ChemPubSoc Europe

DOI: 10.1002/chem.201504515

CHEMISTRY A European Journal Communication

Organic Synthesis

Reaction between Azidyl Radicals and Alkynes: A Straightforward Approach to *NH*-1,2,3-Triazoles

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Abstract: Reaction between nitrogen-centered radicals and unsaturated C–C bonds is an effective synthetic strategy for the construction of nitrogen-containing molecules. Although the reactions between nitrogen-centered radicals and alkenes have been studied extensively, their counterpart reactions with alkynes are extremely rare. Herein, the first example of reactions between azidyl radicals and alkynes is described. This reaction initiated an efficient cascade reaction involving inter-/intramolecular radical homolytic addition toward a C–C triple bond and a hydrogen-atom transfer step to offer a straightforward approach to *NH*-1,2,3-triazoles under mild reaction conditions. Both the internal and terminal alkynes work well for this transformation and some heterocyclic substituents on alkynes are compatible. This mechanistically distinct strategy overcomes the inherent limitations associated with azide anion chemistry and represents a rare example of reactions between a nitrogen-centered radicals and alkynes.

Recent years have witnessed a renaissance of radical chemistry,[1] particularly, in the use of radical reactions for constructing complex molecules in a highly efficient and atom-economic manner with excellent regio- and stereoselectivities.[2] Among these radicals, nitrogen(N)-centered radicals are of great important because they offer straightforward strategies to synthesize nitrogen-containing compounds, which are very important for drug development and other fine chemicals.[2a] For example, the Hofmann–Löffler–Freytag reaction is a classical strategy for remote sp^3 C–H amination employing a N-centered radical.[3] Meanwhile, the homolytic addition of a N-centered radical to the alkene C–C double bond[4] has also been recognized as an appealing synthetic strategy for hydroamination[5] and difunctionalization[6] of alkenes. In the sharp contrast, however, the reaction between nitrogen-centered radicals and alkynes is extremely rare (Scheme 1).[7] This challenging situation is mainly attributed to the lack of a suitable trapping handle to harness the highly reactive and unstable β-*N*-substituted vinyl radical for further transformations.[2b] Neale developed a useful synthetic cascade reaction involving the addition of an aminium radical to alkynes (Scheme 1 a).[7a] Wille and Luning elaborately designed a cascade reaction consisting of a N-centered radical addition to alkyne/1,5- or 1,6-HAT/cycloaddition/oxidative termination to produce the bicyclic ketones (Scheme 1 b).[7b,c] Very recently, Zhang reported an elegant cascade reaction of an alkyne initiated by a N-centered radical that originated from *N*-fluorobenzene-sulfonimide (Scheme 1 c).[7d] We herein disclose the first reaction between azidyl radicals and alkynes involving inter-/intramolecular radical homolytic addition and a subsequent hydrogen atom transfer (HAT), which finally afforded a highly efficient approach to *NH*-1,2,3-triazoles (Scheme 1 d).

NH-1,2,3-triazoles are of great importance as structural motifs because they are not only widely found in pharmaceuticals and materials,[8] but also can be used as valuable intermediates for a series of important transformations (Scheme 2).[9] However, their potential applications are still far less exploited than they could be due to the lack of a general approach to their synthesis. Generally, the synthesis of *NH*-1,2,3-triazoles is accomplished by deprotection of N1-substituted 1,2,3-triazoles[10] or cycloaddition of activated alkynes[11] and alkenes.[12] Unfortunately, these strategies suffer from the use of volatile and toxic hydrazoic acid or activated alkenes and alkynes with strong electron-withdrawing groups under harsh reaction conditions. We reasoned that these limitations might be overcome by employing radical strategies, which are generally less sensitive to the electronic effect.[1c] As shown in Scheme 1 d, the 1,2,3-triazole framework could be constructed if the azide group of the β-azidovinyl radical, formed in situ from the homolytic addition of an azidyl radical to an alkyne, could trap the vicinal carbon-centered radical through the terminal nitrogen atom (N^{γ})[13] in an intramolecular manner. *NH*-1,2,3-triazoles could be obtained by a subsequent HAT step.

