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Modular synthesis of mono, di, and tri-1,4-disubstituted-1,2,3-triazoles through copper-mediated alkyne–azide cycloaddition

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ABSTRACT

The synthesis of 1,2,3-triazoles was developed employing sequential copper azide–alkyne cycloaddition, tosylation, sodium azide, and copper azide–alkyne steps. This approach allowed the synthesis of two and three 1,2,3-triazole rings. A preliminary study to gain further insight into the reaction was performed using in situ ReactIR technology.

Introduction

The copper(I)-mediated 1,3-dipolar cycloaddition of azides and terminal alkynes[1] (CuAAC) increases the reaction rates and governs the regioselectivity, favoring 1,4-disubstituted 1,2,3-triazole formation. This discovery by Sharpless and Meldal is considered to be the most popular reaction of the 'click' chemistry concept[2] and represents the most straightforward synthesis of 1,2,3-triazoles. Click chemistry has evolved as a powerful strategy with many applications in modern chemistry, drug discovery, macromolecules, radiopharmaceuticals, material sciences, synthesis of bis-bidentate Pd(II) complexes, and biology, to cite just a few (Fig. 1).[3]

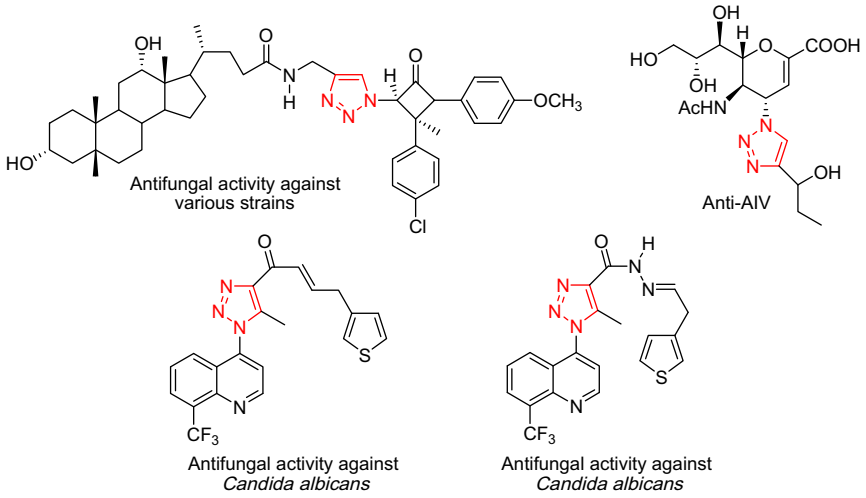

Figure 1. Structures of biologically active 1,2,3-triazoles.

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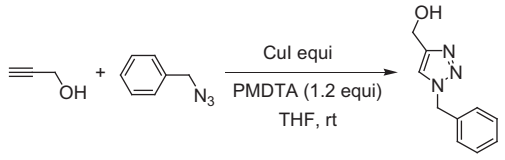
Table 1
Screening of CuI equivalents for the click reaction



Entry	CuI equiv	Conventional yield (%)	Ultrasound yield (%)
1	0.1	44	53
2	0.5	53	63
3	1.0	67	76

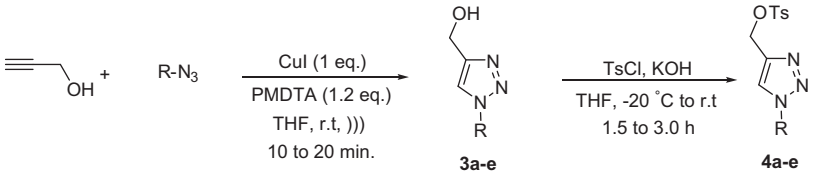
This reaction leads to the efficient formation of the corresponding 1,4-disubstituted-1,2,3-triazoles as a sole regioisomer using alkyl, aryl, or sulfonil azides.[1,4,5] The reactions take place with high yields, under mild conditions, and use copper sources that have no impact on most of the other functional groups.

This Cu(I)-mediated reaction has been largely successful because it provides virtually quantitative yields and because the robust reaction is not sensitive to solvents and functional groups. The use of Cu(I) is superior to that of the other metal catalysts in this reaction because it is cheap and easy to handle than the other catalysts described to accomplish the same transformation. Most of the other metal-catalyzed reactions involve the reduction of stable Cu(II) sources, such as $CuSO_4$, and use sodium salts or the comproportionation of Cu(II)/Cu(0) species.

