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Synthetic Methods

Lewis Acid Mediated Tandem Reaction of Propargylic Alcohols to Tetrazoles Involving C–O- and C–C-Bond Cleavage Reactions and a C–N-Bond Formation

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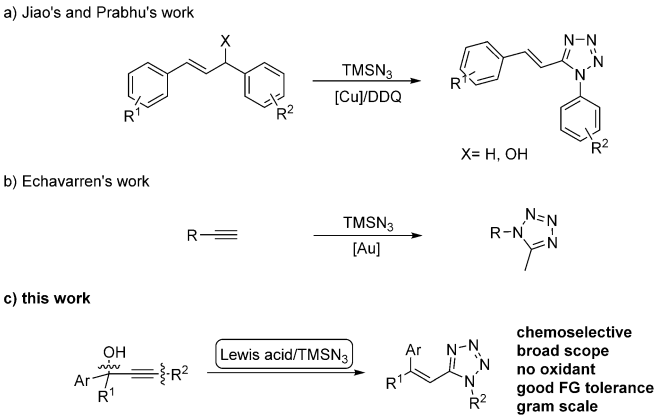
Abstract: A novel and direct synthesis of 1-aryl-5-arylvinyl-tetrazoles from easily prepared propargylic alcohols and $TMSN_3$ is developed in the presence of TMSCl under mild conditions (TMS = trimethylsilyl). The process involves an allenylazide intermediate, followed by a C–C-bond cleavage and C–N-bond formation to afford the desired products. Moreover, this method offers a good functional-group applicability and can be scaled-up to grams (yield up to 85%).

1,5-Disubstituted tetrazoles represent a key molecular motif with widespread occurrence in medicinal chemistry and agrochemicals, as well as in important synthetic intermediates.[1] With the wide application of 1,5-disubstituted tetrazoles in pharmaceutical research, the exploration of efficient synthetic strategies towards these compounds has attracted much attention among synthetic chemists. In this respect, numerous efforts have been made to prepare 1,5-disubstituted tetrazoles.[2–9] Among various methods that introduce a nitrogen source, using azide-containing compounds, which show a high chemical reactivity towards functionalizing the starting materials by different types of reaction modes, has been proven to be efficient. For example, compounds such as ketones,[2] amides,[3] oximes,[4] imidoyl,[5] imidoylbenzotriazoles,[6] and nitriles[7] could generate 1,5-disubstituted tetrazoles with azide-containing compounds. Moreover, the Jiao and Prabhu groups recently reported the Cu-catalyzed direct transformation of simple hydrocarbon or allylic alcohols in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant to form 1,5-disubstituted tetrazoles, respectively (Scheme 1a).[8] In 2013, Echavarren and co-workers developed a gold-catalyzed reaction of alkynes with $TMSN_3$ for the synthesis of 1,5-disubstituted tetrazoles by C–C-bond cleavage (Scheme 1b).[9] Although a great number of pioneering methodologies have been established, new practical and efficient approaches to 1,5-disubstituted tetrazoles from readily available starting materials are still extremely attractive and desirable.



Scheme 1. New strategies for the synthesis of 1,5-disubstituted tetrazoles.

Propargylic alcohols have served as versatile synthons for the construction of various synthetic intermediates, allenes in particular.[10] Our continuous interest in the potential reactivity of propargylic alcohols stimulated us to employ them as precursor of allenyl cations. Recently, our group[11] and others reported[12] that the dehydration of propargylic alcohols by Lewis acids generates allenyl-cation intermediates, which could further undergo divergent reactions with various nucleophiles. Thus, we envisioned whether $TMSN_3$ could be used as a nucleophile in the reaction with propargylic alcohols to produce the 1,5-disubstituted tetrazole nucleus through C–O- and C–C-bond cleavage reactions and C–N-bond formation. To the best of our knowledge, the direct transformation of propargylic alcohols to form 1,5-disubstituted tetrazoles has not been disclosed yet. Herein, we report the TMSCl-mediated reaction of propargylic alcohols with $TMSN_3$ as the nitrogen source to produce 1-aryl-5-arylvinyl-tetrazoles with high chemoselectivity, which tolerates a variety of propargylic alcohol substrates under mild conditions.