To verify the viability of our hypothesis, we tested various azidyl radical sources with 1,2-diphenylethyne as the model substrate. To our delight, *NH*-1,2,3-triazole **2 a** was indeed obtained in 56% yield using the combination of $TMSN_3$ and $PhI(OAc)_2$ as the azidyl radical source (Table 1, entry 1). The yield of *NH*-1,2,3-triazole was significantly increased when the azide donor was replaced by NaN_3 (entry 2). Other oxidants,

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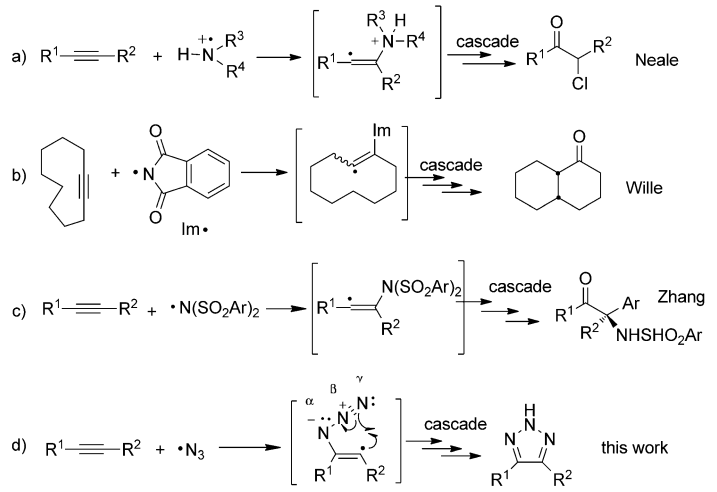
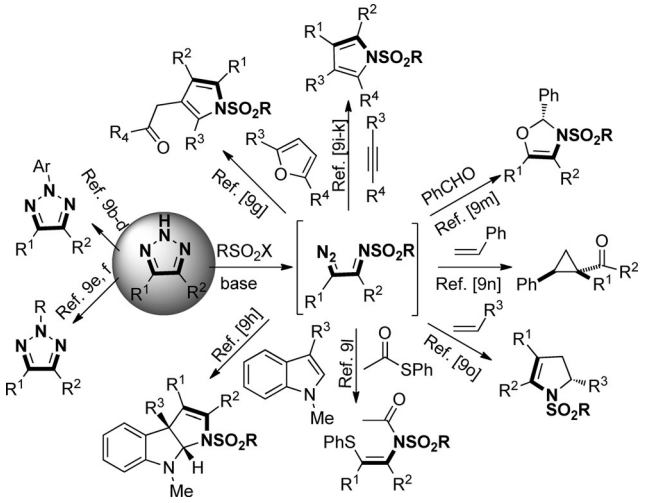
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201504515.



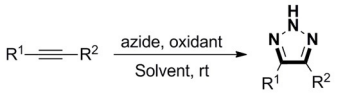
Scheme 1. Reactions between N-centered radicals and the C–C triple bond of alkynes.

phenyl ring generally offered lower yields than their electron-neutral and -rich congeners (**2a–i**). This outcome might be partially attributed to the electrophilic nature of the azidyl radical.[5e] Alkynes bearing reactive functional groups, such as -OH, -NR_2, and -SBu, which would be incompatible with conventional strategies, were well tolerated (**2w, 2x, 2ad**, and **2ae**). It is notable that aromatic heterocycles such as pyridine and thiophene are also compatible (**2q–s** and **2v**). Alkynes containing a vicinal tertiary carbon center could also be used as a valid substrate (**2x**). More importantly, the bromo and silyl group can also be tolerated, thereby allowing the possibility for further functionalization (**2r–u**, and **2z–ac**). Even the reaction of a diyne proceeded smoothly to afford the bis-*NH*-1,2,3-triazole in good yield (81%, **2u**). Terminal alkynes also worked well for this reaction (**2af–**



Scheme 2. Representative synthetic applications of *NH*-1,2,3-triazoles as valuable reaction intermediates.