Recently, studies using terminal diynes show the synthesis of bis-triazoles carried out by employing the sequential Cu-catalyzed cycloaddition reactions involving triisopropylsilyl-protected diynes and azides[6] or a one-pot reaction.[7]

Herein, we describe the initial efforts toward the modular synthesis of asymmetrically di-and tri-1,4-disubstituted-1,2,3-triazoles involving click chemistry using propargyl alcohol and sodium azide.

Table 2
Synthesis of 1,4-disubstituted-1,2,3-triazoles and the corresponding tosylated derivatives



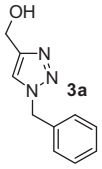
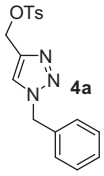
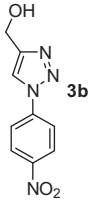
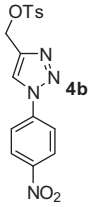
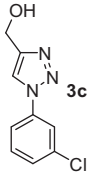
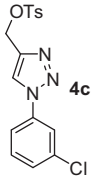
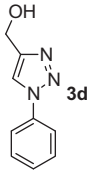
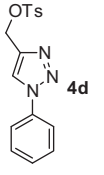
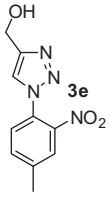
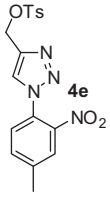
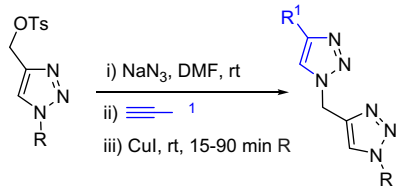
Entry	Product	Yield (%)	Entry	TsProduct	Yield (%)
1	 **3a**	74	6	 **4a**	76
2	 **3b**	75	7	 **4b**	50
3	 **3c**	66	8	 **4c**	90
4	 **3d**	70	9	 **4d**	86
5	 **3e**	90	10	 **4e**	74

Table 3
Synthesis of (1*H*-1,2,3-triazol-4-yl)methyl-1*H*-1,2,3-triazol-4-yl)methanol



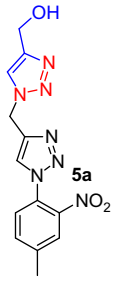
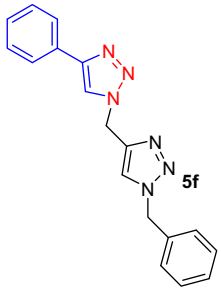
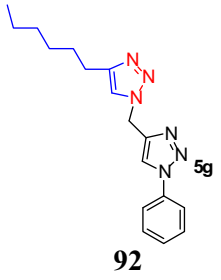
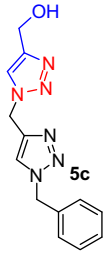
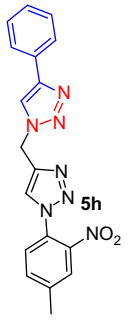
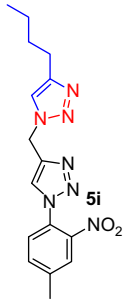
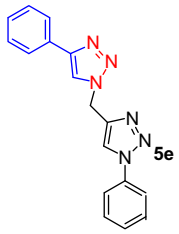
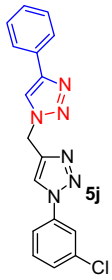
Entry	Product/yield (%)	Entry	Product/yield (%)
1	 **69**	6	 **60**
2	 **63**	7	 **92**
3	 **51**	8	 **72**
4	 **69**	9	 **64**

Table 3 (*continued*)

Entry	Product/yield (%)	Entry	Product/yield (%)
5	 **79**	10	 **71**

Results

Using the conditions described earlier,[8] the initial reactions were carried out on propargylic alcohol and organic azides to form the corresponding 1,4-disubstituted-1,2,3-triazoles using THF as the solvent followed by the addition of PMDETA (1,1,4,7,7-pentamethyl-diethylenetriamine) as the base in an anhydrous nitrogen atmosphere using ultrasound as the energy source.

