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# Efficient synthesis of deuterated 1,2,3-triazoles

Zsombor Gonda, Krisztián Lőrincz, Zoltán Novák *

*Institute of Chemistry, Eötvös Loránd University, Pázmány Péter stny. 1/a, Budapest, Hungary*

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ABSTRACT

A wide variety of 1-monosubstituted 1,2,3-triazoles were synthesized efficiently via a copper-catalyzed click-reaction between azides and acetylene gas, generated in situ from $CaC_2$ with the addition of $H_2O$ or $D_2O$.

Since the independent reports of Meldal[1] and Sharpless[2] on the copper-catalyzed azide-alkyne cycloaddition (CuAAC), several improvements and applications have proved the efficiency and importance of this synthetic transformation.[3] Besides utilization of the CuAAC click-reaction in organic synthesis[4] and materials science,[5] ligand-affected reaction rate acceleration is one of the most important research directives in this field of organic chemistry.[6] However, the CuAAC reaction provides an excellent tool for the selective synthesis of 1,4-disubstituted 1,2,3-triazoles, while procedures for the preparation of 1-monosubstituted triazole derivatives are under developed.[7] As a monoprotected acetylene surrogate, trimethylsilyl acetylene is applicable for the click-reaction, and subsequent deprotection of the formed triazoles at position 4 provided the desired 1-monosubstituted triazole.[8] There are two recent examples of the direct addition of acetylene gas to the azide moiety in the presence of 10–30 mol % copper catalysts.[9] Kuang and co-workers demonstrated, for the first time, the applicability of $CaC_2$ as an acetylene source, but only aromatic azides proved to be suitable substrates in the reported procedure.[9a]

As 1-monosubstituted triazoles possess important antibacterial and other biological activity[10] we aimed to develop a simple and efficient procedure for the synthesis of various 1-monosubstituted triazoles based on in situ generated acetylene from $H_2O$ and a carbide source. The utilization of $CaC_2$ offers the possibility for introduction of deuterium atoms instead of hydrogen when $D_2O$ is used for the generation of acetylene gas. Isotope-labeled molecules have important roles in mechanistic studies both from chemistry and biology.

As we found previously, bis-triphenylphosphano complexes of Cu(I) salts demonstrate prominent activity in the CuAAC reaction.[6h] Therefore, we first used $CuOAc(PPh_3)_2$ and $CuNO_3(PPh_3)_2$ complexes as catalysts for the synthesis of 1-monosubstituted triazoles. Among the catalysts tested the copper(I) nitrate complex showed higher activity and the reaction of benzyl azide and acetylene gas generated in situ from $CaC_2$ and water gave full conversion in eight hours at 25 °C (Table 1, entries 1 and 2). On replacing the water with $D_2O$, we found that the reaction took place with the same efficiency affording the expected triazole ring (entry 3). The mass spectra of the products showed high incorporation of deuterium atoms into the benzyl triazole. The ratio of the 4,5-dihydro **2a**, the monodeuterated isomers **3a**,**b** and the 4,5-dideutero compound **4a** was found to be approximately 2:13:85.[11] However, the aforementioned copper complexes gave full conversions to **2a**. Utilization of simple $CuSO_4{\cdot}5H_2O$ (40 mol %) also provided the benzyl triazole with almost the same efficiency in the presence of KOAc.

As was expected, the high water content of the copper salt caused a significant change in the isomeric ratio of the deuterated products (20:52:28). Although, anhydrous $CuSO_4$ in toluene resulted in only 39% conversion (entry 6), EtOH and DMSO were suitable solvents for the $CuSO_4$-catalyzed click-reaction (entries 7 and 8).

However, in these solvents the deuterium incorporation was lower due to the presence of the OH hydrogen in the alcohol, and supposedly the minor water content present in DMSO.

Organic bases usually accelerate the CuAAC reaction. Application of triethylamine as the solvent for the cycloaddition of acetylene and benzyl azide in the presence of anhydrous $CuSO_4$ gave full conversion and a high amount of the dideutero triazole product was obtained (entry 9). Additionally, CuI as the catalyst was also

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* Corresponding author. Tel.: +36 1 372 2500x1610; fax: +36 1 372 2909.
*E-mail address:* novakz@elte.hu (Z. Novák).

