

Zinc Mediated Azide–Alkyne Ligation to
1,5- and 1,4,5-Substituted 1,2,3-Triazoles

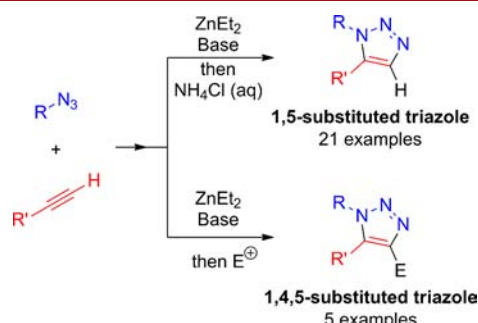
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ABSTRACT



A mild method for regioselective formation of 1,5-substituted 1,2,3-triazoles is described. The zinc-mediated reaction works at room temperature and is successful across a wide range of azido/alkynyl substrates. Additionally, the triazole 4-position can be further functionalized through the intermediate aryl-zinc to accommodate a diverse three-component coupling strategy.

The 1,2,3-triazole has risen to prominence in recent years as a superbly versatile heterocycle, with the 1,4-isomer being readily prepared from azide and alkyne components using copper-catalyzed azide alkyne cycloaddition (CuAAC).¹ This reaction reliably functions under mild conditions, displays superb substrate scope, and has driven a vast range of triazole application across the chemical, biological, and materials sciences.² Methods for accessing the alternate 1,5-isomer, by contrast, are far less developed. The synthesis of both triazole geometrical isomers has conventionally been achieved using the thermal Huisgen cycloaddition between azides and alkynes to afford a mixture of the 1,4- or 1,5-substituted 1,2,3-triazoles.³ However, the separation of

these products is frequently a tedious and sometimes insurmountable challenge.⁴ Existing methods for the exclusive construction of 1,5-triazoles require strongly basic conditions, utilizing alkali⁵ or magnesium⁶ acetylides, and have proven too demanding for many useful substrate classes. Alternatively, bulky ruthenium catalysts⁷ are capable of forming the desired 1,5-triazole (also 1,4,5-substituted triazoles). However, the cost of using a noble metal catalyst in this RuAAC procedure is an impediment to the development of a general, cost-effective application.⁸

With these concerns in mind, a milder and more economical route toward 1,5-substituted triazoles is sorely

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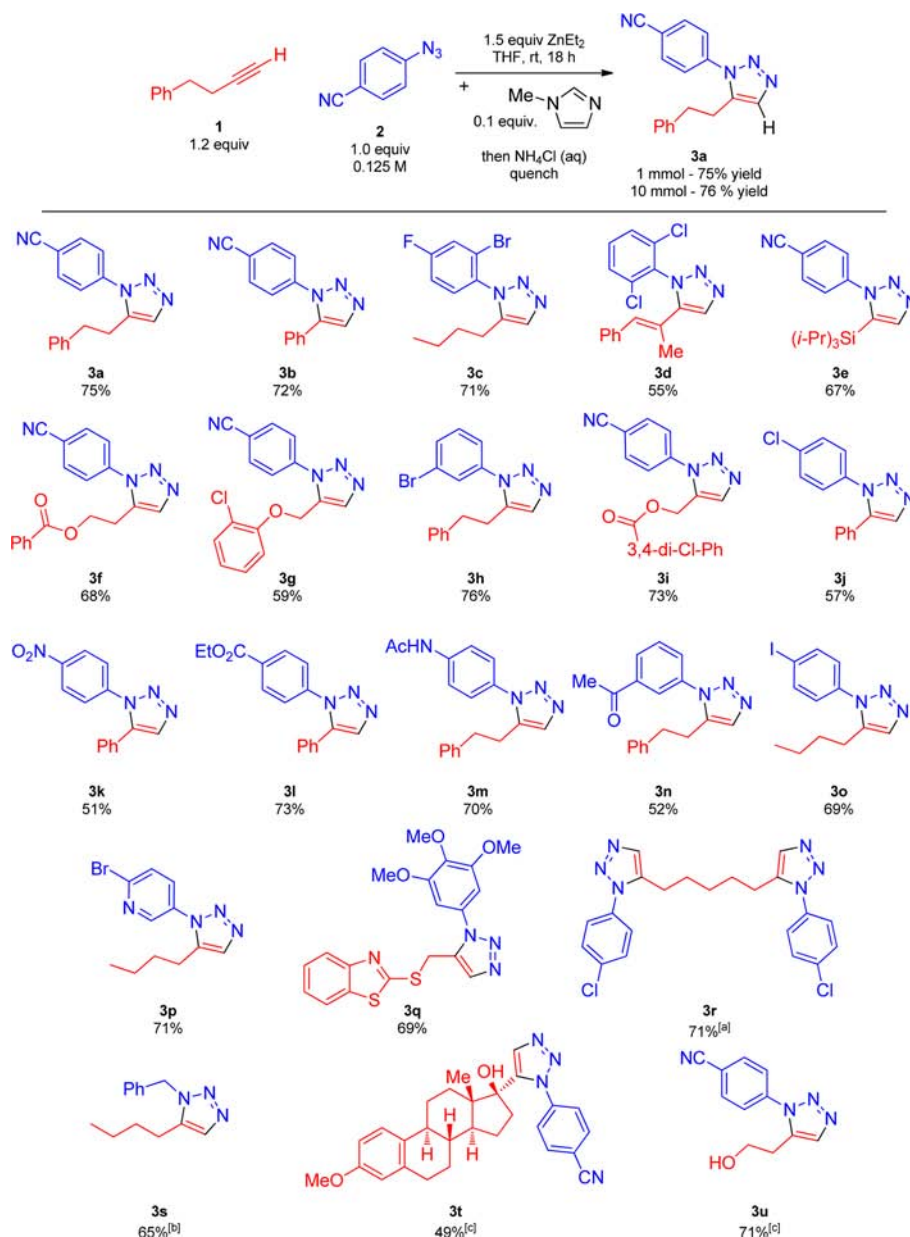
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Scheme 1. Optimized Reaction Conditions and Substrate Scope



