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Silver-Catalyzed Tandem Hydroazidation/Alkyne–Azide Cycloaddition of Diynes with TMS-N_3: An Easy Access to 1,5-Fused 1,2,3-Triazole Frameworks

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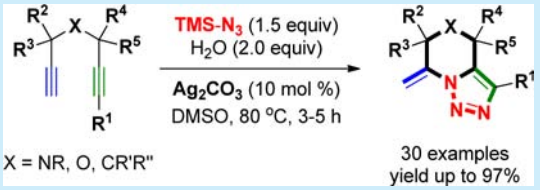
Supporting Information

ABSTRACT: A general cascade hydroazidation and alkyne–azide 1,3-dipolar cycloaddition of diynes using silver catalysis is reported. A wide variety of diynes participated in the reaction with trimethylsilyl azide (TMS-N_3) in the presence of H_2O, affording the corresponding 1,5-fused-1,2,3-triazoles in good-to-excellent yields. This unprecedented protocol is operationally simple with a broad substrate scope, good functional group tolerance, and high reaction efficiency, thus providing easy access to various fused 1,2,3-triazoles.



Among the triazole family, the members of 1,2,3-triazoles have emerged as a very popular and important class of organic compounds.[1] The era of 1,2,3-triazoles started with O. Dimroth, who observed the formation of 1,2,3-triazoles when azides are added to acetylenes.[2] Yet, despite the subsequent synthesis of 1,2,3-triazoles in 1931 by Alder and Stein from the reaction of bicycle[2,2,1]-hept-2-enes with phenylazide,[3] followed by Huisgen in 1960s with a thermal 1,3-dipolar cycloaddition reaction between alkynes and azides,[4] only after the Sharpless[5a] and Meldal[5b] groups' discovery of copper-catalyzed regioselective synthesis of 1,2,3-triazoles did these compounds come to the limelight, leading scientists to report effective methods for the synthesis of 1,2,3-triazoles by different approaches.[6] Several members of these molecular entities have indeed shown a wide spectrum of applications including medicinal chemistry. In medicinal chemistry much attention has been focused toward the synthesis and investigation of the biological activity.[7] The 1,2,3-triazoles have been explored to act as effective surrogates for backbone peptide bonds,[8] to induce turn formation of peptoid oligomers,[9] and promote the formation and stabilization of helix-like secondary structures of peptides.[10] Likewise, 1,2,3-triazoles fused with other heterocyclic moieties have also gained equal importance due to their diverse array of pharmaceutical functionalities such as antitumor, antiproliferative, antivirus, and glycosidase inhibitory activities.[11] 1,2,3-Triazoles particularly condensed with heterocycles at the 1,5-positions exhibited significant biological activities;[11c−g] for example, 1,2,3-triazolo[1,5-*a*]quinoxaline has shown good affinity toward benzodiazepine and adenosine receptors,[11e,f] and the morpholine-fused triazole is potent as a γ-secretase modulator (GSM) for the treatment of Alzheimer's disease[11g] (Figure 1). Consequently, convenient access to these heterocyclic frameworks is highly appealing.

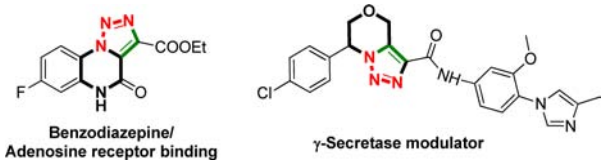


Figure 1. Examples of some biologically active 1,5-fused-1,2,3-triazoles.

In recent years, several synthetic approaches from different starting materials toward 1,2,3-triazoles fused at the 1,5-positions with a heterocyclic moiety such as piperizine,[12] morpholine,[13] or piperidine[14] have been developed (Scheme 1). Among them, the most used method relies on the intramolecular thermal 1,3-cycloaddition of a preconstructed C/N/O atom-tethered alkyne and azide conjugates. However, significant disadvantages exist in these methods, such as the requirement for elaborately designed and tedious multistep synthesized starting materials and the lack of substitution diversity. Furthermore, a general synthetic method for piperizine-, morpholine-, and piperidine-fused 1,2,3-triazoles has not been established so far. As part of our efforts toward developing novel organic reactions based on alkynes,[15] and especially from our recently reported chemo- and regioselective hydroazidation of alkynes with TMS-N_3 that led to vinyl azides,[15c,e] we herein wish to report a tandem cyclization of diynes with TMS-N_3 by means of silver catalysis, thus providing a powerful and general method for pharmaceutically relevant 1,5-fused 1,2,3-triazoles.