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



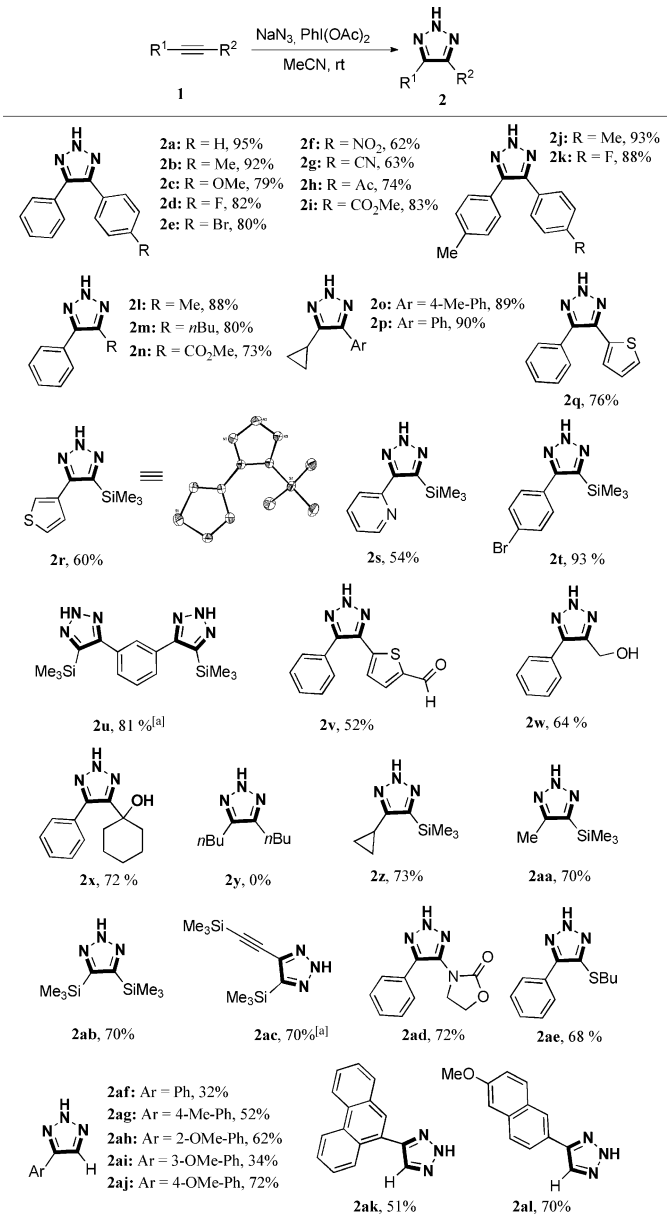
Entry	Azide (equiv)	Oxidant (equiv)	Solvent	Yield [%]
1	$TMSN_3$ (2)	$PhI(OAc)_2$ (2)	MeCN	56
2	NaN_3 (2)	$PhI(OAc)_2$ (2)	MeCN	83
3	NaN_3 (2)	$PhI(CF_3CO_2)_2$ (2)	MeCN	53
4	NaN_3 (2)	$PhI(OAc)_2$ (2)	$CHCl_3$	34
5	NaN_3 (2)	$PhI(OAc)_2$ (2)	DCE	28
6	NaN_3 (2)	$PhI(OAc)_2$ (2)	DCM	52
7	NaN_3 (2)	$PhI(OAc)_2$ (2)	acetone	51
8	NaN_3 (2)	$PhI(OAc)_2$ (2)	$PhCH_3$	25
9	NaN_3 (2)	$PhI(OAc)_2$ (1)	MeCN	90
10	**NaN_3 (1.5)**	**$PhI(OAc)_2$ (1)**	**MeCN**	**95**