Initially, 0.1 mmol of propargylic alcohol **1a** with $TMSN_3$ (3.0 equiv) and TMSCl (1.0 equiv) was used in the presence of molecular sieves (13X) in 1,2-dichloroethane (DCE) at 80 °C; to our delight, the desired product 5-(2,2-diphenylvinyl)-1-(4-methoxyphenyl)-1*H*-tetrazole (**2a**) was obtained in 40% yield after

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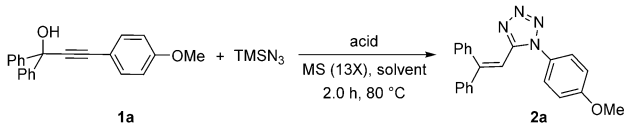
Table 1. Optimization of the reaction conditions.[a]



1a 2a

Entry	Acid ([equiv])	$TMSN_3$ [equiv]	Solvent	Yield [%][b]
1	TMSCl (1.0)	3.0	DCE	40
2	TfOH (1.0)	3.0	DCE	< 5
3	*p*-TsOH (1.0)	3.0	DCE	< 5
4	MsOH (1.0)	3.0	DCE	< 5
5	TMSCl (1.0)	4.0	DCE	75
6	TMSCl (1.0)	5.0	DCE	85
7	TMSCl (1.0)	5.0	CH_3NO_2	90
8	TMSCl (1.0)	5.0	1,4-dioxane	20
9	TMSCl (1.0)	5.0	MeCN	70
10[c]	TMSCl (1.0)	5.0	CH_3NO_2	trace
11[d]	TMSCl (1.0)	5.0	CH_3NO_2	20
12[e]	TMSCl (1.0)	5.0	CH_3NO_2	25
13	TMSCl (0.5)	5.0	CH_3NO_2	50
14	TMSCl (1.2)	5.0	CH_3NO_2	88

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), $TMSN_3$ (0.4 mmol), and molecular sieves (13X; 30 mg) in solvent (1.0 mL) at 80 °C. [b] Isolated yield. [c] The reaction was carried out in the absence of molecular sieves (13X). [d] Reaction performed at room temperature. [e] 4 Å molecular sieves was used instead of 13X molecular sieves. TMS = trimethylsilyl, MsOH = mesylic acid, TfOH = trifluoromethanesulfonic acid, *p*-TsOH = *p*-toluenesulfonic acid.

2.0 h (Table 1, entry 1). Subsequently, several representative protic acids, such as TfOH, *p*-TsOH, and MsOH, were screened, but no superior results were obtained (Table 1, entries 2–4). Next, by increasing the load of $TMSN_3$ to five equivalents, **2a** was obtained in 85% yield (Table 1, entries 5 and 6). CH_3NO_2 proved to be the most efficient solvent in this transformation, which increased the yield of **2a** to 90% (Table 1, entries 7–9). Only a trace amount of **2a** was obtained in the absence of molecular sieves (13X, Table 1, entry 10), which might be owing to the molecular sieve acting as a solid acid to activate the dehydration of the propargylic alcohol.[13] **2a** was obtained only in a lower yield when molecular sieves 4 Å was used instead of molecular sieves 13X (Table 1, entry 12). A higher yield was not obtained by adjusting the amount of TMSCl (Table 1, entries 13 and 14). Ultimately, the use of TMSCl (1.0 equiv) in the presence of molecular sieves (13X) in CH_3NO_2 at 80 °C proved to be the most efficient, which was identified as the standard conditions.

