. The sequence outlined in Scheme 1 was expected to allow for the synthesis of a broad range of novel bistriazoles (such as **2a**), azidobistriazoles (such as **3a**) and tristriazoles (such as **4a**), depending only on the alkynes employed in the cycloaddition reactions.

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Scheme 1 Synthesis of tristriazole **4a** by cycloaddition starting with diazide **1** and subsequent azidation. a: MeO₂C–C≡CH (2.2 eq.), CuSO₄·5H₂O (20 mol%), TBTA (3 mol%), Na ascorbate (42 mol%), rt, tBuOH/H₂O. b: IBX–SO₃K (4.0 eq), NaI (20 mol%), NaN₃ (10.0 eq), rt, DMSO/H₂O.

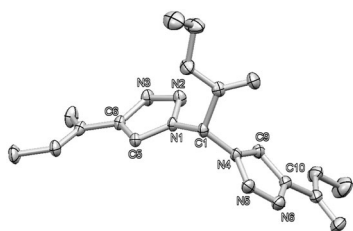


Fig. 1 Crystal structure of **2a**; ellipsoids are drawn at 50% probability. Hydrogen atoms are omitted for clarity.¹⁴

In every case, diazide **1** should be the starting material of choice due to its unique ability to undergo smooth deacetylation under the cycloaddition conditions. To this end, several bistriazoles **2** were generated through CuAAC reaction. As shown in Table 1, deacetylation of **1** took place in good yields when bistriazoles **2** were formed with arylalkynes. Aliphatic alkynes reacted with markedly reduced yields. Regarding the mechanism, we reasoned that the reaction proceeds *via* a retro-Claisen in which

water assumes the role of the nucleophile. When the reaction is stopped after 30 minutes, a mixture of acetylated and deacetylated bistriazoles was obtained in most cases. We note that the hydrogen atom attached at the alpha-carbon shows a tremendous downfield shift, ranging from 7.46 to 7.98 ppm in the ¹H NMR spectrum. For a tetrahedral carbon (see Fig. 1), this downfield shift is quite astonishing.

The results of the azidation are also listed in Table 1. In general, elevated reaction temperatures of 60 °C were required in order to obtain acceptable yields for the azidobistriazoles **3** (although traces of product formation were found as well at room temperature). The azidation proved to be scalable: azidobistriazole **3a**, for example, was isolated with 63% yield in a preparative amount of 870 mg. In all cases, the formation of the azidomethylenebistriazoles was accompanied by the loss of the ester moieties. Despite their high local nitrogen content, compounds of type **3**, however, never exhibited explosive behaviour and showed no degradation when stored under ambient conditions. We also point out that azidobistriazoles **3** are not stable under basic conditions; with LiOH in aqueous

Table 1 Synthesis of geminal bistriazoles **2** and azidobistriazoles **3** from ethyl 2,2-diazido-3-oxobutanoate (**1**)^a

chemical shift (¹ H NMR)					
	1	2	3		
Entry	R	Yield ^b (%)	Yield ^b (%)	δ ^c (ppm)	δ ^c (ppm)
1	CO ₂ Me	2a (78)	3a (63) ^d	7.78	8.77
2	CO ₂ Bn	2b (19)	3b (24) ^{d,e}	7.98	8.56
3	<i>c</i> -C ₃ H ₅	2c (34)	3c (26)	7.46	8.06
4	4-BrC ₆ H ₄	2d (76)	3d (19)	7.72	8.28
5	4- <i>n</i> PrC ₆ H ₄	2e (91)	3e (36)	7.68	8.27
6	C ₆ H ₅	2f (74)	3f (35)	7.71	8.30

^a Conditions: a: alkyne (2.2 eq.), CuSO₄·5H₂O (20 mol%), TBTA (3 mol%), Na ascorbate (42 mol%), rt, tBuOH/H₂O. b: IBX–SO₃K (4.0 eq.), NaI (20 mol%), NaN₃ (10.0 eq.), 60 °C, DMSO/H₂O. ^c Isolated yields. ^d Determined by ¹H NMR analysis of the product in CDCl₃ at 400 MHz or 600 MHz. ^e Reaction at room temperature. ^f 2.0 equiv. of IBX–SO₃K were used.