[a] Reaction conditions: 1,2-diphenylethyne (0.2 mmol), NaN_3 and $PhI(OAc)_2$ in solvent (3.0 mL) was stirred at room temperature for 8 h under nitrogen. DCM: dichloromethane, DCE: 1,2-dichloroethane.

such as $PhI(CF_3CO_2)_2$, PhIO, $Mn(OAc)_3$, and TBHP, proved to be less effective for this reaction (for details of reaction-condition optimization, see the Supporting Information). Solvent was found to have a remarkable influence on the reaction efficiency and acetonitrile was identified as the optimal solvent (entries 2–8). The loading of $PhI(OAc)_2$ and NaN_3 was also evaluated. The highest yield of up to 95% was obtained in the presence of 1 equivalent of $PhI(OAc)_2$ and 1.5 equivalents of NaN_3 (entry 10).

With the optimized reaction conditions in hand, we turned our attention to the substrate scope of the reaction. A variety of internal and terminal alkynes with different electronic properties were tested, and the results are shown in Scheme 3. Unlike conventional strategies limited to electron-deficient substrates, the electronic effects of alkynes have little influence on this reaction. Both electron-donating and -withdrawing groups were tolerated for 1,2-diphenylethyne derivatives (**2a–i**). Substrates bearing electron-withdrawing groups on the **al**). A similar trend with internal alkynes with respect to the electronic effect was observed, as evidenced by the fact that electron-rich terminal alkynes gave higher yields. Although aliphatic internal alkyne (**2y**) did not react under the optimized reaction conditions, aromatic alkynes bearing one aliphatic substituent reacted smoothly to afford the target *NH*-1,2,3-triazole in good to excellent yields (**2l–p**, **2w**, and **2x**). In addition, an aliphatic internal alkyne bearing a substituent such as a silyl group that can stabilize the in situ formed vinyl radical also worked well (**2z–ac**).

To gain insight into the reaction mechanism, a control experiment with 2 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to probe whether radical species were involved in the reaction was performed. The reaction was completely retarded by TEMPO although no radical intermediate was trapped (see the Supporting Information). Furthermore, an electron paramagnetic resonance (EPR) experiment was conducted. As shown in Figure 1a, a typical EPR signal was ob-



Scheme 3. Scope of the radical cascade reaction. Reaction conditions: 1,2-diphenylethyne (0.2 mmol), NaN_3 (0.3 mmol), $PhI(OAc)_2$ (0.2 mmol), in CH_3CN (3.0 mL) was stirred at room temperature for 8 h under nitrogen. [a] Alkyne (0.2 mmol), NaN_3 (0.6 mmol), $PhI(OAc)_2$ (0.4 mmol).

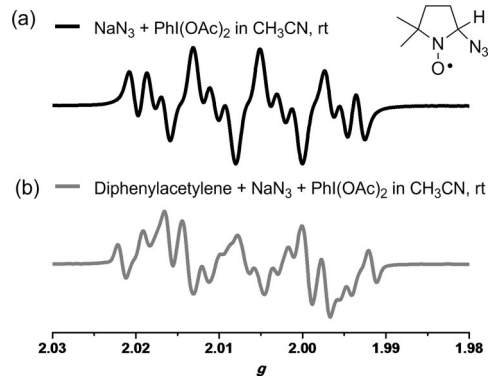
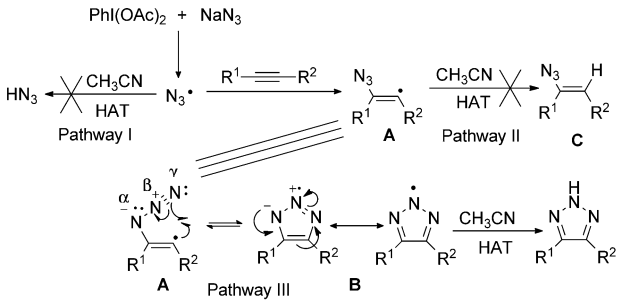


