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Copper(I)-Catalyzed Cycloaddition of Bismuth(III) Acetylides with Organic Azides: Synthesis of Stable Triazole Anion Equivalents

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Abstract

Readily accessible and shelf-stable 1-bismuth(III) acetylides react rapidly and regioselectively with organic azides in the presence of a copper(I) catalyst. The reaction tolerates many functional groups and gives excellent yields of the previously unreported, bench-stable 5-bismuth triazoles. This uniquely reactive intermediate can be further functionalized under extremely mild conditions to give fully substituted 1,2,3-triazoles.

Keywords

Click Chemistry; Copper(I)-catalysis; Organobismuth Chemistry

The copper(I)-catalyzed azide–alkyne cycloaddition^[1] (CuAAC; Scheme 1a) is now widely used as a reliable method for covalently connecting diverse building blocks.^[2] The experimental simplicity of the reaction and the robust nature of 1,2,3-triazole products have enabled numerous applications of this process in synthetic and medicinal chemistry,^[3] bioconjugations,^[4] material science,^[5] and polymer chemistry.^[6] The recent discovery that 1-iodoalkynes also readily react with organic azides, regioselectively producing 5-iodo-1,2,3-triazoles (Scheme 1b),^[7] further expanded the utility of this copper-catalyzed reaction.

Although 5-iodo-1,2,3-triazoles can be efficiently and directly prepared using this method, their subsequent functionalization is not always straightforward, often resulting in the formation of proto-dehalogenated products, although some exceptions can be noted.^[7–8]

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With this in mind, we envisioned the use of a pre-formed metalated acetylide that could both promote the cycloaddition reaction and form a stable 5-metalated triazole. Direct functionalization of the 5-position of the triazole could be accomplished from this metalated intermediate, bypassing inefficient transmetalation steps and eliminating the undesired proto-dehalogenation side reaction.

Reactions of bromoalkynes, as well as gold and aluminum acetylides as active cycloaddition partners in the CuAAC have been recently reported.^[9] However, the synthetic utility of these acetylides is limited by their own instability, low reactivity with organic azides, high cost, and instability of the resulting triazolides. Thus, we set out to utilize a stable acetylide that would surmount all of the above limitations; ideally it would be reactive with azides under copper catalysis and would produce stable, yet sufficiently reactive triazolidine products that additionally could be versatile precursors for the construction of fully substituted 1,2,3-triazoles.

Herein, we report that 1-bismuth(III) acetylides, a bench-stable, easily accessible and non-toxic class of σ -acetylides,^[10] undergo an efficient cycloaddition with organic azides in the presence of a copper catalyst forming 5-bismuth(III) triazolides (Scheme 2). The reaction exhibits a broad substrate scope, proceeds under mild conditions (at ambient temperature), and delivers stable bismuth(III) triazolides in reliably high yields. These unique and previously unreported metalated triazolides undergo several mild and chemoselective reactions in the absence of transition metals forming various 5-substituted triazoles inaccessible by other means.

Although organobismuth chemistry is well described in the chemical literature,^[11] only a handful of stable 1-bismuth(III) acetylides have been reported.^[12] The rarity of these bismuth compounds is likely due to their low hydrolytic stability, difficult preparation and, most importantly, a general lack of utility. Nevertheless, Akiba and co-workers demonstrated that oxygen or nitrogen ligands proximal to the metal center greatly increase the stability of bismuth(III) complex regardless of the electronic nature of the attached carbon ligand (sp^2 or sp^3).^[13] Building on this observation, Suzuki and co-workers reported an elegant use of diphenyl sulfone as a ligand for bismuth(III), which allowed preparation of a hydrolytically stable bismuth(III) acetylide.^[12d]

To explore reactivity of various bismuth(III) acetylides, a common precursor, 10-iodophenothiabismine 5,5-dioxide (Scheme 3), was synthesized in large batches (>20 g) from commercially available starting materials in two steps and an overall 68% yield. Following a slightly modified procedure of Suzuki and co-workers, the diphenyl sulfone bismuth(III) acetylide **1** was easily prepared by reaction with lithiated 4-ethynyl toluene (generated *in situ*). As already mentioned, acetylide **1** is a bench-stable, free-flowing powder that shows no degradation after several months (>8) of storage open to air and moisture.

