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Regioselective synthesis of [1,2,3]-triazoles catalyzed by Cu(I) generated in situ from Cu(0) nanosize activated powder and amine hydrochloride salts

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Abstract—A straightforward and efficient method for the regioselective synthesis of functionalized 1,4-disubstituted [1,2,3]-triazoles, from terminal alkynes and azides, has been established utilizing Cu(0) as the source of the catalytic species. The presumed catalytic Cu(I) species is generated by the combination of 10 mol% copper nanosize activated powder and 1 equiv of an amine hydrochloride salt. The addition of an amine hydrochloride salt into the reaction mixture enhanced the dissolution of copper metal, and subsequently facilitated the formation of the Cu(I)-acetylide intermediate required for the regioselective cycloaddition.

[1,2,3]-Triazoles with general structures **3** and **4** are important five-membered nitrogen heterocycles, involved in a wide range of industrial applications such as agrochemicals, corrosion inhibitors, dyes, optical brighteners as well as biologically active agents.[1] The well established approach utilized thus far for the synthesis of the [1,2,3]-triazole ring system relies on the thermal 1,3-dipolar Huisgen cycloaddition between alkynes **1** and azides **2** (Scheme 1, a).[2] However, this non-catalyzed process exhibits several disadvantages, including: (i) the requirement for high temperature conditions with the potential for the decomposition of labile products, (ii) the synthesis of the desired [1,2,3]-triazoles generally in low yields, and (iii) poor regioselectivity, given that the non-catalyzed cycloaddition affords a mixture of 1,4- and 1,5-disubstituted triazoles, unless the alkyne is substituted with an electron withdrawing group.[3]

Over the years, several efforts to control the 1,4- versus 1,5-regioselectivity have been reported.[4] However, the regioselective and high yielding synthesis of 1,4-substituted triazoles with general structure **3** via a Cu(I) catalyzed [3+2] cycloaddition of terminal alkynes and azides has only recently been described (Scheme 1, b).[5]

It is postulated that the reaction proceeds via a copper-acetylide intermediate, generated from Cu(I) and the terminal alkyne, which then participates in an annealing process upon its coordination with the reacting azide.[5b] Although Cu(I) could be introduced directly in the form of different copper salts, the presence of a nitrogen containing base as well as prior exclusion of oxygen from the reaction are usually required in order to minimize the formation of undesired by-products, primarily diacetylenes.[5a] Alternatively, the catalytic Cu(I) species could be generated in situ from $CuSO_4$ and sodium ascorbate.[5b] The latter method eliminates the problem of by-product formation and has been used successfully in a H_2O/*t*-BuOH solvent system, without the need for prior exclusion of oxygen or the presence of a nitrogen base.

The observation by Sharpless and Fokin suggesting that even Cu(0) coiled metal turnings, albeit in stoichiometric quantity,[5b] can be used as a source of the catalytic species for the regioselective formation of [1,2,3]-triazoles sparked our interest for further investigation. Indeed, although longer reaction times are required when Cu(0) is used, we felt these findings had substantial implications and the potential for further development.

Keywords: Cu(I) generated in situ; Triazoles; Regioselective synthesis.
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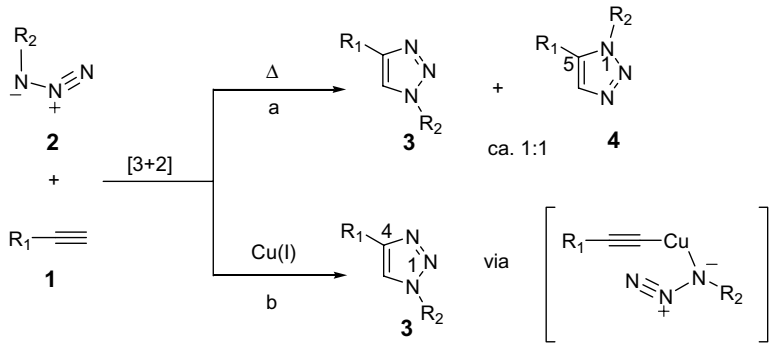
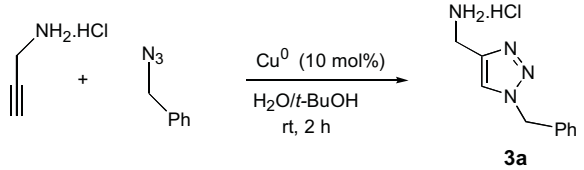


Scheme 1.