In order to find an appropriate amount of CuI the reaction was performed with three different amounts of the catalyst, having benzyl azide and propargylic alcohol as the model reagents, using conventional reaction condition and with ultrasound. The best result was achieved with 1.0 equiv of CuI and ultrasound (Table 1).

To further investigate the scope and limitations of this methodology, we carried out the reaction with various organic azides, as summarized in Table 2.

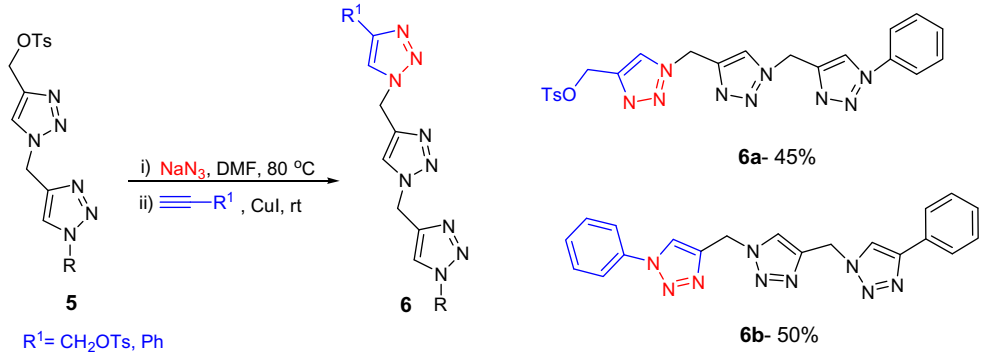
It was observed that the reaction changed from yellowish to dark colors with the addition of the base, depending on the group linked to the azide. All products were obtained as a white solid in moderate to good yields and very short reaction times (see Table 2, entries 1–5).[9]

The next step was the conversion of the hydroxyl group in the corresponding tosyl group using a procedure described in the literature.[10] All the tosylated products were obtained as a white solid in moderate to good yields as can be seen in Table 2 (entries 6–10).

In general, no significant differences in the reactivity were observed for the examined aromatic azides and the aliphatic azide. However, the aromatic azides furnished yields ranging from 90% to 66% (entries 2–5), whereas the aliphatic azide furnished the product in 74% yield (entry 1). Introducing an electron-withdrawing substituent on the phenyl rings gave the observed products in 66–90% yield (entries 2, 3 and 5). Replacing the organic azides with sodium azide failed to facilitate cyclization under Cu-catalyzed conditions.

With the tosylate 1,2,3-triazole compounds in hand, the second one-pot cyclization reaction was carried out to achieve a new bis-1,2,3-triazole ring.[11] The reaction was performed in DMF as the solvent and with propargyl alcohol, phenylacetylene, octyl-, and hexyl-acetylene, leading to the bis-1,2,3-triazoles in moderate to high yields and with short reaction times (Table 3).

The flexibility of the developed methodology using tosylated propargyl acetylene can be extended to prepare a sequence of tri-1,2,3-triazole rings in a one-step reaction starting from the bis-1,2,3-triazole as shown in Scheme 1. The products were obtained in moderate yields.



Scheme 1. Synthesis of tri-1,2,3-triazole rings in a one-step reaction starting from the bis-1,2,3-triazole.

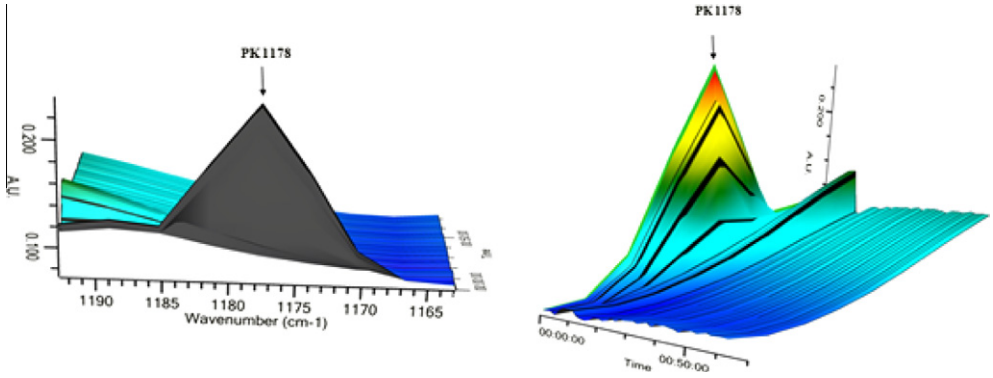


Figure 2. In situ IR spectroscopy monitoring of starting material consumption.