Table 2 Synthesis of geminal tristriazoles **4** from azidobistriazoles **3**^a

chemical shift (¹ H NMR)					
	3	4			
Entry	R	R'	#	Yield ^b (%)	δ (ppm)
1	CO ₂ Me	CO ₂ Me	4a	79	10.34 ^d
2	CO ₂ Bn	CO ₂ Bn	4b	60	9.62 ^c
4	<i>c</i> -C ₃ H ₅	<i>c</i> -C ₃ H ₅	4c	69	9.17 ^c
5	4- <i>n</i> PrC ₆ H ₄	4- <i>n</i> PrC ₆ H ₄	4d	75	9.54 ^c
6	C ₆ H ₅	C ₆ H ₅	4e	77	9.52 ^c
7	CO ₂ Me	CO ₂ Bn	4f	64	10.32 ^d
8	CO ₂ Me	<i>c</i> -C ₃ H ₅	4g	64	10.26 ^d
9	CO ₂ Me	C ₆ H ₅	4h	82	10.39 ^d

^a Conditions: a: alkyne (3.0 eq.), CuSO₄·5H₂O (40 mol%), Na ascorbate (84 mol%), rt, tBuOH/H₂O. ^b Isolated yields. ^c Determined by ¹H NMR analysis of the product in CDCl₃ at 400 MHz or 600 MHz. ^d Determined by ¹H NMR analysis of the product in d₆-DMSO at 400 MHz or 600 MHz.



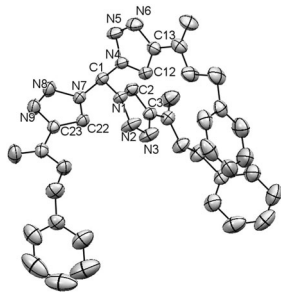


Fig. 2 Crystal structure of **4b**; ellipsoids are drawn at 50% probability level. Hydrogen atoms are omitted for clarity.¹⁵

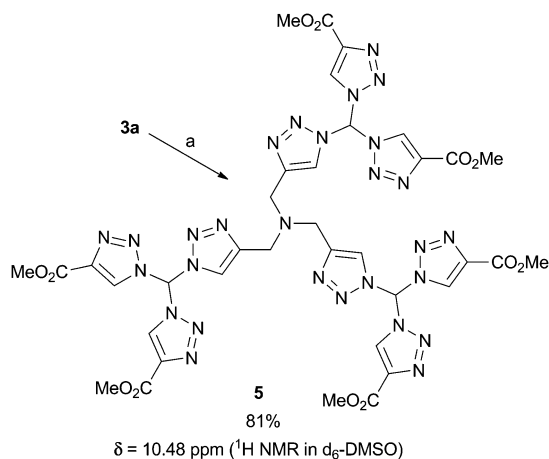


Fig. 3 Synthesis of the first evolution dendritic structure **5**. Conditions: a: tripropargyl amine (0.2 eq.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (40 mol%), Na ascorbate (84 mol%), rt, $t\text{BuOH}/\text{H}_2\text{O}$.

THF for example, they immediately engage in a strongly exothermic reaction under vigorous evolution of gas.