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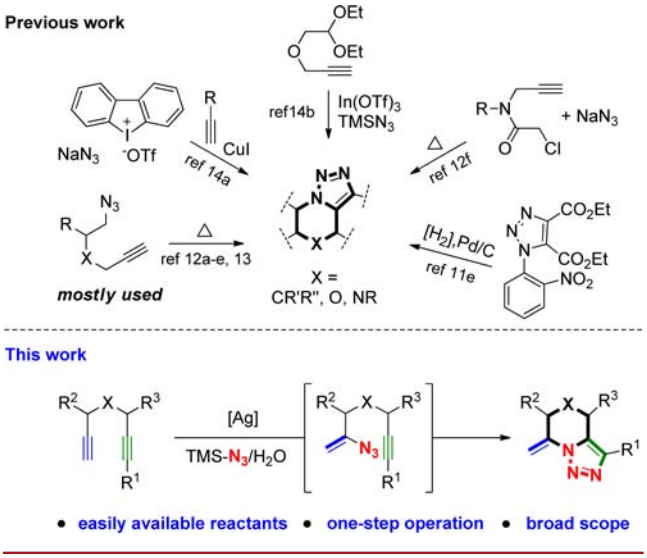
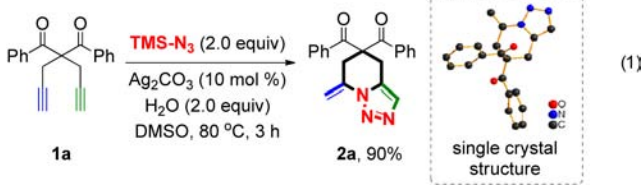
Scheme 1. Synthetic Routes to 1,5-Fused 1,2,3-Triazoles



Diynes and TMS-N_3 are two classes of easily available and versatile starting materials.[16] Instead of the monoalkynes in the hydroazidation, we performed the reaction of diyne (**1a**) with TMS-N_3 in the presence of 2 equiv of H_2O under silver-catalyzed conditions (eq 1). Unexpectedly, a 1,5-fused 1,2,3-



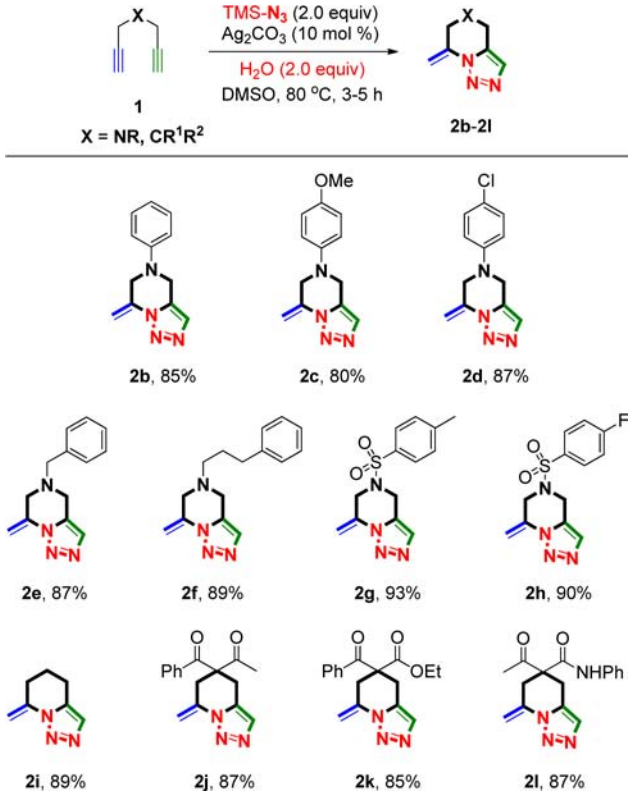
(1)

triazole **2a** was obtained in 90% yield. The bicyclic structure was unequivocally resolved by X-ray crystallographic analysis. To the best of our knowledge, this is the first example of cascade reactions of diynes with TMS-N_3 leading to fused heterocyclic frameworks.