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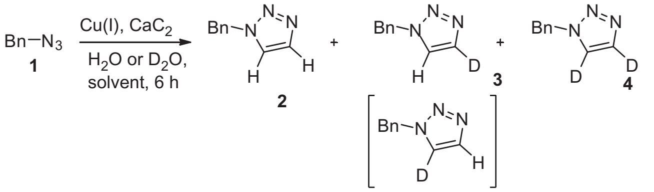
**Table 1**
Optimization of the copper-catalyzed click-reaction of acetylene and benzyl azide[a]



| Entry | Catalyst | Solvent | $H_2O/D_2O$ | Conv.[b] (%) | Ratio, **2**:**3**:**4**[c] |
|---|---|---|---|---|---|
| 1 | $CuOAc(PPh_3)_2$ | Toluene | $H_2O$ | 25 | 100:0:0 |
| 2 | $CuNO_3(PPh_3)_2$ | Toluene | $H_2O$ | 100 | 100:0:0 |
| 3 | $CuNO_3(PPh_3)_2$ | Toluene | $D_2O$ | 100 | 2:13:85 |
| 4 | $CuSO_4{\cdot}5H_2O$[d] | Toluene | $H_2O$ | 90 | 100:0:0 |
| 5 | $CuSO_4{\cdot}5H_2O$[d] | Toluene | $D_2O$ | 98 | 20:52:28 |
| 6 | $CuSO_4$[d] | Toluene | $D_2O$ | 39 | 1:6:93 |
| 7 | $CuSO_4$[d] | EtOH | $D_2O$ | 100 | 12:48:40 |
| 8 | $CuSO_4$[d] | DMSO | $D_2O$ | 100 | 3:28:69 |
| 9 | $CuSO_4$[d] | $Et_3N$ | $D_2O$ | 100 | 1:5:94 |
| 10 | CuI | EtOH | $D_2O$ | 100 | 12:48:40 |
| 11 | CuI | DMSO | $D_2O$ | 100 | 7:27:66 |
| 12 | CuI | Toluene | $D_2O$ | 16 | 1:5:94 |
| 13 | CuI | $Et_3N$ | $D_2O$ | 100 | 1:5:94 |
| 14 | CuI[e] | $CH_2Cl_2$ | $D_2O$ | 0 | n.a. |
| 15 | CuI[e] | Acetone | $D_2O$ | 20 | 21:49:30 |
| 16 | CuI[e] | $Et_3N$ | $D_2O$ | 73 | 2:11:87 |
| 17 | CuI[e,f] | $Et_3N$ | $D_2O$ | 100 | 1:5:94 |
| 18 | CuI[f,g] | $Et_3N$ | $D_2O$ | 100 | 0:17:83 |

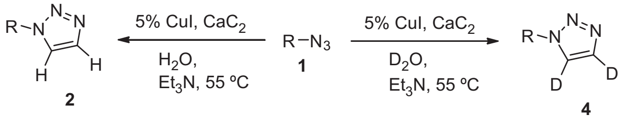
[a] Reaction conditions: 0.25 mmol $BnN_3$, 1 mmol $CaC_2$, 40 mol % Cu(I), 200 µl solvent, 200 µl $H_2O/D_2O$.
[b] Conversions were determined by GC–MS.
[c] Approximate ratio calculated on the basis of the MS spectra of the products.
[d] 0.5 mmol KOAc was added.
[e] 10 mol % CuI was used.
[f] Reaction was carried out at 55 °C.
[g] 5 mol % CuI was used.

tested in toluene, EtOH, DMSO and $Et_3N$ and provided similar results with $CuSO_4$ regarding the conversions and distributions of the triazole isomers (entries 10–13).

Solvents such as $CH_2Cl_2$ and acetone were not effective in the presence of 10 mol % CuI (entries 14 and 15). When a reduced amount of CuI (10 mol %) was used in $Et_3N$ the reaction took place with only 73% conversion (entry 16) but with this catalyst loading at 55 °C the deuterated triazole was formed with full conversion (entry 17). Decreasing the amount of copper to 5% was optimal for the transformation (entry 18).

To assess the scope of the conditions developed we aimed to synthesize several 1-monosubstituted triazoles. We also intended to prepare the fully deuterated analogs of the target molecules. Benzyl azide reacted smoothly both with acetylene gas and deuterated acetylene in the presence of 5 mol % CuI in triethylamine at 55 °C. The products (**2a** and **4a**) were isolated in good yields (Table 2, entries 1 and 11). Nitro, bromo and iodo substituents on the phenyl ring of the benzyl azide had no influence on the click-reaction and the corresponding triazoles were obtained in fair to good yields (entries 2–4 and 12–14). It is of note that deuterium incorporation also occurred at the benzylic position during the formation of 1-(4-nitrobenzyl)-1,2,3-triazole **(4b)** due to the enhanced benzylic C–H acidity of this substrate. Secondary azide **1e** was transformed into triazole **2e** in excellent yield both with $C_2H_2$ (entry 5, 92%) and $C_2D_2$ (entry 15, 86%). Reaction of azidomethyl-phenylsulfide with acetylene also afforded the desired products containing hydrogen or deuterium atoms in the triazole ring in 67% and 68% yields, respectively (entries 6 and 16). Various aliphatic azides bearing cyano **1g**, chloro **1h** or alkene **1i** functional groups also proved to be good substrates for the click-reaction under the developed conditions. The 1,2,3-triazole derivatives