Figure 1. Electron paramagnetic resonance experiment.

served when NaN_3 and $PhI(OAc)_2$ were mixed in 3.0 mL CH_3CN at room temperature for 1 hour. The data analysis suggested that an azidyl radical was generated and quickly trapped by 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) to form a relatively stable radical (DMPO-N_3).[14] A new EPR signal was detected after the addition of 1,2-diphenylethyne into the system (Figure 1 b), indicating that the azidyl radical could react with 1,2-diphenylethyne to form new radical species, albeit the structure of which could not be identified. These EPR experiments indicated that an azidyl radical was formed through the oxidation of NaN_3 with $PhI(OAc)_2$ as the oxidant. This azidyl radical then initiated the cascade reaction of the alkyne and finally afforded the desired product.

Theoretically, both concerted and stepwise mechanisms are reasonable for this "click reaction" between azidyl radical and alkyne. A mechanistic DFT study of the reaction was conducted to investigate the reaction mechanism. According to the DFT calculation, the transition structure of the concerted azidyl radical addition to the triple bond could not be identified and thus the concerted mechanism was unfavorable. A plausible stepwise mechanism was proposed based on experimental and theoretical calculation results (Scheme 4). An azidyl radical



Scheme 4. Proposed reaction mechanism.

is produced when NaN_3 is treated with $PhI(OAc)_2$.[15] Two pathways are possible for the trapping of the azidyl radical: abstract a hydrogen atom to release hydrazoic acid (pathway I) or homolytic addition to an alkyne to furnish the highly reactive vinyl radical **A**. Premature termination of the vinyl radical **A** by HAT will produce vinyl azide **C**, which was not detected (pathway II). On the other hand, followed by an intramolecular homolytic addition of the terminal (N^{γ}) nitrogen atom of the azide functional group, the in situ formed vinyl radical **A** transforms (eventually through the initially formed σ-radical) into a new N-centered π-radical **B**, which undergoes subsequent HAT to afford the final *NH*-1,2,3-triazole (pathway III). The energy barrier between pathways I, II, and III and the observed different reactivity of diaryl versus dialkyl alkynes was further investigated in a DFT study using 1,2-diphenylethyne **1a** (R = Ph) and but-2-yne **1y′** (R = CH_3) as model substrates (Figure 2). The relative free energies were obtained by employing the B2PLYP-D3//B3LYP-D3/def2-TZVP[16] level of theory. As shown in Figure 2, the energy barriers of both pathways I and II are higher than that of pathway III. The free energy of formation

