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[3 + 2] Cycloaddition of Nitrile Ylides with Diazonium Salts: Copper-Catalyzed One-Pot Synthesis of Fully Substituted 1,2,4-Triazoles

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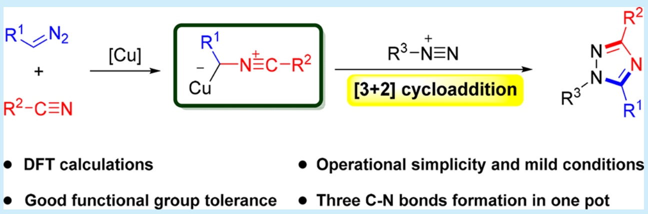
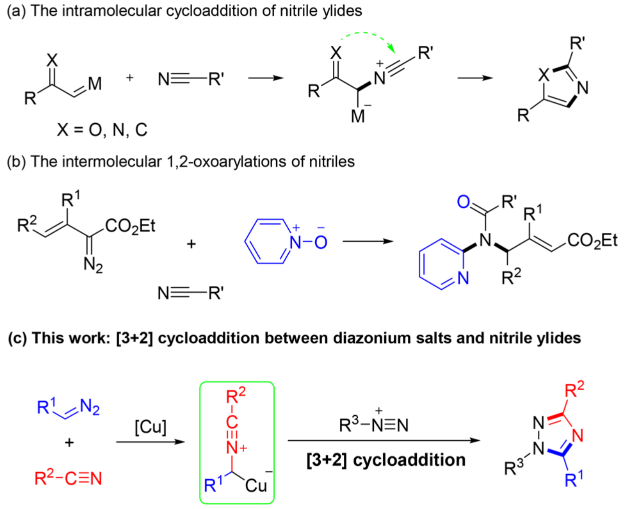
Supporting Information

ABSTRACT: A novel [3 + 2] cycloaddition between nitrile ylides and diazonium salts was well-established. This copper-catalyzed three-component reaction was distinguished by mild conditions, ready availability, and operational simplicity, thus opening access to 1,2,4-triazoles with a diverse set of substitution patterns.



The nitrile ylides are privileged and readily accessible 1,3-dipoles and have become attractive and powerful synthons for building various heterocyclic compounds.[1,2] The intramolecular cycloaddition of nitrile ylides, which were generated from the nucleophilic reaction of nitriles and carbenoids, has evolved into a classic and proverbial reaction process for synthesis of nitrogen-containing heterocyclic compounds (see Scheme 1a).[1] In sharp contrast, the relevant reports about intermolecular interception of nitrile ylide are very rare.[2] In 2014, Liu and co-workers reported an elegant gold-catalyzed 1,2-oxoarylation of nitriles through the intermolecular nucleophilic attack to nitrile ylides with pyridine-derived *N*-oxides (see Scheme 1b).[2a] Very recently, we developed an efficient copper-catalyzed three-component cascade reaction via the interception of nitrile ylide with carboxylic acids for the synthesis of unsymmetrical glycine esters.[2c] To the best of our knowledge, trapping of nitrile ylide with a triple bond system to perform intermolecular [3 + 2] cycloaddition has not yet been reliably implemented. As illustrated in Scheme 1c, we hypothesized that diazonium salts, which are a class of readily available and versatile synthetic precursors,[3,4] could undergo [3 + 2] cycloaddition with nitrile ylides generated in situ from nitriles and diazo compounds to form the desired 1,2,4-triazoles. Substituted 1,2,4-triazoles and their derivatives, as privileged nitrogen-containing structural units, have found wide application in medicines,[5] pesticides,[6] materials science,[7] and organocatalysts,[8] and many chemists have committed to developing practical methods to deliver this skeleton.[9−11]

Scheme 1. Transformation of Nitrile Ylides



Our initial studies focused on searching for an optimal catalytic condition to generate 1,2,4-triazole **4a** efficiently, using *p*-methoxyphenyldiazonium tetrafluoroborate (**1a**), ethyl 2-diazoacetate (**2a**), and acetonitrile (**3a**) as reaction substrates. Delightfully, an 85% yield of the target product **4a** was obtained in the presence of 20 mol % CuBr and 1.0 equiv Li_2CO_3 at 40 °C for 1 h (see Table S1, entry 1, in the Supporting Information). Next, we tested other transition-metal catalysts, such as $Cu(OTf)_2$, CuOTf $Pd(OAc)_2$, $Rh_2(OAc)_4$, AuCl, AgOAc, $Mn(OAc)_2{\cdot}4H_2O$, $Co(acac)_2$, $Fe_2(CO)_9$, leading to significantly decreased yields (see Table S1, entries 2−10). Not surprisingly, no product **4a** was observed in the absence of the copper catalyst (see Table S1, entry 11). Replacing Li_2CO_3 with other inorganic bases resulted in lower yields (see Table S1, entries 12−17), and the cascade reaction hardly worked when organic bases, including 4-dimethylaminopyridine (DMAP), triethylenediamine (DABCO), triethylamine (TEA), were used for this 1,2,4-triazole formation reaction (see Table S1, entries 18−20).