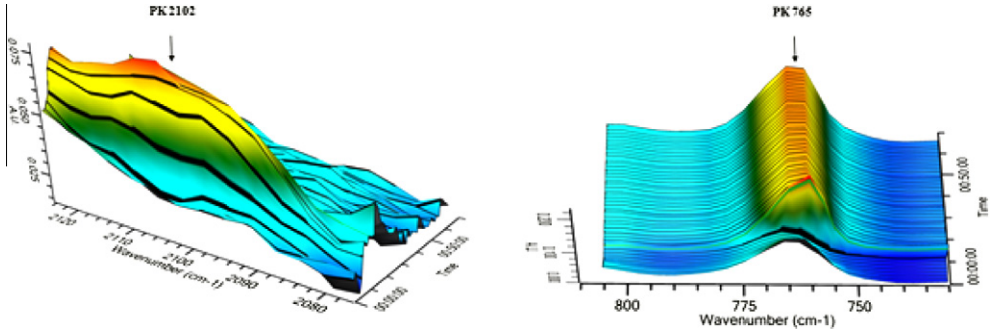


Figure 3. In situ IR spectroscopy monitoring: (A) triazole azide formation and consumption. (B) product formation.

The low yield observed was probably due the bis-triazole reactant is chelating to the catalyst and deactivating it, hence the low yields due to unreacted starting materials.[3k]

As part of the optimization study, each stage of the substitution–cycloaddition process was studied using in situ ReactIR spectroscopy, which is a useful tool for monitoring and optimizing the reaction process.[12,13] During the experiment, it was found that the ν_{SO2} of the tosyl group could be observed easily. As soon as sodium azide was added, the peak at 1178 cm^{-1} which was assigned to the vibrational stretching of the sulfone in the tosyl group disappeared. This information indicates that the substitution occurs quite rapidly at room temperature (Fig. 2). Moreover, there was a rapid increase in the band at 2102 cm^{-1}, indicating the formation of a triazolic azide. This peak was assigned to the vibrational stretching of N_3, which is related to azides.[14]

After the addition of phenyl acetylene and copper iodide, the peak of triazolic azide disappeared and an interesting peak at 765 cm^{-1} was visible in the IR spectrum (Fig. 3). This band remained constant for few minutes. In this context, the real-time infrared technique is very suitable for a precise interpretation of some parameters concerning the reaction, such as its duration and product formation. Through this analysis, we could determine that the substitution occurs instantly at room temperature, and also that the one-pot procedure lasts for only 15 min.

Summary

In summary, a modular method for the generation of functionalized one, bis-, and tri-1,4-disubstituted 1,2,3-triazoles has been

developed employing a sequence of Cu(I)-catalyzed 1,3-cycloaddition of organic azides with terminal alkynes, the CuAAC 'click' reaction, in good to excellent yields. The execution of this strategy is simple and suitable for the rapid assembly of molecular complexity, with new bonds being formed. The new 1,2,3-triazoles were fully characterized by HRMS, IR, ^{1}H, and ^{13}C NMR. A preliminary study to gain further insight into the reaction was performed using in situ ReactIR technology. Further studies on this methodology, applications, and the mechanism of the reaction are currently ongoing in our laboratory and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.004.