With the optimized conditions in hand, we explored the scope of this reaction for the transformation of tertiary propargylic alcohols with $TMSN_3$, as shown in Table 2. Various tertiary propargylic alcohols **1a**–**w** could be easily converted into the corresponding products **2a**–**w** in moderate to excellent yields. The structure of **2a** was confirmed by X-ray diffraction (see the Supporting Information).[14] Firstly, substrates containing a methoxy or alkyl groups on the aryl substituent could give the corresponding products in high yields (**2a** and **b**, **2d**–**f**, **2h**). Fluoro-substituted propargylic alcohols were also tolerated under the optimal conditions, and the corresponding products could be isolated in excellent yields (**2l** and **j**), indicating the compatibility of this transformation with electron-deficient substituents. Moreover, with substituents at the *ortho*-position on the aryl ring, the desired products were obtained in good yields (**2c**, **2g**, **2k**), which indicates that steric hindrance has no influence on the efficiency of this reaction. Notably, substrates containing a chloro or bromo group on the aryl ring (**1l**–**n**) could give the corresponding products in excellent yields (**2l**–**n**), which provides an opportunity for further transformations through orthogonal cross-coupling reactions. Furthermore, sensitive functional groups, such as nitro and ester groups, were tolerated and afforded the desired products in excellent yields (**2o** and **p**), again indicating that this reaction has good functional groups tolerance. When a substrate containing several alkyl substituents on the aryl ring was employed, the reaction proceeded well and gave higher yields (**2q**). Fortunately, the heteroaryl-substituted substrate **1r** containing a 2-thienyl group could give the desired product **2r**. In addition, alkyl and halogen substituents (R^1, R^2) on aryl rings attached to the benzylic position (**1s**–**u**) were compatible in this transformation, and good yields were obtained in all cases. When unsymmetric tertiary propargylic alcohols (**1v**-**w**) were employed in this reaction, the regioisomers **2v** and **w** were obtained in high yields under the optimal conditions. However, alkyl-substituted tertiary propargylic alcohol **1x** did not afford the desired product after 4.0 h. This might be owing to the fact that the alkyl group can not migrate to the nitrogen atom in the rearrangement process. When changing the tertiary propargylic alcohol from a twofold aryl-substituted to a 1-methyl-1-phenyl-substituted one (**1y**), the desired product **2y** could not be observed under the standard conditions. Thus, it was confirmed that the 1-methyl-1-phenyl-substituted tertiary propargylic alcohol is more likely to undergo an intramolecular dehydration to afford the 1,3-enyne compound **5y**.[15]

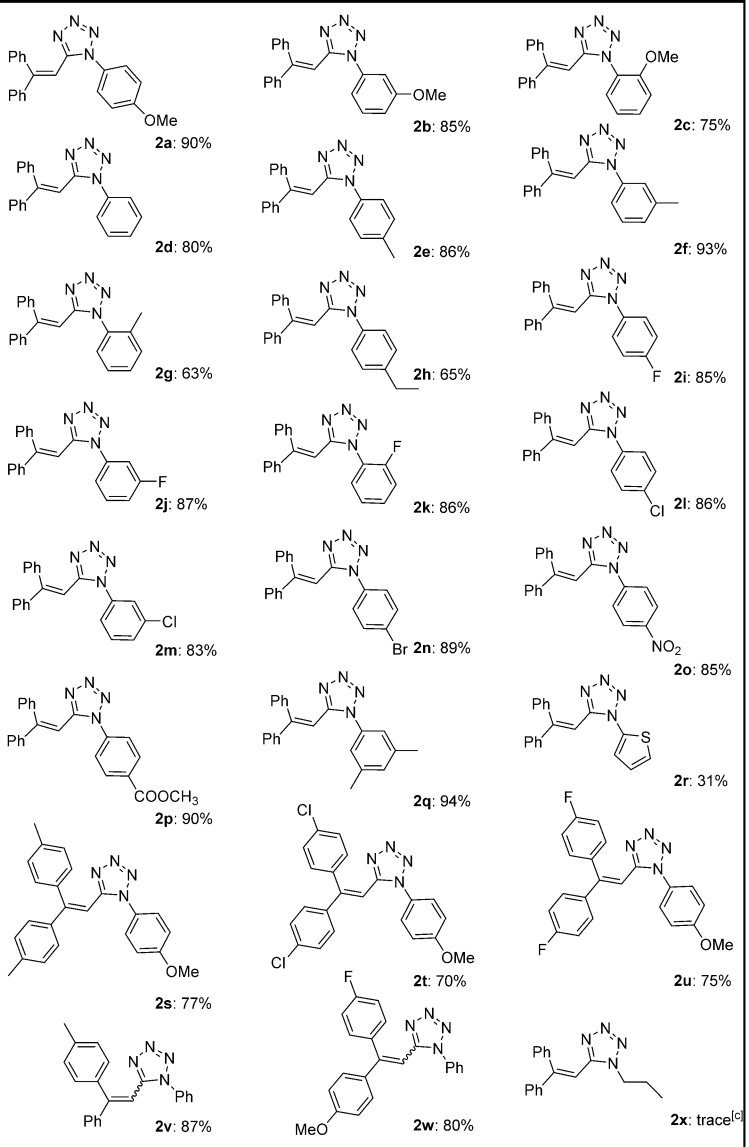
To further explore the scope of this method, the compatibility with secondary propargylic alcohols under the optimal conditions was investigated, as shown in Table 3. Various secondary propargylic alcohols with electron-rich and electron-poor substituents on the aryl substituent reacted efficiently to afford the corresponding products **4a**–**d** in excellent yields. Notably, when unsymmetric secondary propargylic alcohols were employed in this reaction, the desired products (**4a**–**d**) could be obtained with high *E* stereoselectivity.