^a Standard conditions but 2.4 equiv azide and 3.0 equiv ZnEt_2 . ^b As standard but 72 h. ^c As standard but 2.5 equiv ZnEt_2 and 72 h.

needed, as is a suitable method for the further functionalization of the 4-position. Such reactions could see significant application, as the alternative 1,5-linkage would afford molecules and materials with new and contrasting properties to 1,4-triazoles synthesized *via* CuAAC. In response to these demands we have investigated a zinc-mediated method for triazole synthesis, inspired by significant advances in the formation of zinc acetylides and their further reaction with

carbonyl functional groups.⁹ It was anticipated that the less nucleophilic zinc reagents (with respect to magnesium or lithium) would permit a much wider substrate scope and permit further functionalization.

We quickly discovered that simple addition of stoichiometric ZnEt_2 [1 M in hexanes] to a THF/toluene solution of alkyne **1** and azide **2** would exclusively form the desired

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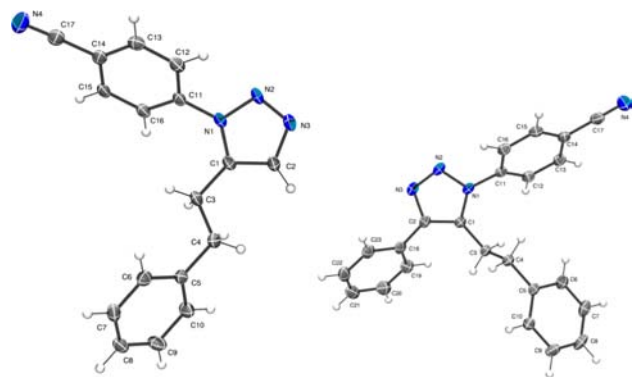


Figure 1. X-ray crystal structures of **3a** and **3x** proving the 1,5 and 1,4,5 configurations of the triazole products. Thermal ellipsoids at 50%.¹³

1,5-substituted triazole isomer (Scheme 1). Proof of the geometry was initially determined by comparison with the 1,4-isomer formed under CuAAC, followed by single crystal X-ray crystallography of **3a** (Figure 1) and an analog (**3x**) subsequently prepared (*vide infra*). However, repeating the reaction with resynthesized **2** gave no reaction at all, with only starting materials observed. We surmised that a catalytic base could be required to form the zinc acetylide and that residual aniline from the azide synthesis¹⁰ was promoting the reaction. Addition of 10% *N*-methylimidazole (NMI) promptly restored reactivity, and screening could continue.¹¹ A range of solvents were found to be suitable including CH₂Cl₂, 1,4-dioxane, MeCN, PhCF₃, *i*-PrOAc, and PhMe; although THF afforded a better purity profile and is readily available anhydrously. A concentration of 0.125 M was utilized to ensure all the zinc species remained in solution, and a slight excess of alkyne and ZnEt₂ were used to drive the reaction to completion. The reaction was typically complete after 18 h at ambient temperature or in 2 h at 100 °C in a microwave reactor. Yields were lower in the latter case due to the formation of an azide derived aniline byproduct (typically ~10%). The final optimized conditions are outlined in Scheme 1 and afforded the 1,5-product (**3**) in an isolated yield of 75% on a 1 mmol scale. The reaction was then directly scaled up to 10 mmol and afforded just over of 2 g of **3a** in a very similar 76% isolated yield.