With this fruitful result in hand, we first investigated the substrate scope of this silver-catalyzed tandem cyclization between various terminal 1,6-diynes and TMS-N_3 (Scheme 2). A wide range of 1,6-diynes (**1b**–**l**) reacted with TMS-N_3 under the standard reaction conditions thereby affording the corresponding fused 1,2,3-triazoles (**2b**–**l**) in good-to-high yields. All the reactions proceeded smoothly and were completed within 3–5 h. When X was NR, i.e. *N*-protected *N*,*N*-dipropargyl amines, we could obtain piperazine fused 1,2,3-triazoles (**2b**–**h**) in 80–93% yields. Various substituents, such as electron-donating (alkyl and aryl) and -withdrawing groups (*p*-toluenesulfonyl and *p*-fluorobenzenesulfonyl) on the nitrogen atom of propargyl amines, were well tolerated. In the case of X = CR^1R^2, i.e. terminal 1,6-diynes, the products, piperidine fused 1,2,3-triazoles (**2a**, **2i**–**l**), were obtained in 85–90% yield. Notably, the most simple 1,6-heptadiyne **1i** could smoothly react with TMS-N_3 to afford bicyclic product **2i** in 90% yield. This compound provides an ideal scaffold for further synthetic derivatization.

Encouraged by these results, we next turned our attention to unsymmetrical diynes. Terminally monosubstituted diynes (**3a**–**q**) were prepared and applied to the reaction with TMS-N_3 under standard reaction conditions. As shown in

Scheme 2. Scope of symmetrical diynes



Scheme 3, a range of 1,5-fused 1,2,3-triazoles (**4a**–**p**) were formed in good-to-excellent yields. The terminally monosubstituted 1,6-diynes (**3a**–**j**), bearing a variety of functional groups such as alkyl, alkenyl, aryl, heteroaryl at the R^1 position, were well participated in the silver-catalyzed tandem hydroazidation and 1,3-dipolar-cycloaddition reactions with TMS-N_3 to give the target 1,5-fused 1,2,3-triazoles (**4a**–**j**) in 75–97% yields. The substrate scope could be remarkably expanded to bis-propargyl ethers with varied substituents at C-3 and C-5 positions, which led to highly substituted morpholine fused 1,2,3-triazoles (**4k**–**p**) in 75–87% yields. To our delight, the presence of substituents at the C-3 or C-5 position had no major influence on the reaction outcome. Notably, the reaction of substrates (**3i**, **3k**–**m**) containing a sterically bulky quaternary carbon center with TMS-N_3 also smoothly afforded the corresponding fused triazole products (**4i**, **4k**–**n**) in good yields.

Triazolobenzodiazepines have shown high affinity toward benzodiazepine receptors, and they are also emerging as powerful pharmacophores in their own right.[17] Therefore, we checked the possibility of utilizing this method to synthesize 1,2,3-triazoles fused to a cyclic system with a larger ring size. In this context when the easily accessible unsymmetrical 1,7-diyne **5** was allowed to react with TMS-N_3 under the silver-catalyzed conditions, the corresponding 1,4-diazepine fused 1,2,3-triazole **6** was obtained in 78% yield (eq 2), which constitutes an extremely simple way to access this kind of fused heterocyclic framework.[18]

In addition to bicyclic 1,5-fused 1,2,3-triazoles, this silver-catalyzed protocol was also checked in the construction of tricyclic skeletons. Toward this end, the easily available *o*-diethynylbenzene (**7**) were selected and applied to the tandem reaction with TMS-N_3 under standard conditions (Scheme 4).