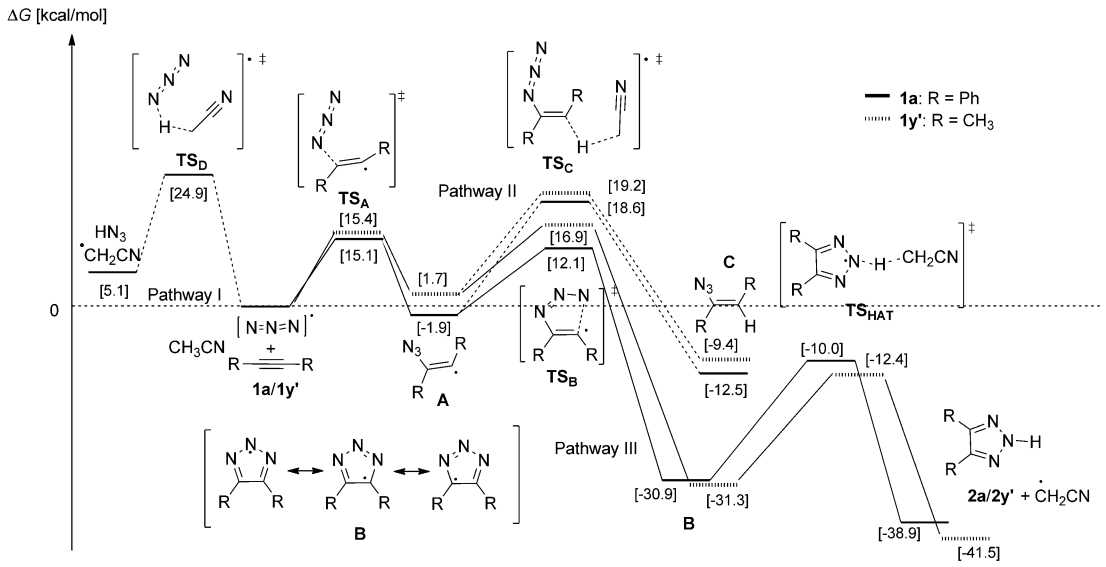


Figure 2. DFT-computed free energies of the reaction between the azidyl radical and alkynes. Bold: 1,2-diphenylethyne, hashed: but-2-yne.

of the vinyl radical intermediates **1a-A** and **1y′-A** along the transition structures **1a-TSA** and **1y′-TSA** revealed a distinct difference between the two alkynes: whereas **1a** reacts exothermically (-1.9 kcal mol^{-1}), the dimethyl alkyne only forms small amounts of **1y′-A** under thermodynamic control ($\Delta G = +1.7$ kcal mol^{-1}). In addition, the barrier towards ring closure (**1y′-TSB**) is larger than the barrier of dissociation. In contrast, the 1-phenyl-vinyl radical **1a-A** undergoes (exothermic) formation of the triazolyl ring **1a-B** faster than fragmentation occurs. Both 1,2,3-triazolyl radicals **1a-B** and **1y′-B** are by over 30 kcal mol^{-1} more stable than the reactants, indicating the formation of the delocalized radical as the driving force of the reaction. Our DFT calculations demonstrated that both the activation barrier and reaction free energy allow the 1,2,3-triazolyl radicals **1a-B** and **1y′-B** to abstract a hydrogen atom from CH_3CN to form the *NH*-1,2,3-triazole **2a** (and **2y′**, if the previous steps would not disfavor this pathway). The free energy barrier of 19–21 kcal mol^{-1} is overcome under the experimental conditions (room temperature), and the reaction is exothermic (9–10 kcal mol^{-1}). The origin of the hydrogen atom was further confirmed by isotopic experiment. As expected, an *ND*-1,2,3-triazole was obtained when the reaction was conducted in deuterated acetonitrile (for details, see the Supporting Information).

In conclusion, we have successfully developed an oxidative "click reaction" between a variety of alkynes and sodium azide. This reaction not only offers an efficient and practical method for the synthesis of *NH*-1,2,3-triazoles, but also illustrates a novel reactivity of the azidyl radical, which initiated a cascade, including inter-/intramolecular radical homolytic addition toward alkynes and a HAT under mild reaction conditions. A substituent group on the alkynes stabilizing the in situ formed vinyl radical on the alkynes is crucial for this transformation. Compared with the conventional ionic processes, in which the substrate scope is limited to electron-deficient alkenes or alkynes, this radical-cascade protocol facilitates the use of a broad range of viable substrates. The azide group plays two important roles: inducing the formation and trapping of the reactive vinyl radical. Both the homolytic addition of the azidyl radical to alkynes and the subsequent intramolecular reaction between the vinyl radical and azide functional group are unprecedented. These features make this strategy not only theoretically important but also synthetically useful. It is foreseeable that the results reported here will spur the application of azidyl radical chemistry and shed light on the design of new reactions between N-centered radicals and alkynes in the future.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (21462023, 21262018) and the Natural Science Foundation of Jiangxi Province (20143ACB20007, 20133ACB20008). We thank Prof. A. Studer for valuable discussions and suggestions.

Keywords: alkynes · azidyl radicals · cascade reactions · nitrogen · triazoles

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Received: November 11, 2015
Published online on December 14, 2015