An obvious advantage of this method is that the reaction can be scaled-up to gram scale; when the easily prepared secondary propargylic alcohol **3b** was used as substrate under the standard conditions, the desired product (*E*)-1-(4-methoxyphenyl)-5-styryl-1*H*-tetrazole (**4b**) was obtained in a high yield of 85%, which provides potential application in organic synthesis or, prospectively, even in industry (Scheme 2).

Finally, we explored the mechanism of this transformation. It is generally approved that propargylic alcohols can easily rearrange to the corresponding α,β-unsaturated carbonyl compounds through a Meyer–Schuster rearrangement under acidic conditions.[16] We assumed that one possible pathway would be a tandem sequence involving a Lewis acid mediated Meyer–Schuster rearrangement of the propargylic alcohols to

Table 2. Reaction scope for the transformation of tertiary propargylic alcohols.[a,b]

1a–x **2a–x**



[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), $TMSN_3$ (0.5 mmol), and molecular sieves (13X; 30 mg) in CH_3NO_2 (1.0 mL) at 80 °C. [b] Isolated yield. [c] For 4.0 h.

starting material to undergo this transformation under the standard conditions; however, the desired product **2a** was not observed (Scheme 3). These results clearly indicate that α,β-unsaturated ketones and amides are not involved in this novel transformation.

On the basis of the above observations and previous reports[8,12], we propose a plausible mechanism for this tandem transformation (Scheme 4). Initially, dehydration of the propargylic alcohol in the presence of TMSCl and molecular sieves (13X) gives the propargylic cation intermediate **A**, which can generate an allenyl-cation intermediate **B** through tautomerization of the propargyl cation. Subsequent attack of the azide anion on the allenyl cation affords allenylazide intermediate **C**. Protolysis of intermediate **C** forms intermediate **D**, which can release nitrogen gas through a highly chemoselective 1,2-aryl shift to form intermediate **E**. Then, intermediate **E** is attacked by another azide anion through a [3+2] cycloaddition[18] to generate the desired 1-aryl-5-arylvinyl-tetrazole product.

In conclusion, a novel and direct synthesis of 1-aryl-5-arylvinyl-tetrazoles from easily prepared propargylic alcohols and $TMSN_3$ has been developed in the presence of TMSCl. The process may involve an allenylazide intermediate, followed by a C–C-bond cleavage and C–N-bond formation to afford the desired products. This transformation offers a new synthetic strategy for the synthesis of important nitrogen-containing compounds and, furthermore, extends the application of azides to organic transformation of alkynols. The synthetic utility of this tandem reaction has been demonstrated by its applicability to a wide range of propargylic alcohol substrates and its scale-up to grams (yield up to 85%).

Experimental Section

General procedure for the synthesis of 1-aryl-5-arylvinyl-tetrazoles

Propargylic alcohol **1a** (31.4 mg, 0.1 mmol), molecular sieves (13X; 30.0 mg), TMSCl (9.0 μL, 0.1 mmol), and azidotrimethylsilane (75 μL, 0.5 mmol) in CH_3NO_2 (1.0 mL) were stirred at 80 °C under air. After 2 h, as monitored by TLC, the mixture was concentrated and purified by flash chromatography on silica gel (petroleum ether/EtOAc = 8:1, add Et_3N) to afford **2a** as a white solid (32.0 mg, yield 90%).

the α,β-unsaturated ketones, then followed by a Schmidt reaction to form the amides,[17] which subsequently react with $TMSN_3$ to generate the products.[3] To verify this hypothesis, two possible key intermediates, that is, the α,β-unsaturated ketone **6** and cinnamamide **7**, were prepared and used as