Compelled to conduct additional studies in search of means to enhance the catalytic process for the regioselective synthesis of this ring system, we surmised that the use of a catalytic amount of Cu(0) nanosize activated powder, with a larger surface area relative to the coiled metal turnings, could enhance the formation of copper-acetylide and subsequently facilitate the cycloaddition process. Our initial attempts using 10 mol% of activated copper powder, with different azides and terminal alkynes in a H_2O/*t*-BuOH solvent system for 2 h, provided only trace amounts of the desired product or recovered starting materials. However, when an equimolar mixture of propargyl amine hydrochloride and benzyl azide was subjected to the same reaction conditions, efficient dissolution of copper powder was observed along with the regioselective formation of the corresponding 1,4-disubstituted triazole **3a**[6a] (Scheme 2). Given that no reaction occurred when propargyl amine was utilized as the free base, we speculated that the presence of an amine ligand and a slightly acidic environment,[7] which would presumably be ensured with the addition of an amine hydrochloride salt, might be required to induce the dissolution of copper and subsequently, trigger the generation of the Cu(I) catalytic species.

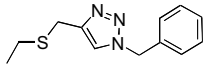
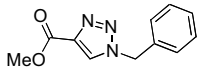
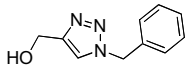
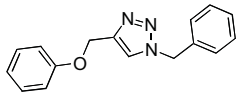
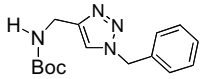
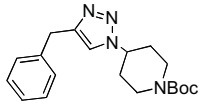
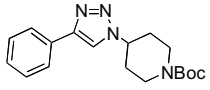
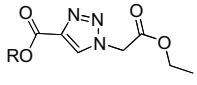
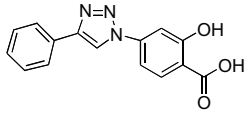
In order to test our hypothesis, the cycloaddition reaction between several azides and terminal alkynes, in the presence of 10 mol% Cu(0) powder and 1 equiv of NEt_3·HCl salt, was attempted. Indeed, as we had expected, the reaction proceeded smoothly at room temperature and led to the facile and regioselective formation of the desired 1,4-disubstituted [1,2,3]-triazoles (Table 1). The chemistry works well with aliphatic (entries 6–8), benzylic (entries 1–5) and aryl azides (entry 9), and tolerates a wide spectrum of electron donating and electron withdrawing functional groups in both the alkyne and azide starting material.



Scheme 2.

The reaction worked equally well, albeit required longer reaction times (12–24 h), even when less than 1 mol% copper was used as the catalyst.[9] However, trace amount of product was observed under the optimized reaction conditions and within the same reaction times when Et_3N was utilized as the free base. It is noteworthy to mention that the reaction worked well with a second-

Table 1.

Entry	Product[a]	% Yield[b]
1		91 (**3b**)
2		92 (**3c**)
3		92 (**3d**)
4		95 (**3e**)
5		94 (**3f**)
6		96 (**3g**)
7		93 (**3h**)
8a R = Et 8b R = Me 8c R = H		88 (**3i**) 91 (**3j**) 95 (**3k**)
9		83 (**3l**)

[a] All reactions were completed within 2 h and carried out in a H_2O/*t*-BuOH solution containing 10 mol% of activated Cu nanosize powder and 1 equiv of Et_3N·HCl salt.

[b] Isolated yields. All compounds produced satisfactory ^1H NMR, ^{13}C NMR, and mass spectra and matched those reported in literature.[8]

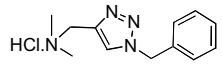
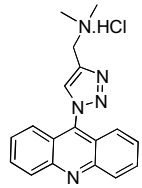
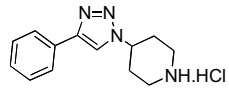
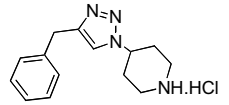
ary amine hydrochloride salt such as $Et_2NH{\cdot}HCl$, but failed with NH_4Cl.

Although the compounds reported in Table 1, except **3e**[5b] and **3f**,[14] have previously been successfully synthesized via a thermal Huisgen [3+2] cycloaddition reaction, the previous methods required laborious isolation and resulted in low yields (15–50%) from a regioisomeric mixture of the corresponding 1,4- and 1,5-triazoles.[8] In contrast, the efficient and regioselective synthesis of these compounds was achieved in a straightforward manner by application of our enhanced protocol.