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9. *General procedure*: **Synthesis of 1,4-disubstituted-1,2,3-triazoles**. In a 50 mL two-neck flask under a nitrogen atmosphere, a propargyl alcohol solution (0.28 g, 0.3 mL, 5 mmol) was added with a dissolved organic azide (1.2 equiv, 6 mmol) in THF (8 mL) and the copper catalyst (1 equiv, 5 mmol). The reaction was then put in a ultrasound bath for homogenization, followed by the addition of PMDETA (1.03 g, 1.25 mL, 6 mmol) drop by drop until the starting material was consumed, followed by TLC. The resulting aqueous phase was washed with ethyl acetate, the organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under vacuum. The crude product was purified by column chromatography using as the eluent a mixture of hexane/ethyl acetate (2/8) (see Supplementary data for reaction time). (**1-Benzyl-1*H*-1,2,3-triazol-4-yl**)**methanol** (**3a**): The product was obtained as a with solid, MP. 78–79 °C, in 74% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (s, 1H), 7.39–7.34 (m, 3H), 7.27–7.25 (m, 2H), 5.51 (s, 1H), 4.76 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 54.17, 56.08, 121.93, 128.13, 128.77, 129.12, 134.58, 148.35. IR cm^{-1} (ethyl acetate solution): 3600, 2989, 1759, 1241, 1055, 927. HRMS calcd for $C_{10}H_{11}N_3O$ 189.0902. Found: [M+Na] = 212.0794.
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General procedure: **Synthesis of Tosyl triazoles**. In a two neck flask of 50 mL under nitrogen atmosphere was added KOH (0.64 g, 5 mmol) and tosyl chloride (0.45 g, 2.2 mmol) dissolved in THF (8 mL). The suspension was cooled to 0 °C and the required triazole (2 mmol) was added in one portion. The mixture was stirred for 2 h at room temperature. In the end of reaction the aqueous phase was washed with ethyl acetate, the organic phase obtained was dried with $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by column chromatography using as eluent a mixture of hexane/ethyl acetate (7/3). (**1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl**)**methyl-4-methylbenzenesulfonate** (**4c**)**:** The product was obtained as a white solid in 90% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 (*s*, 1H); 7.74 (*d*, *J* = 8.4 Hz, 1H), 7.65 (*d*, *J* = 1.9 Hz, 1H), 7.52 (*tt*, *J* = 2.0/7.30 Hz, 2H), 7.42–7.34 (*m*, 2H), 7.27 (*d*, *J* = 8.4 Hz, 2H), 5.22 (*s*, 2H), 2.36 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 145.2, 142.0, 141.2, 140.5, 137.5, 135.7, 135.5, 133.0, 131.5, 130.9, 130.8, 130.2, 129.9, 129.2, 128.9, 128.2, 128.0, 125.8, 124.3, 122.2, 121.7, 120.8, 118.5, 62.9, 21.6. IR (neat) *v*: 4433, 3509, 2988, 2349, 2088, 1759, 1460, 1241, 1055, 848, 624 cm^{-1}.
11. *General procedure*: **Synthesis of bis- and tris-1,2,3-triazoles**. In a 50 mL two-neck flask under a nitrogen atmosphere, the starting material (0.5 mmol) was added with sodium azide (1.1 equiv, 0.55 mmol) dissolved in DMF. The mixture was stirred until the starting material was consumed, followed by TLC. After the conversion of the starting material, acetylene (1.2 equiv, 0.6 mmol) and the copper catalyst (1.0 equiv, 0.5 mmol) were added under vigorous stirring. At the end of reaction, the aqueous phase was washed with ethyl acetate, the organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under vacuum. **1-Phenyl-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1*H*-1,2,3-triazole** (**5e**): The product was obtained as a white solid in 79% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm); 7.99 (*s*, 1H); 7.92 (*s*, 1H); 7.75 (*d*, *J* = 7.0 Hz, 2H); 7.63 (*d*, *J* = 7.1 Hz, 2H), 7.48–7.25 (*m*, 6H); 5.74 (*s*, 2H); ^{13}C NMR (75 MHz,, $CDCl_3$) δ (ppm): 148.4, 136.7, 130.4, 129.9, 129.2, 128.9, 128.3, 125.8, 121.4, 120.7, 119.9, 45.5. IR (neat) *v*: 4435, 3509, 2988, 2088, 1759, 1460, 1241, 1055, 926, 623 cm^{-1}. HRMS calcd for $C_{17}H_{14}N_6$ 302.1280. Found [M+Na] = 325.1172. **1-Phenyl-4-((4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-1,2,3-triazole** (**6b**): The product was obtained as a white solid in 50% yield**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (s, 1H), 8.00 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 7.9 Hz, 2H), 7.54–7.32 (m, 7H), 5.80 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.4, 142.6, 136.7, 130.4, 129.9, 129.2, 128.9, 128.3, 125.8, 121.4, 120.7, 119.9, 45.5. IR cm^{-1} (ethyl acetate solution): 3511, 2988, 2088, 1759, 1461, 1244, 1058, 849.
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