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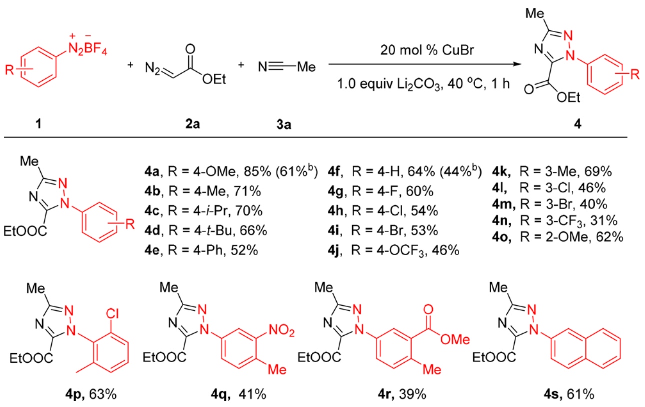
With the optimized reaction conditions being identified, the scope of aryldiazonium tetrafluoroborate was investigated as shown in Scheme 2. The benzene ring of diazonium salt with electron-donating groups at the *para*-, *meta*-, and *ortho*-position proceeded well, affording the corresponding 1,2,4-triazole in moderate to good yields (**4a**–**4f**, **4k**, **4o**). Notably, substrates containing halogen groups were also tolerated well and delivered the desired products in satisfactory yields under the standard reaction conditions (**4g**–**4i**, **4l**, **4m**). The reaction efficiency was relatively low when aryldiazonium-bearing electron-withdrawing groups, such as trifluoromethoxy (**4j**), trifluoromethyl (**4n**), nitro (**4q**), and ester (**4r**), were used as reaction partners. Finally, both multisubstituted phenyl diazoniums (**4p**–**4r**) and naphthyl diazonium (**4s**) worked well for this 1,2,4-triazole formation reaction. Unfortunately, 4-nitrophenyl diazonium salt was not a suitable substrate for this transformation.

Scheme 2. Scope of Diazonium Salts[a]

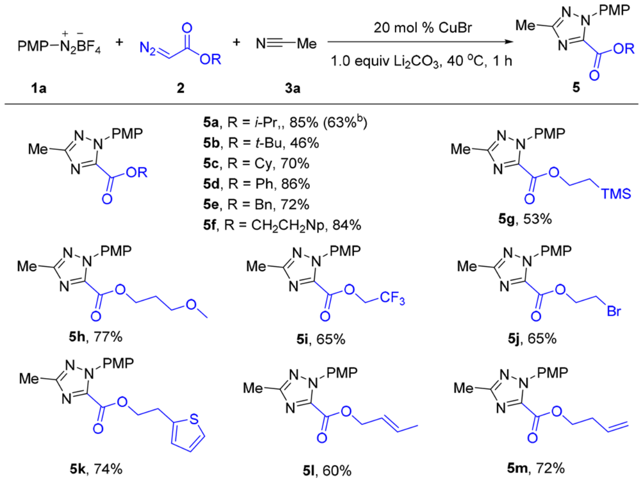


[a]Conditions: **1** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.5 mL), CuBr (20 mol %), and Li_2CO_3 (1.0 equiv) in a test tube was stirred at 40 °C for 1 h under air. [b]The isolated yield for a reaction performed on a 1.0 mmol scale is shown in parentheses.

We next tested the scope with respect to the diazo compounds, as shown in Scheme 3. Various diazo acetates were successfully employed as reaction partners in this reaction (**5a**–**5f**), and the decrease of yield was detected due to the steric hindrance (**5b**). A wide range of functional groups, such as trimethylsilyl (**5g**), ether (**5h**), trifluoromethyl (**5i**), bromo (**5j**), thienyl (**5k**), were well-tolerated in this transformation, leading to the desired products in satisfactory yields. Note that both terminal and internal vinyl did not interfere with this process, which provided an opportunity for further synthetic manipulation (**5l**, **5m**).