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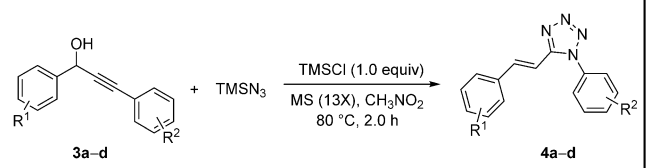
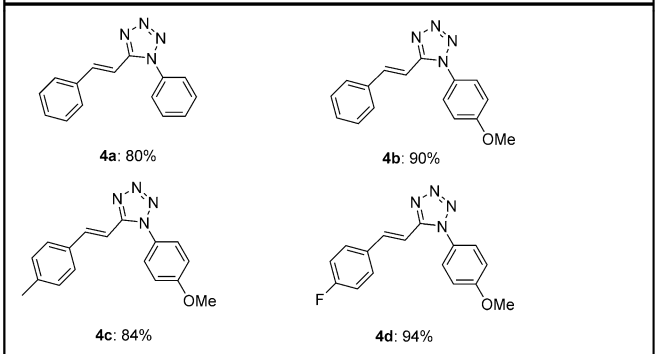
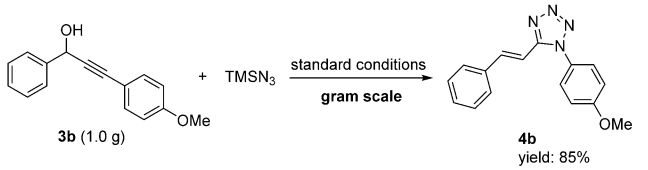
Table 3. Reaction scope for the transformation of secondary propargylic alcohols.[a,b]





[a] Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), $TMSN_3$ (1.0 mmol), and molecular sieves (13X; 60 mg) in CH_3NO_2 (2.0 mL) at 80 °C. [b] Isolated yield.



Scheme 2. Scale-up experiment.

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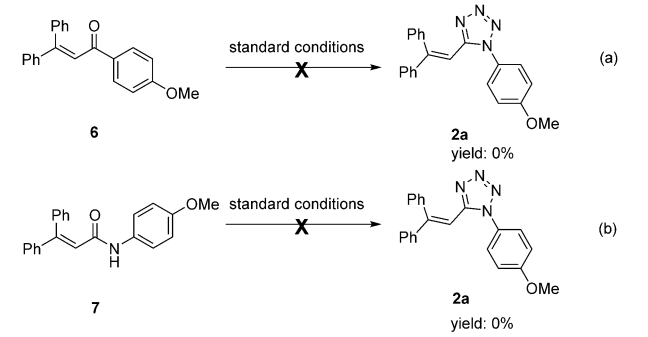

Scheme 3. Control experiments.

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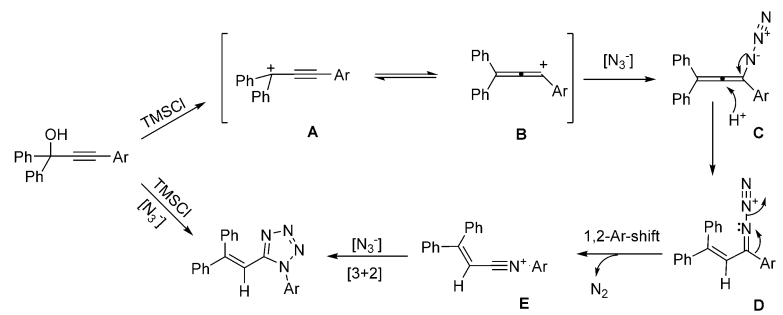

Scheme 4. Proposed mechanism.

Keywords: 1-aryl-5-arylvinyl-tetrazoles · C–C-bond cleavage · C–N-bond formation · Lewis acids · propargylic alcohols

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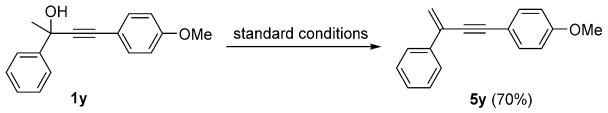
[14] CCDC 993234 (**2a**) contains the supplementary crystallographic data for this paper (see the Supporting Information). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[15] 1-Methyl-1-phenyl-substituted tertiary propargylic alcohol **1y** tends to undergo an intramolecular dehydration under the standard con-

ditions to afford the 1,3-enyne compound **5y**, see: S. Swaminathan, K. V. Narayanan, *Chem. Rev.* **1971**, *71*, 429.



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