The alkyne substrate range encompasses both alkyl and aryl terminal alkynes (Scheme 1) including enyne (**3d**) and silylated (**3e**) functionalities. Further success was found with propargylic ethers (**3g**), esters (**3i**), and thioethers (**3q**) although 1,2-diphenyl acetylene, tosyl azide, and (iodoethynyl)benzene failed to provide the desired product. Important substrate classes unsuitable for the magnesium system were able to withstand our zinc mediated conditions

Table 1. Further Functionalization of the Aryl Zinc Reagent (**4**)

entry	quench	product	yield
1	1 mL D ₂ O/ 1 mL D ₃ CCO ₂ D		71% ^[a]
2	2 equiv Br ₂		76% ^[a]
3	2 mol % Pd(PPh ₃) ₄ 2 equiv PhI		68% ^[b]
4	5 mol % Ni(acac) ₂ 		66% ^[b]
5	2 equiv MgCl ₂ 		52% ^[b]

^a Standard conditions with quench added directly. ^b Standard conditions with third component addition to reaction as a THF solution and stirred for 18 h at rt.

including esters (entries **3f**, **3i**, and **3l**), amides (**3m**), ketones (**3n**), nitriles, nitros (**3k**), aryl iodides (**3o**), heterocycles (**3p** and **3q**), and *ortho*-substituents (**3c** and **3d**). Dienes (**3r**) were also suitable starting materials, suggesting this method could find application in polymer or dendrimer synthesis.¹² These substrates are not productive in the RuAAC method due to the formation of unreactive ruthenacycles.⁷

Alkyl azides were not generally suitable as substrates, although benzyl azide could be reacted in good yield using extended reaction times (72 h) at ambient temperature (**3s**). Efforts to accelerate the reaction through heating resulted in poor yields and significant decomposition of starting materials. Further difficult examples included substrates with free alcohols. Nevertheless, a successful reaction could be achieved by the addition of extra ZnEt₂ and extended reaction times (72 h) at ambient temperature (**3t** and **3u**). Formation of triazole **3t** *via* the zinc method is of particular interest, representing the successful functionalization of the

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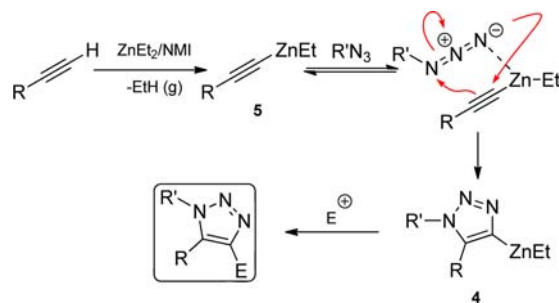
hindered propargyl alcohol mestranol (a commercial estrogen) in excellent yield. The reaction evidently has the capacity for late stage elaboration of sterically hindered, chiral molecules and biologically important scaffolds.

Further insight into the mechanism of the reaction was discovered when the mixture was quenched with D_2O/D_3CCO_2D rather than with NH_4Cl (aq).¹⁴ 1H NMR and LCMS determined an 89% deuterium incorporation at the triazole 4-position (**3v**, Table 1). Implying that a stoichiometric aryl-zinc intermediate (Scheme 2, **4**) was formed in the reaction in a way analogous to the previously described magnesium methods.⁶ This aryl-zinc reagent (**4**) was then used for further elaboration to afford a number of 1,4,5-trisubstituted 1,2,3-triazoles and to demonstrate this technology's potential for the synthesis of highly diverse libraries through three-component coupling. The initial exploration successfully incorporated bromine (**3w**) and thus offers a partner for palladium catalyzed cross-coupling at some later stage. Conversely, the aryl-zinc itself easily underwent palladium mediated cross-coupling with iodobenzene (**3x**) and thus offers a myriad of opportunities for biaryl synthesis. The ketone and alcohol products (**3y** and **3z**) present significant opportunities for further molecular diversity through a 'capping' step to incorporate four distinct components in only a few steps.

With our accrued observations we have proposed a reaction mechanism in Scheme 2 to help explain the observed reactivity of this system. It is reasonable to assume from previous reports that the transformation passes through the initial metalation of the alkyne-H, mediated by the amine base, to form the zinc acetylide **5**.^{9f,g,11} Reversible precoordination between the azide and zinc acetylide could be expected to occur before the [3 + 2]-cycloaddition can take place, explaining the necessity for stoichiometric quantities of $ZnEt_2$ in the reaction and the formation of the aryl-zinc intermediate **4**. Harnessing the further reactivity of this aryl-zinc species (**4**) has been demonstrated by the trapping experiments set out in Table 1.

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Scheme 2. Proposed Mechanistic Pathway



In conclusion we present a significant addition to the regioselective formation of 1,5-substituted 1,2,3-triazoles, a method that has proved successful across a wide range of azido/alkynyl substrates. Additionally, the 4-position can be further functionalized through the intermediate aryl-zinc to accommodate a diverse three-component coupling strategy. The inherently benign nature and efficient construction of these triazoles make this protocol ideal for both library synthesis and the late stage functionalization of complex molecules. Equally, the procedure is operationally straightforward, eminently scalable, and expected to be of interest across the chemical community.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.