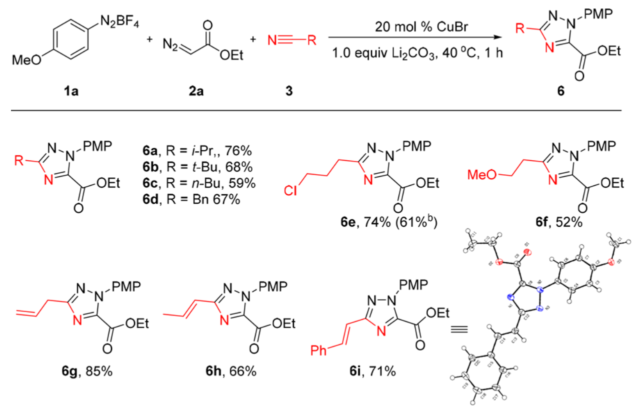
As illustrated by the examples shown in Scheme 4, nitriles bearing various alkyl groups participated well in this transformation. Primary, secondary, and tertiary nitriles smoothly underwent cyclization to give the corresponding products in good yields (**6a**–**6c**). Incorporation of different functional groups into the nitriles, including benzyl (**6d**), chloro (**6e**), or ether group (**6f**), exhibited inconspicuous effects on product formation. More attractively, the reactions were also suitable for vinyl nitriles to deliver the desired products (**6g**–**6i**), which were hardly achieved using previous methods. In addition, the exact structure of product **6i** was expressly determined by X-ray crystallography.

Scheme 3. Scope of Diazo Compounds[a]



[a]Conditions: **1a** (0.2 mmol), **2** (0.6 mmol), **3a** (0.5 mL), CuBr (20 mol %), and Li_2CO_3 (1.0 equiv) in a test tube was stirred at 40 °C for 1 h under air. [b]The isolated yield for a reaction performed on a 1.0 mmol scale is shown in parentheses.

Scheme 4. Scope of Nitriles[a]

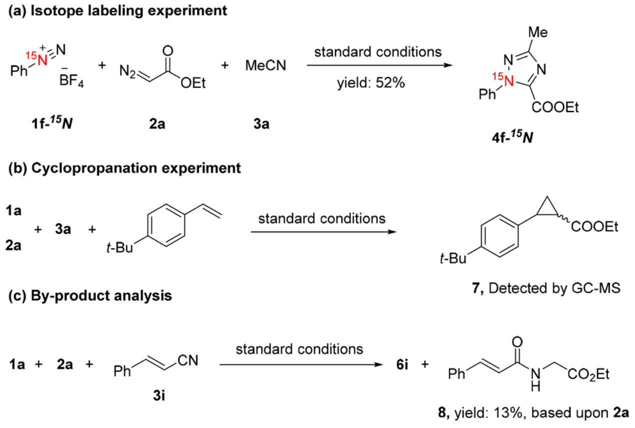


[a]Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), **3** (0.5 mL), CuBr (20 mol %), and Li_2CO_3 (1.0 equiv) in a test tube was stirred at 40 °C for 1 h under air. [b]The isolated yield for a reaction performed on a 1.0 mmol scale is shown in parentheses.

A battery of preliminary studies was performed to gain mechanistic insight into this 1,2,4-triazole formation reaction. Isotope tracer technique showed that the two N atoms of the target 1,2,4-triazole molecules originated from aromatic diazonium salt (Scheme 5a). When 4-*tert*-butylstyrene was added to our model reaction, the cyclopropanation product **7** was detected by GC-MS, which implied that a carbene intermediate was involved in this process (Scheme 5b).[12] Notably, analysis of the reaction mixture of nitrile **3i** indicated that the amidated compound **8** was generated in 13% yield (Scheme 5c), suggesting that the in situ generation of nitrile ylide intermediate and subsequent interception by water were involved in this transformation.[1]

Computational studies were performed to provide a mechanistic insight into this 1,2,4-triazole formation reaction (see Figure 1). First, the Cu-catalzyed N_2 elimination from both **2a** and **1a** cation were evaluated. Computational results show that the free-energy barrier of extrusion of N_2 from diazo compound **2a** is 14.3 kcal/mol, which is 15.9 kcal/mol lower