Similarly, exploiting the chemistry shown in Scheme 2 led to the design and synthesis of several amino functionalized triazoles, starting from the corresponding hydrochloride salts of amino containing azides (entries 3 and 4) or amino containing alkynes (entries 1 and 2) (Table 2).[10] The cycloaddition reaction was found to work comparably, even without the addition of an external amine hydrochloride salt, regardless of whether the amine salt resided on the alkyne or the azide component. This class of compounds, not readily accessible by previous non-catalyzed methods, were synthesized in this manner without the need for prior use of protecting groups.[11]

The dissolution of copper in aqueous systems is a well known process[12a] and thus the generation of Cu(I) species might presumably proceed via a stepwise mechanism. First, oxidative dissolution of copper, facilitated by the presence of an amine hydrochloride salt,[12b] followed by its coordination with a nitrogen based ligand, could result in the production of a Cu(I)-amino complex and posterior formation of the copper acetylide complex.[12c] Subsequently, Cu(I) could be easily oxidized to Cu(II) and/or disproportionated[12d] to Cu(0) and Cu(II) due its thermodynamic instability. Formation of the more stable Cu(II) species eventually prevails, as it was evidenced by the appearance of a blue coloured solution when the reaction was completed.

Table 2.

Entry	Product[a]	% Yield[b]
1		93 (**3m**)
2		95 (**3n**)
3		90 (**3o**)
4		94 (**3p**)

[a] All reactions were completed within 2–5 h and carried out in a H_2O/*t*-BuOH solution containing 10 mol% of Cu nanosize activated powder.

[b] Isolated yields as free bases. All compounds produced satisfactory ^1H NMR, ^{13}C NMR, and mass spectra.

In summary, we have developed a mild and efficient protocol for the copper-catalyzed 1,3-dipolar cycloadditions of terminal alkynes and azides, *in which the presence of an amine hydrochloride salt enhances the dissolution of* Cu(0) *resulting in the facile generation of the catalytic* Cu(I) *species*. This set of conditions nicely complement[13] the work developed previously by Meldal and Sharpless, and provides facile access to functionalized triazoles not easily synthesized via the thermal Huisgen conditions. The operational simplicity of this method and the purity of the recovered products[14] makes it attractive not only for the large scale synthesis of this class of biologically active molecules, but for the synthesis of screening libraries for drug discovery as well.

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6. (a) Spectral data for compound **3a**: ^1H NMR (D_2O) δ 7.96 (s, 1H), 7.27–7.20 (m, 5H), 5.46 (s, 2H), 4.64 (s, 2H); ^{13}C NMR (D_2O) δ 134.7, 129.3, 129.0, 128.3, 125.6, 54.1, 34.2. MS (ES^+) for $C_{10}H_{12}N_4$ (M+H) 189.

7. The pH of the reaction mixture was slightly acidic (pH = 5) upon the addition of $Et_3N{\cdot}HCl$. After the reaction was completed, it turned slightly basic (pH = 8).
8. For compound **3b**, see: Biagi, G.; Livi, O.; Ramacciotti, G. L.; Scartoni, V.; Bazzichi, L.; Mazzoni, M. R.; Lucacchinni, A. *Il Farmaco* **1990**, *45*, 49–57; For compound **3c**, see: Blass, B. E.; Coburn, K. R.; Falukner, A. L.; Seibel, W. L.; Srivastava, A. *Tetrahedron Lett.* **2003**, *44*, 2153–2155; For compound **3d**, see: De las Heras, F. G.; Alonso, R.; Alonso, G. *J. Med. Chem.* **1979**, *22*, 496–501; For compound **3e**, see Ref. 6b. For compounds **3g** and **3h**, see: William, R.; Leeson, P. D.; Moore, K. W. *PCT Int. Appl.* **1996**, 24–27; For compound **3i**, see: Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J.; Sanchez, J. M. *Org. Prep. Proced. Int.* **1995**, *27*, 603–612; For compound **3l**, see: Da Settimo, A.; Livi, O.; Biagi, G.; Lucacchinii, A.; Caselli, S. *Fármaco Edizione Scientifica* **1983**, *38*, 725–737; The requisite 4-azido salicylic acid was prepared according to Gano, K. W.; Monbouquette, H. G.; Myles, D. C. *Tetrahedron Lett.* **2001**, *42*, 2249–2251.
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