Examining the scope of the synthesis of bismuth(III) acetylides (Scheme 3) revealed that methyl ester **2**, olefin **5**, alkyl chloride **6**, N,N-disubstituted aniline **7**, and trimethylsilyl acetylene **9** were all compatible with the reaction conditions. In all cases, the triazolidine products were free-flowing white powders, stable to hydrolysis and oxidation, and were

formed in good to excellent yield (**1–9**, 58–99%). Also of note, they were isolated simply by aqueous workup, trituration, and filtration.

With the diverse array of bismuth acetylides at our disposal, we examined their copper-catalyzed cycloaddition with organic azides. An initial survey of experimental conditions, which included a broad range of copper(I)/(II) salts, solvents and ligands, showed that the reaction of acetylide **1** and azide **10** formed mixtures of both the 5-*H* and 5-bismuth triazolides. Notably, formation of the 5-*H* triazole was completely suppressed only when the electronically-deficient copper(I) catalyst, copper(I) triflate (CuOTf), in the absence of other ligands was used (Scheme 4). Under these optimized conditions, the cycloaddition of **1** and **10** proceeded at ambient temperature in a THF solution with 5 mol% CuOTf, yielding 5-bismuth(III) triazolidine **11** as the sole product (Scheme 4).

This catalytic system was applied to a series of structurally and functionally diverse azides and 1-bismuth(III) acetylides (Scheme 6). In all cases, the 5-bismuth(III)-1,2,3-triazoles were obtained as exclusive products in good to excellent yield at ambient temperature (**12–27**, 60 – 91%). Many functional groups were compatible with the synthesis of these triazolides, including esters **18** and **20**, acetals **13** and **22**, nitrile **14**, carbamate **15**, amide **18**, free alcohol **19**, tertiary amine **25** and substituted silane **27**. Furthermore, these products were typically isolated by aqueous workup, trituration with a non-polar solvent, and filtration. This process was easily performed on larger scales; triazolidine **11** was prepared on a 10 mmol scale, delivering over six grams of the product in 90% yield (Scheme 4).

To better understand the bonding in this congested heterocyclic system, we obtained the single-crystal X-ray structure of triazolidine **11** (Scheme 5a). Of note in this complex is the long bismuth–triazole bond (C-5, 2.258 Å) and the relatively short intramolecular bismuth–oxygen bond (S–O, 2.999 Å). This complex, likely due to the tethered diphenyl sulfone ligand, exists in a constrained trigonal pyramidal geometry. We hypothesize that the strong bismuth–oxygen interaction stabilizes the complex yet renders it more nucleophilic than traditional triaryl bismuth complexes.^[14] With this in mind, we reasoned that reaction of this complex with different electrophiles would chemo- and regioselectively decorate the triazole via the formation of a bismuthonium complex,^[14] followed by ligand coupling (or self-decomposition),^[15] leading to the selective formation of the fully substituted 1,2,3-triazole (Scheme 5b).

Initial exploration of this reactivity manifold performed on triazolidine **11** verified our hypothesis, giving various fully substituted 1,2,3-triazoles (**28–33**, Scheme 7). We found that carbonyl electrophiles such as acyl chlorides, diphosgene, and oxalyl chloride worked efficiently, giving triazoles **28**, **29a**, **b** and **30** respectively, at room temperature and without the need of transition metal catalysts.^[16] In the case of diphosgene and oxalyl chloride, an additional oxygen or nitrogen-based nucleophile was reacted with the resulting intermediate, forming ester and amide-based products (**29a**, **29b**, and **30**). These reactions were found to achieve the highest efficiency in the presence of an amine base (TEA, DIPEA, DMAP, etc.). We speculate that these additives act both as ligands for the bismuth center and, in some cases (i.e. DMAP), can further activate the electrophile. When used in the correct proportions, these amines tempered the reactivity and delivered consistent yields of the fully

substituted triazoles. Interestingly, when higher concentrations of the amines were employed, the addition of the electrophile could be fully suppressed, giving credence to the amine's role as a ligand for the bismuth center.

A noteworthy dichotomy arose when triazolide **11** was reacted with various chlorinated sulfur-based electrophiles. For example, treatment with thionyl chloride followed by quenching with diethylamine gave sulfinic amide **31a** in 81% yield at room temperature. This method was expanded to form the sulfinic ester **31b** in 94% yield. However, when triazolide **11** was reacted with sulfuryl chloride, 5-chlorotriazole **32a** was formed in 88% yield. Reaction with bromine (Br₂) gave similar results, yielding 5-bromotriazole **32b** in 93% yield. The formation of **32a** and **32b** likely involves a redox process, wherein an unstable bismuth(V)-intermediate is formed, followed by facile reductive elimination at ambient temperature to give the 5-halotriazole.