Scheme 5. Mechanistic Studies



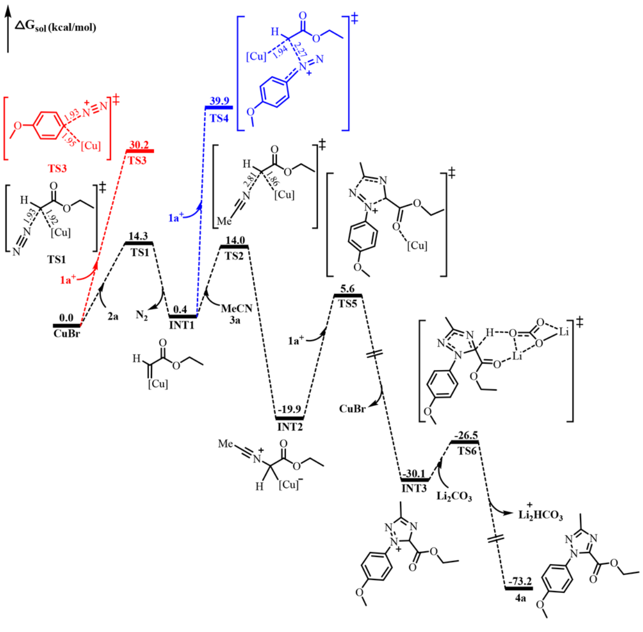


Figure 1. Energy profiles (in kcal/mol) for the formation of the Cu-carbenoid **INT1** and the subsequent nucleophilic attacks of **1a**$^+$/**3a**. Bond lengths are shown in Ångstroms.

than that obtained from the **1a** cation. Thus, the formation of the Cu-carbenoid intermediate **INT1** is more likely to occur. Subsequently, the substrate acetonitrile (**3a**) may undergo a nucleophilic attack to the carbenoid site of **INT1** to afford the nitrile ylide intermediate **INT2**. The predicted free-energy barrier is 13.6 kcal/mol, relative to separated **INT1** and **3a** and the generated **INT2** is thermodynamically stable. One may propose that the nucleophilic attack of the diazonium salt **1a** to the carbenoid of **INT1** might also be possible. Computational results suggest that a much higher energy barrier (39.5 kcal/mol) is required to undergo such a reaction route, which is unlikely to occur, compared with the nucleophilic attack of **3a**. Afterward, a [3 + 2] cycloaddition reaction between the generated **INT2** and **1a** cation could occur, yielding the intermediate **INT3**. The predicted free-energy barrier for this process is 25.5 kcal/mol. Finally, a deprotonation step assisted by Li_2CO_3 occurs to furnish the final product 1,2,4-triazole (**4a**).

Based on the above experimental results and DFT calculations, a plausible mechanism for the construction of 1,2,4-triazole is illustrated in Figure 2. The transformation begins with the formation of carbenoid **A** from the copper catalyst coordinated with diazo compounds. Subsequently, the nitrile performs as a nucleophile to attack **A** to generate intermediate **B**.[1,2] The resulting intermediates **B** subsequently undergo [3 + 2] cycloaddition with diazonium salt to afford the five-membered ring intermediate **C**, which strips a proton and isomerizes to access the target 1,2,4-triazole in the presence of base. On the other hand, a small amount of nitrile ylide intermediate **B** can be trapped by water to generate undesired amides as byproducts.

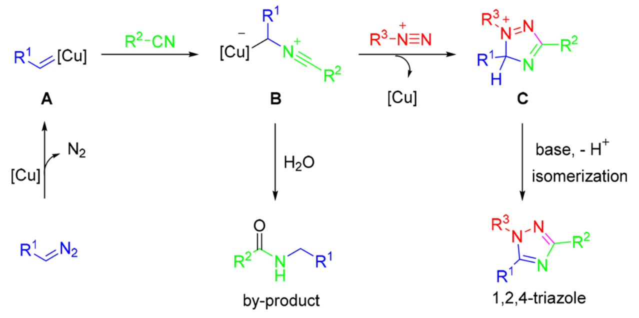


Figure 2. Proposed mechanism.

In summary, we have demonstrated a copper-catalyzed intermolecular [3 + 2] cycloaddition reaction to afford 1,2,4-triazoles in moderate to high yields, which proceeds via the trapping of an intermediary nitriles ylides species by diazonium salt. This methodology offers a simple and efficient strategy to construct structurally diverse 1,2,4-triazos from readily available starting materials in a one-step fashion under mild condition. The preliminary experimental results show that diazonium salts served as the two N atoms resource for the target 1,2,4-triazoles skeletons. Further investigations on the interception of nitriles ylides with other reagents are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02172.

Experimental procedures and full spectroscopic data for all new compounds, computational method, Figure S1, and Cartesian coordinates and energies (PDF)

Accession Codes

CCDC 1827426 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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