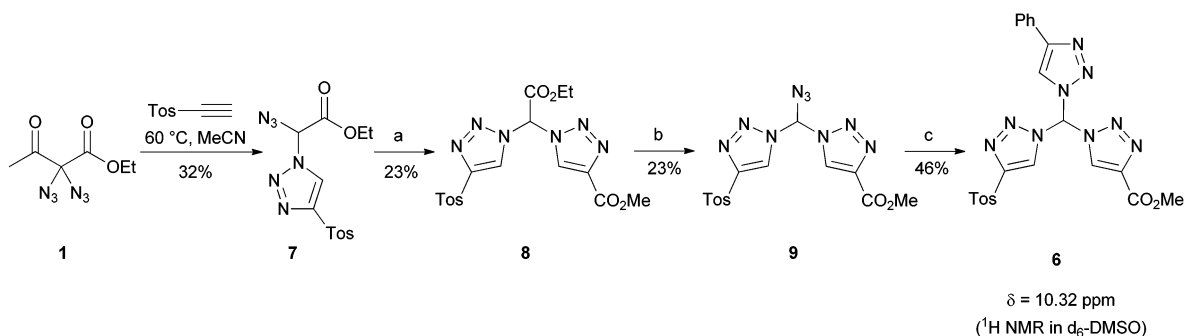
Azidomethylenebistriazoles **3** were then converted into the geminal trisubstituted triazoles **4** as summarized in Table 2. The overall sequence allows for the preparation of homosubstituted trisubstituted triazoles ($R = R'$) and trisubstituted triazoles with two different substituents ($R \neq R'$). Again, we found extraordinary downfield shifts in the ^1H NMR spectra for the central tetrahedral hydrogen.

This observation points to a quite acidic character, a feature that will become the theme of future studies from our group.

Single crystal analysis of compound **4b** was possible and is depicted in Fig. 2. The $\text{C}\alpha\text{-N}$ bonds have a length of 1.449 Å/1.453 Å and are, therefore, in perfect agreement with an average C–N single bond. Two triazole rings are pointing in the same direction, whereas one ring has the opposite orientation. The central carbon shows an almost ideal tetrahedral geometry.

To underline the possibilities with our leading sequence toward trisubstituted triazoles, we briefly looked into two variations: firstly, an excess of **3a** was connected with tripropargylamine under formation of trisubstituted triazole **5** (Fig. 3). The six ester groups in the periphery of the nitrogen rich system allow for further functionalization, thus the overall molecule **5** provides a starting point for dendritic growth. Secondly, we were able to generate trisubstituted triazole **6** with three different triazole units attached to the central carbon atom. As shown in Scheme 2, the synthetic strategy was slightly altered, and diazide **1** was combined first under thermal cycloaddition conditions with tosyl acetylene, an appropriately electron-deficient alkyne. Although double cycloaddition was preferred, it was possible to isolate monosubstituted triazole **7** in 32% yield. Of note, a single cycloaddition to azidotriazoles such as **7** was never possible when employing copper-catalyzed CuAAC conditions. In those cases, the exclusive formation of bistriazoles **2** was observed indicating that the second cycloaddition proceeds with a markedly increased rate. It was then possible to convert azide **7** into bistriazole **8** using copper-catalyzed conditions; the subsequent azidation gave rise to azide **9** where two different triazole moieties were incorporated. Finally, copper-catalyzed cycloaddition with phenylacetylene led to the desired geminal trisubstituted triazole **6**, a chiral (but racemic) compound containing three different triazole units.

In conclusion, we have described unconventional variants of the now classical CuAAC reaction and an exceptional azidation under oxidative conditions that combine to a straightforward sequence for the synthesis of a diverse array of geminal bis- and trisubstituted triazoles, most of which are not accessible with established methods. Several compounds with an unprecedented substitution pattern were presented; synthetic applications and studies on their photochemical properties will be reported in due course.



Scheme 2 A strategy for the synthesis of geminal trisubstituted triazoles with three different substituents. a: $\text{MeO}_2\text{C}-\text{C}\equiv\text{CH}$ (1.1 eq.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (20 mol%), TBTA (1 mol%), Na ascorbate (42 mol%), rt, $t\text{BuOH}/\text{MeCN}/\text{H}_2\text{O}$. b: $\text{IBX}-\text{SO}_3\text{K}$ (4.0 eq.), NaI (20 mol%), NaN_3 (10.0 eq.), rt, $\text{DMSO}/\text{H}_2\text{O}$. c: $\text{Ph}-\text{C}\equiv\text{CH}$ (4.0 eq.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (40 mol%), Na ascorbate (84 mol%), rt, $t\text{BuOH}/\text{H}_2\text{O}$.

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Notes and references

‡ Organic azides are always potentially explosive compounds and should be handled with appropriate care and safety equipment.

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- Structure was deposited with CCDC 1428562.
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