Most interestingly, triazolide **11** reacted with nitrosonium tetrafluoroborate at room temperature, quantitatively producing the nitroso triazole **33** as a stable green solid. As an example of the versatile reactivity of this derivative,^[17] it was readily reduced to the corresponding amino triazole **34**, also in quantitative yield (Scheme 8). Further synthetic uses of these nitroso heterocycles (e.g. **33**) are easily envisioned and will be reported in due course.

The outline of the mechanistic proposal of this transformation is shown in Scheme 9. Supported by previous mechanistic investigations of reactions of 1-iodoalkynes^[7] and preformed copper(I)-acetylides,^[18] we hypothesize that the active cycloaddition complex **35** is formed through a weak and reversible π -interaction of copper(I) catalyst with bismuth(III) acetylide. Coordination of the azide reveals the vinylidene-like reactivity of complex **36**, which effects the formation of first covalent bond between the electrophilic terminal nitrogen of the azide and now nucleophilic β -carbon of the acetylide, producing intermediate **37**. The coordination environment of the copper center determines the fate of this heterodinuclear complex: electron-rich ligands favor elimination of bismuth (forming the 5-*H*-triazoles upon the hydrolysis of the copper triazolide), whereas the electron-deficient copper(I) triflate gives only bismuth(III) triazolides. The reactivity of bismuth and other main group elements in this transformation is currently being examined both experimentally and computationally and should shed light on the nature of the fleeting metal-metal interactions in these short-lived but critically important complexes.

The copper(I)-catalyzed synthesis of bismuth(III) triazolides from 1-bismuth(III) acetylides and organic azides described here is a rapid, selective and high-yielding method for the preparation of uniquely stable heterocyclic scaffolds. Additionally, the reaction of bismuth(III) triazolides with various electrophiles allows for the efficient production of fully substituted 1,2,3-triazoles inaccessible by other means. Further mechanistic investigations of this reaction and development of its synthetic applications are currently underway in our laboratory. Moreover, activation of stable bismuth(III) acetylides under copper(I)-catalysts and their subsequent reaction with appropriate electrophilic partners is being explored as a general synthetic tool.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Various copper(I)-catalyzed routes to substituted 1,2,3-triazoles.

Scheme 2.

Copper(I)-catalyzed synthesis of 5-Bismuth(III)-triazolides.

Scheme 3.

Synthesis of bismuth(III) acetylides by reaction with lithium acetylides. General reaction conditions: alkyne (2.18 mmol), bismuth(III) iodide (1.00 g, 1.81 mmol), *n*-BuLi (2.18 mmol), THF (25 mL), -78 to 0°C , 2 h. Values in parentheses represent yields of isolated products. ^aThe reaction was performed on 15 mmol scale. BiAr₂ = phenothiabismine 5,5-dioxide.

Scheme 4.
Optimized synthesis of bismuth triazolide **11**.

Scheme 5.

a) Crystal structure of **11**, highlighting the short (2.999 Å) bismuth-oxygen intramolecular bond. b) Formation and decomposition of a bismuthonium complex (in brackets) to yield 5-substituted triazoles.

Scheme 6.

Substrate scope for the formation of bismuth(III) triazolides via 1-bismuth(III) acetylides and organic azides. General reaction conditions: 1-bismuth(III) acetylide (1 mmol), azide (1 mmol), CuOTf (5 mol%), THF (3 mL), rt, 3 h. Values in parentheses represent yields of isolated products. ^a10 mol% CuOTf was used. ^bFor solubility purposes the reaction was performed in DMF (3 mL). Ar = *p*-tol. BiAr₂ = phenothiabismine 5,5-dioxide. Bn = benzyl. TMS = trimethylsilyl.

Scheme 7.

Conversion of triazole **11** to various 5-substituted-1,2,3-triazoles at room temperature. See supporting information for experimental details.

Scheme 8.

Reduction of the nitroso **33** to amino triazole **34**. See supporting information for experimental details.

Scheme 9.

Proposed catalytic cycle for the copper(I)-catalyzed cycloaddition of bismuth(III) acetylides and organic azides.