**Table 2**
Synthesis of 1-monosubstituted 1,2,3-triazoles[a]



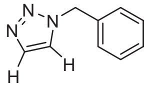
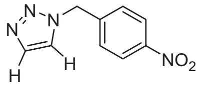
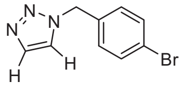
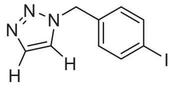
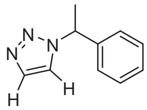
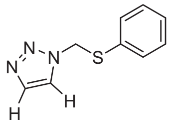
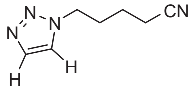
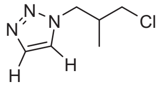
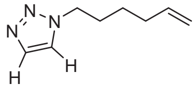
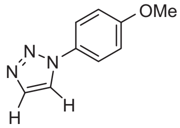
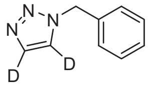
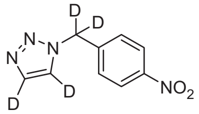
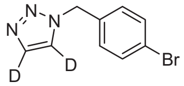
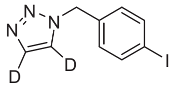
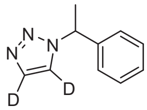
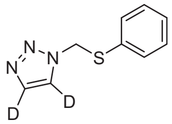
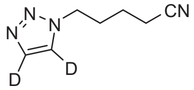
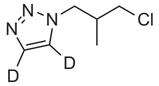
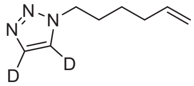
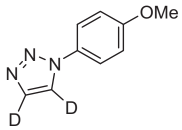
| Entry | Product | | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  | **2a** | 6 | 90 |
| 2 |  | **2b** | 6 | 57 |
| 3 |  | **2c** | 6 | 74 |
| 4 |  | **2d** | 6 | 79 |
| 5 |  | **2e** | 40 | 92 |
| 6 |  | **2f** | 6 | 67 |
| 7 |  | **2g** | 6 | 81 |
| 8 |  | **2h** | 6 | 59 |
| 9 |  | **2i** | 16 | 69 |
| 10 |  | **2j** | 16 | 64 |
| 11 |  | **4a** | 6 | 81 |
| 12 |  | **4b** | 6 | 84 |
| 13 |  | **4c** | 6 | 81 |
| 14 |  | **4d** | 6 | 86 |
| 15 |  | **4e** | 40 | 86 |

**Table 2** (*continued*)

| Entry | Product | | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 16 |  | **4f** | 6 | 68 |
| 17 |  | **4g** | 6 | 91 |
| 18 |  | **4h** | 16 | 66 |
| 19 |  | **4i** | 16 | 70 |
| 20 |  | **4j** | 16 | 42 |

[a] Reaction conditions: 0.44 mmol azide, 0.022 mmol (5 mol %) CuI, 0.22–0.23 g (techn. grade, ⩾2.6 mmol) calcium carbide, 170 μl $H_2O$ or $D_2O$, 335 μl $Et_3N$.

[b] Yield of isolated product.

containing hydrogens at positions 4 and 5 were isolated in 81%, 59% and 69% yields, respectively (entries 7–9). The alkylated 4,5-deuterated triazoles were obtained in similarly good yields (entries 17–19). As demonstrated earlier by Kuang and co-workers,[9a] the click-reaction of aryl azides and acetylene generated from carbide provided the appropriate monosubstituted triazoles. Under our reaction conditions, 4-azidoanisole was easily transformed into 1,2,3-triazole derivatives bearing hydrogen **2j** and deuterium atoms **4j** at positions 4 and 5 in moderate yields (entries 10 and 20).

Although, the click-reactions of different azides with deuterated acetylene all afforded the appropriate 4,5-dideutero triazoles, the total deuterium incorporation was in the range 90–94%. This phenomenon can be attributed to the kinetic isotope effect.

In conclusion, we have developed a synthetic procedure for the copper-catalyzed synthesis of 1-monosubstituted triazoles from structurally diverse organic azides utilizing cheap and easily accessible calcium carbide as an acetylene surrogate. The strategy enables the easy and simple introduction of deuterium atoms into the heterocyclic core of the product providing important isotope-labeled derivatives.

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## Supplementary data

Supplementary data (procedures, optimization studies and characterization of the materials) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.097.

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11. Approximate ratio based on the MS spectrum of the product.