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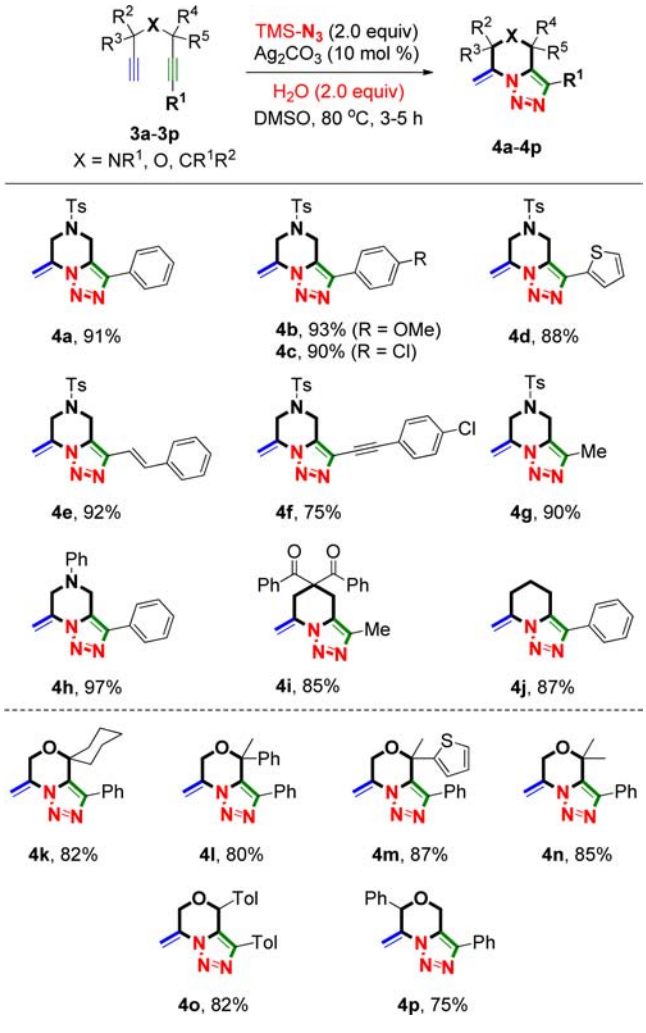
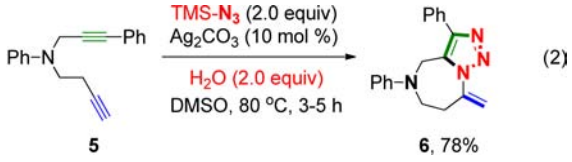
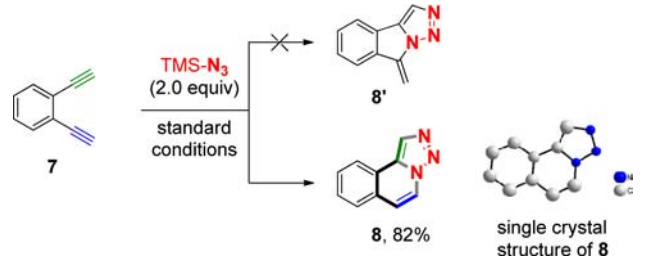
Scheme 3. Scope of Unsymmetrical Diynes





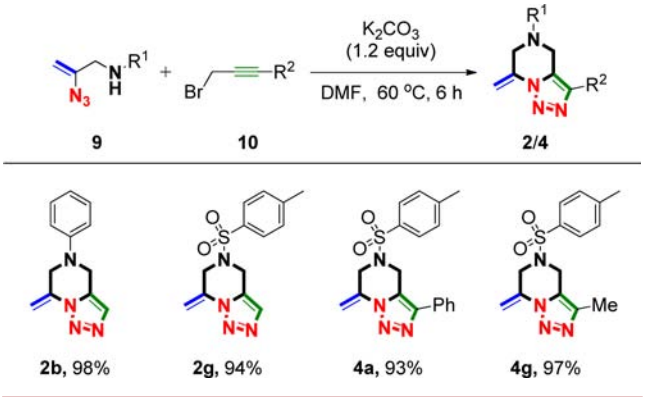
Scheme 4. Reaction of *o*-Diethynylbenzenes with TMS-N_3



However, instead of the desired isoindole-fused 1,2,3-triazoles **8′**, the unexpected triazolo isoquinoline **8** was isolated in 82% yield.[19] The structure of **8** was unambiguously confirmed by X-ray diffraction analysis. The regioselectivity of the hydroazidation observed at the 1-position of terminal alkynes of substrate **7**, not at the 2-position, may be due to the steric hindrance effect.

Mechanistically, the formation of 1,5-fused-1,2,3-triazoles (**2**, **4**, **6**, and **8**) was assumed to involve the sequential hydroazidation/alkyne−azide cycloaddition of diynes with TMS-N_3. To confirm this hypothesis and also to identify in which step the silver catalyst played the key role, the reactions between vinyl azides (**9**) and propargyl bromides (**10**) were designed and carried out under basic conditions, in the absence of Ag_2CO_3 (Scheme 5). Delightfully, the desired products **2**

Scheme 5. An Alternative Route to Piperizine-Fused Triazoles



and **4** could be produced in excellent yields. This result confirmed our mechanistic hypothesis and moreover implied the silver salt mainly played a role in the hydroazidation step. In addition, the reaction developed in Scheme 5 provided a new route to 1,5-piperizine-fused 1,2,3-triazoles.

In conclusion, we have developed the first tandem hydroazidation/alkyne−azide 1,3-dipolar cycloaddition of diynes with TMS-N_3 by means of silver catalysis, which constitutes a general method for the convenient synthesis of diverse pharmaceutically relevant 1,5-fused 1,2,3-triazole frameworks, including the fused heterocyclic units of piperidine, piperazine, morpholine, diazepine, and isoquinoline. This protocol features easily available starting materials, mild conditions, good functional tolerance, high reaction efficiency, and excellent product yields, thus paving the way in medicinal chemistry to explore their pharmaceutical potency in the near future.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra copies. This material isavailable free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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